Resident Primer

Cardiac
Anesthesia Department

UMASS Medical

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Flow in UMass Cardiac Rooms:

Welcome to cardiac anesthesia rotation! Cardiac surgeries are usually performed in room 3 and 4. Currently we have 3 cardiac surgeons: Dr. Walker, and Dr Mandapati and Dr Kourlis. We also have couple of surgeons from B&W temporarily with us, DR Leacche and DR Gosev. Our patients are on the OR table at 7am! They usually arrive to PACU around 5:30 for checking in (unless it is an ICU pickup). For this rotation, any patient in ICU is an anesthesia pickup case, regardless of intubation status! You usually get access to the patient around 6:15 to start IV and A-line. Well-preparation is a key to success!
Both arms are usually tucked. Many of our patients have their cardiac catheterization through radial artery, keep this in mind and if cath was done recently, try to place your Aline on the other side unless contraindicated.
Occasionally a pressure monitor line will be handed to you from surgical side for retrograde catheter pressure during CPB, and we usually connect this to PA transducer and re-zero the transducer!

Preoperative evaluation:

Usual preoperative evaluation with especial attention to following:

-Almost all our cases have Cardiac Catheterization result, Echo result and Carotid Duplex evaluation before coming to the operating room for cardiac surgery. Patients with respiratory problems will also have PFTs. Gather all available information!

-If patient has been on heparin drip or in-house patient with several trips to Cardiac Cath lab and previous exposure to heparin (vascular patient and…) look for possible HIT (e.g. Drop in platelet count or previous HIT positive antibodies). You should have an alternative plan for anticoagulation if HIT positive.

-Almost all our patients will have an intraoperative TEE; ask about any swallowing problem or previous GI surgery or esophageal disease.

-Redo surgeries increase the risk of bleeding and complicates the surgery. Patient may be in OR longer and chance of transfusion is higher. We usually have two large bore IVs with one on each side for redo cases.

-Inform your attending if there are positive antibodies! May be difficult to get blood products when in need!

-Also JW patients should be well informed of possibility of dying from bleeding and should communicate clearly with them what is exactly that they will accept to receive. Some will accept cell-saver and some may not even accept Albumin! They might want to contact their religious advisor to find out.

- History of Plavix use should be checked; recent use will increase risk of bleeding and may need platelet. Look for P2Y12 level if patient recently received plavix.

-Any active symptoms (chest pain, SOB…)? Talk to your attending, patient may need IABP before coming to the OR.

-For patients with Pacemaker or ICD contact EP lab the day before surgery to turn off ICD or change pacer setting in the morning of surgery. Consult your attending about the change.

-Patients on IABP will be transferred by anesthesia team from ICU directly to OR. You may go to ICU and place IV and A-line before transfer. A perfusionist will also accompany patient to OR. You will also need an anesthesia tech to help with transfer.

-Keep IV medication infusions (Heparin, NTG) running. If in doubt talk to your attending about drips, some of them may need to be stopped.

- Patients should take their beta-blocker, ASA (for CABG) and statins on the day of surgery. About use of other medications on the day of surgery talk to your attending.

Usual steps and monitoring

Basic anesthesia set up and routine airway stuff plus following:

-Norepinephrine and nitroglycerin drip ready for almost all cardiac cases to be used on plum pump. Have Phenylephrine drip on dial-a-flow and Amicar for all cases on CPB.

-Our friendly anesthesia technicians set up IVs and transducers for A-line and PA catheter in cardiac rooms and they help with patient transfer and attaching monitors in the morning and the floating of the PA catheter.

- Pacing box in the room and Defibrillator in the room and turned on and synch appropriately

- R2 pads for redo cases

-Fluid warmer ready for use from start for redo and off pump cases

-Warming pad on bed

-BIS and Somanetics for all cases
-Somanetics: The Cerebral Oximeter (Somanetics) is a trend monitor of brain hemodynamic. It is a device that uses near-infrared spectroscopy to measure changes in the balance between oxygen supply and demand in the brain. A low-intensity, near-infrared light is passed through the cortex of the forehead. Returned light from two different distances (3 and 4 cm) the absorption of light can be managed. Two wavelengths are measured, 730 nm and 805 nm. The Somanetics measures blood oxygen saturation of hemoglobin in a region of the brain. The rSO_2 is displays and is an index of oxygen saturation of mixed arterial and venous blood in the brain cortex. This is an index only and only reflects the area monitored and not tissue distant from the sensor. Both side of cortex are monitored because unequal perfusion patterns may be exhibited and the Somanetics may help distinguish unilateral imbalance. An absolute drop in rSO_2 of 12-20 points, a relative change in saturation of 20-30% from baseline or an absolute rSO_2 of less than 50% has correlated with poorer neurologic outcomes.

-BIS monitor is encouraged, especially considering that you are relying on perfusionist for anesthetics during CPB time. Just remember, you are responsible for anesthesia!

-We use a special screen over patient head area which goes up after intubation (Gerato!) .it is a metal bar with a clear plate on top which is aligned over the patient's head to protect head and neck and also gives us enough room to manipulate TEE probe without interfering with surgical field.

-After setting up your room in the morning you will see the patient. Before starting any invasive procedure ask if patient has chest pain or feeling SOB. Notify your attending if that is the case.

-Place a large bore IV in AC (14-16 preferred) and confirm its position by drawing back blood and free flow and then slow down IV fluid especially in patients with low cardiac output! For redo cases consider at least one IV in right side. Make sure that there is no radial artery harvest scheduled for that side before placing an A-line or IV! If patient had his/her cardiac catheterization through radial artery consider opposite side for A-line.

Standard Anesthesia Medications and common medications to be prepared for each case

Sedative agent (midazolam)
Narcotic agent (fentanyl or sufentanil)
Induction agent (usually propofol, sometimes Etomidate or Ketamine)
Muscle relaxant (Rocuronium, Vecuronium or Pancuronium, Succinylcholine)
Talk to your attending about choice of induction agents, narcotic and muscle relaxant!
Heparin should be drawn up and ready for each case!
Amicar for on pump cases
Norepinephrine drip and phenylephrine drip
Nitroglycerin available for CABG cases
Protamine

Antibiotics
-Cefazolin 1-3 gram based on weight for all cases unless there is allergy (60-120 Kg=2 gm, <60 kg=1 gm, and >120 kg=3gm) and repeat every 4 hours
-Vancomycin 1-2 gram infused over 1 hour for all cardiac cases based on weight (<70 kg= 1gm, 70-90 kg=1.25 gm, 90-110kg= 1.5 gm, 110-120 kg=1.75 gm and >120 kg= 2gm) and repeat every 12 hours
-Levofloxacin 750 milligrams (when Cefazolin can not be used) and repeat every 8 hours
-Gentamicin 2mg/kg for cases allergic to both Cefazolin and Levofloxacin

Intraoperative considerations

Before going on CPB:

-Order of events: Monitors (ECG, PSO2, BIS), Catheters (IV, A line, Neck line), induction and Intubation, OGT and Probes (Temp probe, TEE probe), Sternotomy, Pericardiotomy, Heparin administration, Cannulation (Aorta, Venous, retrograde, Vent)
-Some of us will prefer to put central line and PA catheter before induction and some will do after induction. Some of us also use US for neck line. Check with your attending. Induction is important part of anesthesia, the goal is to keep patient where they live! Try to minimize IV fluid especially if patient has low cardiac output.

-Consider external defibrillator ("R2") pad placement for re-do cases! We perform baseline ABG and ACT and TEG after induction (before Amicar bolus). Make sure blood is in the room before start of surgery.

- Surgeon available before induction!

-After prep and drape, surgeons will pass you the cord for the internal defibrillator paddles that you will connect to the defibrillator (turn on, make sure it "syncs" – if needed, defibrillate at 10 J (5-20 J)). You also will receive pacing wires. Make sure that there is an A/V pacemaker in the room for post bypass.

-For Sternotomy: give extra fentanyl if needed and hold the breath

Some patient may have resistance to Heparin. If the ACT does not increase appropriately, normally another 1 mg/kg of heparin is given. If the ACT is still low, either recombinant Antithrombin III is given or FFP which contains Antithrombin.
For Cannulation, BP should be approximately 100 systolic to prevent aortic dissection.

On CPB:

-Order of events: Pump, Cross clamp, cardioplegia, fibrillation, cardiac arrest.

-Systemic anticoagulation is required prior to insertion of cannulas and initiation of CPB. ACT should be over 450 before cunnulating and going on bypass.

-Once on full flow on CPB, stop ventilation and vaporizer and turn down O2 to few hundred cc. Check with perfusionist to make sure they are giving Isoflurane on CPB machine.

-Turn off vasopressors and peripheral IV fluids. Keep Amicar and KVO saline for central line running. If you are running anything through paceport, switch it to introducer.

-We usually pull PA line back a few centimeters to prevent permanent wedging or possible pulmonary artery rupture as the catheter can migrate during bypass. (Check with your attending)

-Perfusionist will usually check an ABG and an ACT few minutes after start of CPB. Check the results!

-Check BIS, CVP, U/O, SvO2 and Blood sugar on CPB. Also it is important to check for electrical activity on CPB and inform the surgeon.
Check SvO2. Normal venous oxygen saturation is approximately 75% meaning that the body extracts approximately 25% of the oxygen that is delivered to it. General anesthesia, muscle relaxants, and hypothermia will decrease the extraction; this explains why we commonly see SvO2 of 90% or perhaps more on bypass. Hyperthermia and inadequate oxygen delivery or inadequate anesthesia may force the body to extract more oxygen and a lower SvO2 results.

-Note times: on/off for bypass & aortic cross-clamp.

-Prepare all necessary drips for coming off while on CPB.

Coming off CPB:

Coming off bypass is one of the most demanding parts of cardiac surgery.

-Order of events: Warming, De-airing maneuvers (head down before remove of x-clamp and tilt to right and left), Hemodynamic stability (-Heart rate: defibrillation and pacing; -Contractility: calcium, -Preload: Volume; -Afterload: Levophed), Respiration, Monitors switched on, Protamine and Decannulation.

-Do Not administer PROTAMINE until the entire team feels it is safe to administer. Inadvertent administration of protamine while a patient is on bypass may be the biggest iatrogenic disaster that could occur in cardiac anesthesia.

We check ACT after giving protamine. Excessive doses of protamine may actually lead to more bleeding. Protamine can cause hypotension from a release of histamine but can also cause catastrophic anaphylaxis and malignant pulmonary HTN and acute RV failure and need for emergent return to bypass. Watch the administration and slow it down or stop if blood pressure drops. Although it can be administered into the central line, peripheral administration may result in less hypotension.

-For long procedures and redo cases consider need for blood products and contact blood bank while still on bypass and have blood products in room before end of CPB. Your attending will help you to decide what to order.
We usually avoid ordering **platelets** way in advance, they tend to clamp together and remember **do not put them in the cooler**!

-If Aline tracing is dampened when coming off bypass, usually cardiac surgeon will hand you a pressure tubing to be connected to arterial transducer and check pressure directly from aortic cannula. If dampening problem does not solve before decannulation femoral A-line will be placed by surgical team.

-For cases that you expect difficulty weaning CPB (low EF, RV failure, long procedure…) prepare vasopressor and inotropic agent of choice by consulting your attending before coming off!

_Use TEG to guide you for treating bleeding problem

Transport to ICU and Sign-out

After chest closure, you should start getting ready for transport. We have friendly anesthesia technicians who help with switching monitors to transport monitor and transferring patient. After separating your IV from fluid warmer try to keep fluid warmer part clean (in case of a disaster!). Have a transport bucket with emergency drugs and a laryngoscope and an extra endotracheal tube and face mask. Remove TEE probe and place an OG tube. Make sure TEE probe wheels are neutral and unlocked before removing to prevent esophageal injury! Detach BIS and cerebral oximetry monitor. Detach CVP cable and CO bag.

Make sure O2 tank is full and have a peep valve if needed. Log out of Pyxis and turn off vapor before leaving the room.
Make sure to check all drips and have enough amounts for transport. Have some 5% albumin for transport in case you need to give volume. Occasionally you may need to carry some blood products with you during transport if it was a prolonged case with significant bleeding!
After arrival to 3-lakeside ICU, let nurses to settle down and then give them a full report following the format of cardiac anesthesia sign out sheet that we use in our department. Document vital signs including CVP, PA pressure and CO/CI in your anesthesia report. Also document pacing mode and amount of blood in chest tubes!

You have successfully finished your case!

Pacemaker and defibrillators: UMASS Policy

PURPOSE: Patients with implanted pacemakers or defibrillators are at increased risk during surgical procedures. Pacemakers and defibrillators may be damaged by the current generated by electrocautery, and the wires leading from the devices to the heart may be dislodged by patient movement. Defibrillators may apply inappropriate tachyarrhythmia therapy in response to the use of electrocautery.

POLICIES:

- Patients with an implanted pacemaker ***or*** defibrillator undergoing elective surgery should have sensing functions disabled preoperatively via interrogation and reprogramming of the device. Once the sensing function is disabled, the patients should remain in a monitored location.
- Patients with an implanted defibrillator undergoing urgent surgery where there is insufficient time to interrogate the device preoperatively may not have unipolar electrocautery used during their surgical procedures. In such cases, no electrocautery or bipolar cautery should be used.
- Patients with an implanted pacemaker undergoing urgent surgery where there is insufficient time to interrogate the device preoperatively should have a magnet placed on it during surgery. Caregivers need to understand that this maneuver may not disable sensing, especially in rate-sensitive devices.
- Patients with an implanted pacemaker ***or*** defibrillator undergoing any surgical procedure should have the device interrogated postoperatively to confirm its proper functioning postoperatively. Until such interrogation occurs, the patients should remain in a monitored location.
- If a patient with an implanted pacemaker ***or*** defibrillator is to undergo a surgical procedure that requires the use of

monopolar electrocautery, the return electrode should be positioned ***between*** the surgical site and the pacemaker or defibrillator. If such positioning cannot be achieved, then bipolar electrocautery should be used.

Current UMASS policy for HIT patients:
USE OF BIVALIRUDIN IN PERSONS WITH HIT

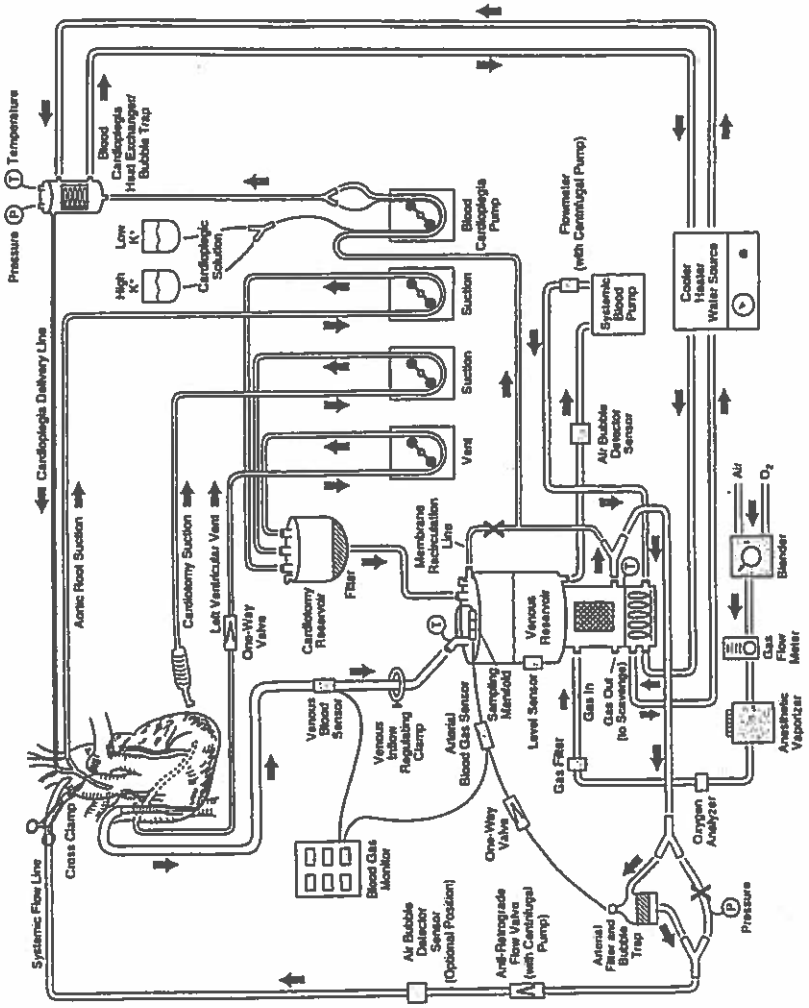
The P&T Committee and the Anticoagulation Task Force have approved the use of bivalirudin as a substitute for heparin for intraoperative anticoagulation in patients with a history of HIT having peripheral vascular surgery. (There is also an ongoing effort to improve the accuracy of the diagnosis of HIT).

Bivalirudin has the shortest duration of any heparin substitute as long as the patient has enough renal function not to require dialysis. In a dialysis-dependent patient, argatroban has a shorter duration than bivalirudin.

The dose listed in the package insert is designed to achieve an ACT value of 3-4 times control. While appropriate for cardiopulmonary bypass or intracoronary stent placement, this dose is too high for peripheral vascular surgery. I suggest the following recipe for a patient with a history of HIT who will have a peripheral vascular procedure requiring intraoperative anticoagulation:

- Bivalirudin is supplied as a 250 mg vial. Dissolve the contents in 5 mL sterile water.
- Dilute to 50 mL with D5 or NS to yield a 5 mg/mL solution and draw up in a 60-mL syringe.
- Use an Alaris pump for administration using the "drug calc" function.
- Draw a baseline ACT.
- Give a loading dose of 0.4 mg/kg over 1 min.
- Begin an infusion of 1 mg/kg/hr.
- Five minutes after the loading dose, draw an ACT.
- If the ACT is twice control, inform the surgeons that they may proceed to clamp the artery.
- If the ACT is less than twice control, administer a bolus dose of 0.2 mg/kg over 30 sec and repeat the ACT in 5 min.
- Check the ACT every hour during the infusion. The goal is to maintain the ACT approximately 2 - 2.5 times control.

Schematic



Schematic diagram of CPB

Familiarize yourself with basic TEE images:

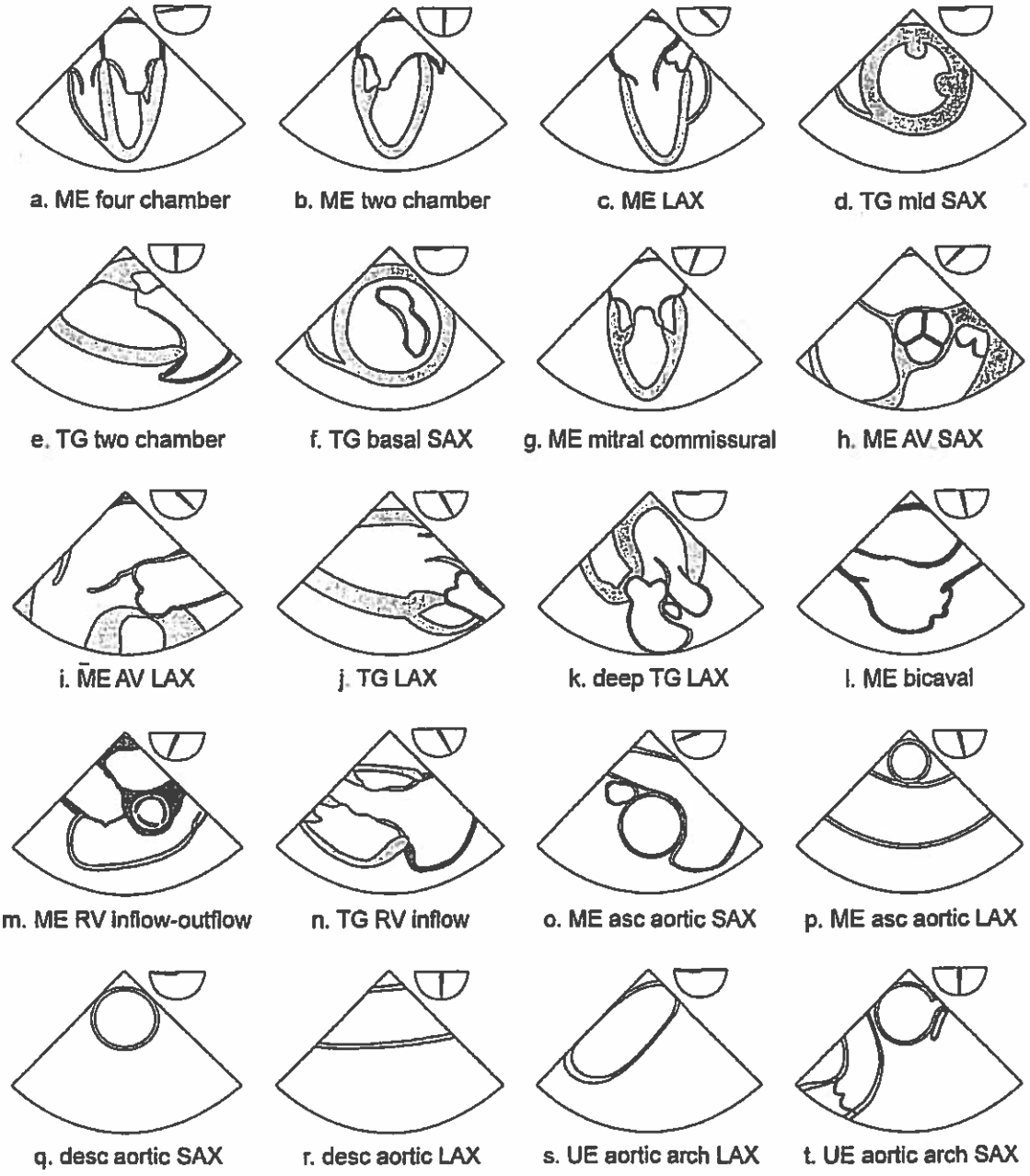


Figure adopted from ASE/SCA Guidelines for Performing a Comprehensive Intraoperative Multiplane Transesophageal Echocardiography Examination
-20 cross-sectional views composing the recommended comprehensive transesophageal echocardiographic examination. Approximate multiplane angle is indicated by the icon adjacent to each view. *ME,* Mid esophageal; *LAX,* long axis; *TG,* transgastric; *SAX,* short axis; *AV*, aortic valve; *RV,* right ventricle; *asc,* ascending; *desc,* descending; *UE,* upper esophageal.

Please read attached articles; they were seemed most important and useful articles to read! They have been selected by group of attending in this service. Best of luck with this rotation!

Preoperative Evaluation and Preparation of the Patient for Cardiac Surgery

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KEYWORDS
• Cardiac surgery • Preoperative evaluation • Risk stratification • Atrial fibrillation • Renal dysfunction • Stroke • Statins • β-Blockers

Coronary artery bypass graft (CABG) and valve surgery are among the most common operations performed worldwide. The incidence of cardiac complications after CABG is at least 10% and costs $2 billion annually.[1] These figures are anticipated to increase as older patients with more comorbidities are referred for cardiac surgery. Objective risk stratification provides the physician and patient with valuable information for assessing the risk/benefit ratio before proceeding with cardiac surgery. Careful patient selection and preparation during preoperative evaluation may minimize morbidity and mortality.

MORTALITY RISK STRATIFICATION

The mortality rate associated with cardiac surgery varies widely and is influenced by multiple preoperative risk factors. Jones and colleagues[2] defined 7 "core" variables that were unequivocally associated with operative mortality, and 13 "level 1" variables

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that were likely to be related to mortality (Table 1). The core variables contained 45% to 83% of the predictive information, whereas the level 1 variables had only modest predictive power.[2] Risk scoring systems that incorporate the influence of multiple risk factors have been developed to estimate perioperative mortality. Although the American College of Cardiology (ACC) and the American Heart Association (AHA) believe that the use of statistical risk models to obtain objective estimates of CABG operative mortality is reasonable,[3] their use must be complementary to clinical judgment, as their performance is limited by their application to different procedures and populations than their original design and validation.

SYSTEM-BASED PREOPERATIVE EVALUATION

If the mortality risk associated with cardiac surgery is not prohibitive, the next phase of preoperative evaluation estimates the risk of other complications and identifies conditions that will delay surgery or need to be addressed before or concomitant with operative intervention. A thorough system-based approach is the preferred strategy for preoperative evaluation.

Cardiovascular

Preoperative evaluation should include a careful physical examination with particular attention to the cardiac and vascular systems. Severe aortic regurgitation (AR) and peripheral vascular disease (PVD) involving the access site femoral or iliac vessels or aneurysmal disease of the aorta are contraindications to perioperative intraaortic balloon pump (IABP) placement. Furthermore, in patients with AR, the regurgitant

Table 1
Predictors of post-CABG mortality

"Core" Variables	"Level 1" Variables
Age	Height
Sex	Weight
Urgency of operation	PCI during current admission
Prior heart surgery	Date of most recent MI
LVEF	History of angina
Percent stenosis of LM coronary artery	Ventricular arrhythmia
Number of major coronary arteries with >70% stenosis	CHF
—	Mitral regurgitation
—	DM
—	CVD
—	PVD
—	COPD
—	Creatinine level

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; Core, variables unequivocally related to operative mortality; CVD, cerebrovascular disease; DM, diabetes mellitus; Level 1, variables with a likely relation to short-term mortality; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Data from Jones RH, Hannan EL, Hammermeister KE, et al. Identification of preoperative variables needed for risk adjustment of short-term mortality after coronary artery bypass graft surgery. The Working Group Panel on the Cooperative CABG Database Project. J Am Coll Cardiol 1996;28:1480.

volume may increase during cardiopulmonary bypass (CPB) resulting in acute left ventricular (LV) distension. Varicose veins or a history of vein stripping or ligation in the lower extremities may preclude use of saphenous vein grafts as bypass conduits and prompt evaluation for alternative conduits. A carotid bruit or significant PVD may signify the presence of cerebrovascular disease (CVD) and requires further evaluation by carotid Doppler to assess the need and timing for carotid revascularization.[4]

Atrial fibrillation

The incidence of atrial fibrillation (AF) after CABG, valve surgery, and combined CABG and valve surgery is approximately 30%, 40%, and 50%, respectively.[5] Postoperative AF is associated with increased in-hospital and long-term mortality, renal failure (RF), stroke, congestive heart failure (CHF), hospital length of stay (HLOS), intensive care unit (ICU) readmission, and cost of hospitalization.[6,7] Age is one of the most reliable preoperative predictors of postoperative AF with a reported 75% increase in the odds of developing AF for every 10-year increase in age.[6] Other established predictors for the development of postoperative AF include history of AF, male gender, decreased LV ejection fraction (LVEF), left atrial enlargement, valvular heart surgery, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), chronic renal failure (RF), rheumatic heart disease, LV hypertrophy, and withdrawal from β-blocker and angiotensin 1 converting enzyme inhibitor (ACEI) therapy.[6,8] Preoperative β-blocker, sotalol, and amiodarone therapy may be used to lower the incidence of postoperative AF. Although digoxin and calcium channel antagonists may be useful for ventricular rate control, they have not been demonstrated to reduce the postoperative incidence of AF.[3,9]

Left ventricular dysfunction

Surgical revascularization in patients with advanced myocardial dysfunction and coronary artery disease (CAD) is superior to medical therapy.[10] LV dysfunction and CHF are associated with higher mortality during CABG.[11] Topkara and colleagues[11] analyzed more than 55,000 patients undergoing CABG from the New York State (NYS) database and found that patients with advanced LV dysfunction had more comorbid conditions, including previous myocardial infarction (MI), RF, and CHF. Patients with LVEF less than 20% undergoing CABG had nearly four times the in-hospital mortality rate, lower rate of discharge to home, and higher incidence of postoperative respiratory failure, RF, and sepsis than patients with an LVEF greater than 40%. Independent predictors of in-hospital mortality in the low LVEF group were hepatic failure, RF, previous MI, reoperation, emergent procedures, female gender, CHF, and age. In high-risk patients, preoperative placement of an IABP reduces the use of inotropic and vasopressor medications, CPB time, in-hospital mortality, and shortens ICU stay.[12]

Although LV dysfunction is often due to MI with associated necrosis and scar formation, it may also be due to hibernating or stunned myocardium, potentially reversible processes with revascularization.[13] A perioperative reduction in the contractile efficiency of previously functioning myocardial segments may be seen in the immediate postoperative period. Preoperative cardiac evaluation in patients with severely reduced LV function should focus on identifying patients with dysfunctional but viable myocardium by either [^{99m}Tc]MIBI, ^{201}Tl, [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET), dobutamine echocardiography, dobutamine magnetic resonance imaging (MRI), or delayed-enhancement cardiac MRI. The sensitivity of these various imaging modalities ranges from 80% to 90% with specificity of 54% to 92%.[14,15] In a patient with marginal preoperative hemodynamic function who can

expect little or no improvement in the immediate postoperative period, the likelihood of complication or death is high and possibly prohibitive for cardiac surgery.

Recent myocardial infarction

The timing and location of a recent MI should be included in the preoperative evaluation. Mortality associated with CABG is increased for the first 3 to 7 days following MI, and if clinically appropriate, a delay in surgery beyond this time period should be considered.[3,16] Following anterior MI, the detection of an LV thrombus by preoperative transthoracic echocardiogram may alter the timing and approach of CABG.[3] Inferior MI that significantly impairs right ventricular (RV) function is associated with hemodynamic consequences that can be exacerbated during CPB, and it is reasonable to delay CABG for 4 weeks to allow RV recovery.[3]

Hematologic

Preoperative anemia is associated with increased morbidity and mortality during cardiac surgery.[17] Kulier and colleagues[17] found that preoperative anemia was an independent predictor of noncardiac complications. In patients with preoperative anemia and a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 4 or more, there were increased cardiac complications but these were likely attributable to other concomitant risk factors. Independent predictors of preoperative anemia are a history of anemia, RF, female gender, advanced age, DM, unstable angina, and history of CABG. As blood transfusions in patients undergoing cardiac surgery have been associated with increased morbidity and mortality,[18] perioperative transfusion strategies that incorporate the degree of anemia and other comorbidities need to be developed for individual patients.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication of heparin therapy associated with arterial and venous thrombosis. There is typically a 50% or greater decrease in platelet count from baseline in association with thrombotic events.[19] In most cases, immunoassays can detect antibodies against complexes of platelet factor 4 (PF4) and heparin. Everett and colleagues[20] found that in patients undergoing cardiac surgery, the preoperative and postoperative incidence of antibodies to PF4/heparin was 4.3% and 22.4%, respectively, but thrombotic events occurred only in 6.3% of patients with a positive antibody. Diagnostic specificity for HIT can be increased by use of platelet activation assays such as the serotonin release assay.[19] Post-CABG, patients with HIT have a higher incidence of saphenous vein graft occlusion than patients without HIT, but no significant difference in left internal mammary artery graft occlusion.[21]

Management of patients undergoing cardiac surgery with antibodies to PF4/heparin and HIT is evolving. During CPB, unfractionated heparin (UFH) is the preferred agent due to familiarity with its use, reversibility with protamine, and ease of intraoperative monitoring. In this syndrome, a typical anamnestic immune response is often not formed, and rechallenge with heparin is a reasonable strategy for patients with HIT who need to undergo CPB.[19] Warkentin and colleagues[19] outline management guidelines for HIT patients undergoing cardiac surgery. An immunoassay for PF4/heparin antibodies should be performed and if positive, a platelet activation assay should be completed (if available). Patients who are PF4/heparin antibody negative or antibody positive by immunoassay, but antibody negative by platelet activation assay, may proceed with cardiac surgery using UFH during CPB. Preoperative and postoperative anticoagulation should be performed with a nonheparin anticoagulant.

In patients with a history of HIT whose platelet counts have recovered but are heparin/PF4 antibody positive, surgery should be delayed if possible until a platelet activation assay is negative, and then surgery can be performed using UFH during CPB. If delaying surgery is not an option, use of a nonheparin anticoagulant is recommended over UFH during CPB. In patients with HIT who remain thrombocytopenic and are heparin/PF4 antibody positive, the preferred strategy is to delay surgery until the platelets have normalized and the heparin/PF4 antibodies are negative or weakly positive. However, if delaying surgery is not feasible, alternative anticoagulation regimes during CPB should be considered.

Hypercoagulable disorders

Balancing the risk of thrombosis with excessive perioperative bleeding is difficult in patients with a hypercoagulable disorder. In hospitalized patients with a hypercoagulable disorder who are not on chronic anticoagulation, preoperative administration of subcutaneous UFH and low molecular weight heparin (LMWH) are important to lower the risk of developing a deep venous thrombosis while mobility is limited.[22] For chronically anticoagulated patients, warfarin therapy should be held at least 5 days before cardiac surgery,[23] and therapeutic anticoagulation may be bridged with UFH or LMWH. In patients with antiphospholipid antibody syndrome, perioperative anticoagulation monitoring can be difficult due to abnormal prolongation in clotting times and consultation with a hematologist and clinical pathologist is often required to design the best management strategy.[4,24]

Renal

Preoperative renal dysfunction is common in patients undergoing cardiac surgery and is an important risk factor for increased morbidity and mortality.[25–27] Cooper and colleagues[25] found that in patients undergoing CABG, the preoperative incidence of mild, moderate, and severe renal dysfunction and dialysis dependence was 51%, 24%, 2%, and 1.5%, respectively, and operative mortality increased with declining renal function. Preoperative estimated creatinine clearance is a better predictor of postoperative adverse events than plasma creatinine level.[27] Although renal dysfunction after cardiac surgery is an independent risk factor for mortality, improved preoperative renal function reduces this effect on mortality.[26]

In a large multicenter study of patients undergoing cardiac surgery, Mangano and colleagues found that the incidence of postoperative renal dysfunction not requiring dialysis was 7.7% and requiring dialysis, 1.4%. Mortality in patients without renal dysfunction was 0.9% but increased to 19% in patients with renal dysfunction and 63% in patients requiring dialysis. Postoperative RF is associated with increased ICU and HLOS, higher mortality, and greater likelihood for discharge to an extended care facility. Although multiple factors are associated with increased risk of postoperative renal dysfunction following cardiac surgery, advanced age, CHF, prior CABG, DM, and preexisting renal disease are factors that identify a high-risk population for renal dysfunction after CABG.[28] Cardiac catheterization performed on the day of cardiac surgery and higher doses of contrast medium are independently associated with higher risk for postoperative RF.[29] Preoperative serum creatinine, age, race, type of surgery, DM, shock, NYHA class, lung disease, recent MI, and prior cardiovascular surgery are associated with increased risk for postoperative dialysis and have been incorporated into a bedside risk algorithm for estimating a patient's probability for dialysis after cardiac surgery.[30]

Perioperative management in patients at high risk for RF and dialysis focuses on minimizing exposure to nephrotoxic drugs and contrast media and maintaining renal

perfusion. If possible, cardiac surgery immediately after cardiac catheterization should be avoided. Although *N*-acetylcysteine has been shown to attenuate contrast-induced declines in renal function, there is no convincing evidence that perioperative administration of *N*-acetylcysteine is protective in cardiac surgery.[31] Future studies will help clarify whether off-pump CABG, which eliminates the need for CPB, is associated with lower risk for postoperative renal dysfunction.

Endocrine

DM is present in approximately 25% of patients presenting for CABG or percutaneous coronary intervention and is associated with worse outcomes after cardiac surgery.[2,3,28,32] Patients with DM without RF or PVD who undergo CABG have similar long-term survival to patients without DM.[33] Preoperative screening for DM is an important aspect of preparing a patient for cardiac surgery. Lauruschkat and colleagues[34] found the incidence of undiagnosed DM in patients undergoing CABG to be 5.2%, and noted that these patients had higher perioperative mortality, required reintubation more frequently, and remained intubated longer than patients without DM and with known DM.

In patients undergoing cardiac surgery, strict perioperative glucose control using perioperative insulin infusions can significantly lower operative mortality and the incidence of mediastinitis.[35,36] There is growing evidence that insulin exerts antiinflammatory effects, beyond its metabolic activities, which may partially explain its cardioprotective properties.[37] Future studies will clarify the role of preoperative glucose control and the optimal perioperative management scheme.

Pulmonary

COPD is the most common cause of preoperative pulmonary dysfunction. Cohen and colleagues[38] noted that patients with clinically significant COPD undergoing CABG had higher rates of pre- and postoperative atrial and ventricular arrhythmias, reintubation, and longer ICU stay and HLOS than matched controls. Although Fuster and colleagues[39] showed that a preoperative FEV1 of 60% of predicted or higher is associated with increased mortality during CABG, Spivack and colleagues[40] did not find a clear role for pulmonary function testing in preoperative evaluation for cardiac surgery. Home oxygen therapy or hypercapnia are clinical parameters that identify a population at higher risk for postoperative respiratory failure.[3,38] Clinical assessment of lung function and severity of COPD is a critical component of preoperative assessment.

The incidence of respiratory failure in patients undergoing cardiac surgery varies widely depending on the definition. Filsoufi and colleagues[41] defined respiratory failure as intubation time of 72 hours or longer and found that the incidence of respiratory failure in the NYS database was 9.1%, with the highest incidence in combined CABG and valve procedures (14.8%). Independent predictors of postoperative respiratory failure were age more than 70 years, female gender, LVEF 30% or less, combined CABG/valve surgery, CHF, DM, PVD, COPD, RF, active endocarditis, reoperation, hemodynamic instability, and IABP insertion. Postoperative respiratory failure was associated with significantly increased morbidity, mortality, and HLOS. To optimize respiratory function before surgery, existing pulmonary conditions or exacerbations should be treated, including smoking cessation, antibiotic therapy for existing pneumonia or bronchitis, diuresis for pulmonary edema, and bronchodilator and steroid treatment of COPD exacerbation.[3] In high-risk patients undergoing CABG, inspiratory muscle training is associated with a reduction in postoperative pulmonary complications.[42]

Neurologic

The incidence of neurologic complications following cardiac surgery, including global encephalopathy, focal neurologic syndromes, and decline in intellectual function and memory, ranges widely from 1% to 80%.[43,44] These complications have largely been attributed to the adverse effects of CPB, which can lead to embolism, hemorrhage, hypoxia, cerebral edema, and metabolic derangements. Advanced age, prior neurologic disease, type of surgery, aortic atheroma, and duration of CPB are predictors of neurologic complications following cardiac surgery.[43,45,46] Stroke is a devastating complication of cardiac surgery with a reported incidence ranging from 0.8% to 7%.[46] Prediction models can be used to estimate the perioperative risk of stroke.[32]

In patients undergoing CABG, the incidence of coexisting carotid artery disease more than 50% is 17% to 22% and more than 80% disease, 6% to 12%.[47,48] Approximately 30% of postoperative strokes are due to significant carotid artery stenosis.[49] Stroke risk increases with the severity of stenosis, and the stroke risk in patients with carotid stenoses of less than 50%, 50% to 80%, and more than 80% is approximately 2%, 10%, and 11% to 18.8%, respectively.[3,50,51] Even in the asymptomatic patient, carotid stenosis of 75% is an independent predictor of stroke risk after CABG.[52] ACC/AHA guidelines state that selective carotid screening should be considered in the following high-risk patient groups: older than 65 years, left main coronary artery stenosis, carotid bruit on examination, PVD, history of smoking, and history of transient ischemic attack or stroke.[3]

The goal of carotid revascularization before CABG is the prevention of cerebrovascular events. Carotid endarterectomy (CEA) and CABG can be performed as either a staged or combined procedure, and the combined incidence of stroke, MI, and death for either procedure is 10% to 12%.[53] In 1 review of 97 studies, there was a trend toward higher mortality, stroke, and MI in patients undergoing combined CEA-CABG relative to staged CEA-CABG.[53] According to the ACC/AHA guidelines, CEA should be considered before CABG or concomitant with CABG in patients with a symptomatic carotid stenosis or in asymptomatic patients with unilateral or bilateral internal carotid stenosis of 80% or more.[3] Carotid artery stenting (CAS) is a less invasive alternative than CEA for carotid revascularization. In a recent review by Guzman and colleagues[54] of 6 studies including 277 patients undergoing staged CAS and CABG, only 2.2% of patients suffered a stroke following CABG. However, the overall 30-day event rate after CABG (including events during CAS) for minor stroke, major stroke, death, and death or any stroke was 2.9%, 3.6%, 7.6%, and 12.3%, respectively. Although it is accepted that cerebral revascularization should take place before coronary revascularization unless it is a true emergency, future studies are necessary to clarify which carotid revascularization strategy is superior.

Nutrition

Preoperative assessment of nutritional status and body mass index (BMI) can identify patients at higher risk for cardiac surgery. Low BMI (<20 kg/m^2) and hypoalbuminemia (<2.5 g/dL) are predictors of increased mortality, postoperative RF, HLOS, and prolonged ventilatory support following CABG.[55,56] In malnourished patients undergoing elective cardiac surgery, nutritional status should be optimized before operation, if possible.

Obese patients undergoing cardiac surgery have increased incidence of infection of the sternal wound and saphenous vein graft harvest site, RF, prolonged ventilation, and HLOS.[56,57] Obesity and obstructive sleep apnea are independent risk factors for developing AF.[58] Obesity and the metabolic syndrome are associated with a higher

risk of developing AF after CABG in patients older than 50 years and 50 years and under, respectively.[59] If clinically appropriate, cardiac surgery may be delayed while efforts at weight loss are attempted.

MEDICATIONS

After risk stratification is completed, the final phase of preoperative evaluation focuses on patient preparation to minimize complications. Perioperative medical therapy improves outcomes in patients undergoing noncardiac and cardiac surgery.[9,60–73] However, despite the potential benefit, these medications are likely underutilized in clinical practice. In patients undergoing CABG, Filion and colleagues[74] noted preoperative aspirin, β-blocker, ACEI, and statin use was 41.4%, 52.4%, 33.4%, and 30%, respectively. On the day of surgery, aspirin use remained stable at 43%, but β-blocker, ACEI, and statin use declined to 42.9%, 8.9%, and 8.9%, respectively. Cardiac surgical patients are also frequently exposed to a variety of antiplatelet agents and anticoagulants, which can potentiate surgical bleeding. Current medical therapy should be reviewed for all patients, keeping in mind which medications should be initiated, continued, and stopped before surgery.

Antiplatelet Therapy

Aspirin, plavix, and glycoprotein (GP) IIB/IIIA inhibitors are beneficial in the management of acute coronary syndrome and during percutaneous coronary intervention (PCI).[75] Early (<6 hours) postoperative administration of aspirin is associated with a reduced risk of saphenous vein graft thrombosis, mortality, MI, stroke, RF, and bowel infarction.[64,68] Preoperative use of aspirin is associated with an increased risk for postoperative bleeding and need for transfusion.[76] Concomitant use of other antiplatelet agents and anticoagulants and certain disease states (eg, aspirin hyperresponders, thrombocytopenia, and renal disease) may potentiate the bleeding risk of aspirin. The preoperative use of clopidogrel in the presence or absence of aspirin in patients undergoing CABG is associated with increased postoperative bleeding, transfusions, and reoperations.[77] In urgent or emergent CABG, aspirin administration should be continued or initiated in the preoperative period as the benefits outweigh the risk of bleeding. In elective CABG, the Society of Thoracic Surgeons (STS) and ACC/AHA recommend that it is reasonable to consider withholding aspirin before surgery for 3 to 5 days or 7 to 10 days, respectively. Aspirin should be resumed within 6 hours of a surgical revascularization procedure if there are no contraindications.[3,78] Clopidogrel should be stopped 5 to 7 days before CABG.[3,75,78]

Eptifibatide and tirofiban are short-acting GP IIB/IIIA inhibitors, and should be discontinued 4 to 6 hours before cardiac surgery. Abciximab is a longer-acting agent, and should be discontinued 12 to 24 hours before surgery.[75,78] After administration, there is little free abciximab circulating in the plasma but large quantities of eptifibatide and tirofiban. Platelet transfusion is an effective strategy to increase the circulating platelet population with available GP IIB/IIIA inhibitors for abciximab but not for eptifibatide and tirofiban.

Anticoagulant Therapy

UFH, LMWH, fondaparinux, and direct thrombin inhibitors are beneficial in the management of acute coronary syndromes and during PCI, and are used for prophylactic and therapeutic anticoagulation.[75] UFH has not been shown to increase postoperative blood loss after cardiac surgery when discontinued shortly before operation. Preoperative LMWH and fondaparinux administration are associated with increased

bleeding, and based on expert opinion, LMWH and fondaparinux should be discontinued 24 hours before surgery and replaced with UFH (if anticoagulation is indicated).[75,78] There are limited data regarding the safety of preoperative administration of direct thrombin inhibitors before CABG. Bivalirudin, a short-acting direct thrombin inhibitor, should be discontinued 3 hours before surgery. Hirudin and argatroban, longer-acting agents, should be stopped earlier than bivalirudin and replaced with UFH before cardiac surgery.[75,78] Warfarin should be stopped at least 5 days before cardiac surgery to allow normalization of the INR.[23] If continued therapeutic anticoagulation is necessary, UFH or LMWH may be initiated preoperatively.

β-Blocker Therapy

β-Blocker therapy improves acute and long-term outcomes for patients with ischemic heart disease.[75,79] In addition, in high-risk patients undergoing major noncardiac and vascular therapy, β-blocker therapy reduces the rate of cardiovascular events.[60,62] There has been cautious extension of their application to cardiac surgical patients due to concerns regarding their negative inotropic effects and possible exacerbation of underlying reactive airway disease. Nearly 40% of patients undergoing CABG do not receive preoperative β-blocker therapy, and patients with higher-risk features (eg, DM, CHF, underlying lung disease, and older age) are less likely to be treated with β-blocker therapy. Preoperative β-blocker therapy is associated with a statistically significant lower rate of 30-day mortality. Although a similar effect is seen in women, the elderly, and patients with chronic lung disease, DM, or moderately depressed LV function during subgroup analysis, a trend toward higher mortality is present in patients with a LVEF less than 30%.[65]

β-Blocker therapy has also been shown to reduce the incidence of postoperative AF when administered pre-[66] and postoperatively.[9] Perioperative interruption of long-term β-blocker therapy increases susceptibility to postoperative arrhythmias.[6] In addition to lowering the incidence of AF, β-blocker therapy is associated with reduced risk of postoperative neurologic complications.[67] The ACC/AHA recommends the use of preoperative or early postoperative β-blocker therapy in patients undergoing cardiac surgery without contraindications to its use.[3]

Sotalol has β-blocker and class III antiarrhythmic drug effects. Sotalol has been found to be more effective in reducing the incidence of postoperative AF than β-blocker therapy[69] but its use is associated with more postoperative bradyarrhythmias and hypotension.[80] The ACC/AHA recommends that low-dose sotalol can be considered in patients who are not candidates for traditional β-blocker therapy to lower the incidence of postoperative AF.[3]

ACEI or Angiotensin-II Receptor Blocker Therapy

ACEI or angiotensin-II receptor blocker (ARB) therapy reduces the risk of developing AF, particularly in patients with systolic dysfunction or LV hypertrophy.[81] In patients undergoing CABG, postoperative withdrawal of ACEI therapy is associated with an increased incidence of new onset and recurrent AF, and perioperative treatment with ACEI is associated with a reduced risk of AF.[6] In an underpowered study of cardiac surgical patients, preoperative ACEI or ARB therapy was associated with a nearly 30% lower risk of developing AF, but this reduction was not statistically significant.[63] In addition, treatment with quinapril for 4 weeks preoperatively and 1 year postoperatively in patients undergoing CABG reduced clinical ischemic events.[70] The antiinflammatory properties of ACEI or ARB therapy likely contribute to these cardioprotective effects.[82] However, preoperative administration of ACEI or ARB therapy

may increase the perioperative requirement for vasopressor drug administration.[83] Although there are no specific guidelines, it is probably reasonable to continue preoperative ACEI or ARB therapy in patients with underlying hypertension given their potential benefits but consider withholding therapy in patients with marginal blood pressure.

Statins

Preoperative administration of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy in vascular and cardiac surgery is associated with 59% and 38% reductions in mortality, respectively.[61] Liakopoulos and colleagues[71] found that preoperative statin therapy in patients undergoing cardiac surgery was associated with a reduction in early all-cause mortality, AF, and stroke. Statin therapy may be protective through lipid-independent or pleiotropic effects including antiinflammatory, antithrombotic, and vasodilatory effects.[84,85] All patients undergoing cardiac surgery should receive statin therapy unless specifically contraindicated.[3]

Amiodarone

Preoperative administration of amiodarone is an effective, well-tolerated therapy for prevention of postoperative AF.[72] In the PAPABEAR trial, a 13-day perioperative course of oral amiodarone in patients undergoing cardiac surgery significantly reduced the overall incidence of atrial tachyarrhythmias regardless of concomitant preoperative β-blocker therapy and postoperative sustained ventricular tachyarrhythmias.[72] A single-day, preoperative loading dose of oral amiodarone did not reduce the incidence of postoperative AF in patients undergoing cardiac surgery.[86] Given that effective amiodarone prophylaxis requires a preoperative treatment period, loading protocols seem limited to elective cardiac surgery. Intravenous amiodarone given immediately after cardiac surgery is also effective in reducing the incidence of AF.[87] ACC/AHA guidelines recommend that preoperative administration of amiodarone should be considered for patients at high risk for developing AF with contraindications to β-blocker therapy.[3]

SUMMARY

Morbidity and mortality associated with cardiac surgery is significant to the patient and costly to the health care system. During preoperative evaluation, statistical risk models should be used to obtain objective estimates of operative mortality and morbidity. In patients with severe LV dysfunction, a cardiac imaging modality should be considered to help identify dysfunctional but viable myocardium. A recent MI, particularly if associated with LV thrombus formation or severe RV dysfunction, may prompt a delay in cardiac surgery. Patients at high risk for renal dysfunction need management strategies aimed at minimizing renal insults. Existing pulmonary conditions should be treated as best possible before initiation of mechanical ventilation. Carotid Doppler should be performed in patients at increased risk for coexistent carotid artery disease, and if significant carotid artery disease is present, CEA should be considered either before or concomitant with cardiac surgery. With regard to medical therapy, β-blocker, ACEI, and statin therapy should be used in the absence of contraindications, and amiodarone therapy instituted in patients at high risk for AF. Clopidogrel should be withheld 5 to 7 days before surgery, and the risk/benefit ratio of preoperative aspirin therapy assessed.

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The Intraaortic Balloon Pump in Cardiac Surgery

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The intraaortic balloon pump (IABP) has been used in cardiac operations since the late 1960s. Over the years, with refinements in technology, its use has expanded; the IABP is now the most commonly used mechanical assist device in cardiac operative procedures. This review provides an evaluation of evidence for the efficacy of IABP use in different clinical scenarios, using the American College of Cardiology/American Heart Association classification of evidence where appropriate. We evaluated complications and outcomes associated with IABP use, and attempted to draw conclusions regarding the use of the IABP in different clinical situations. We examined the trends and variation in utilization over time and across centers. We discussed the IABP in light of new cardiac assist devices and the changing patient population and management strategies. Lastly, we identified areas of future research.

(Ann Thorac Surg 2002;74:1276–87)

Results of cardiac operative procedures continue to improve despite ever-increasing numbers of older and sicker patients [1]. Of those who die, many do so of complications relating to low cardiac output during the perioperative period. The intraaortic balloon pump (IABP) has been widely used during the perioperative period to support patients with low cardiac output. The IABP was first used clinically in 1968 for supporting patients with cardiogenic shock after acute myocardial infarction [2]. Soon its use was expanded to postoperative support and as an aid in weaning patients from cardiopulmonary bypass [3, 4]. Use of the IABP has continued to increase, particularly over the past decade with the expansion of interventional cardiology, and the increasing age and acuity of cardiac surgical patients (Table 1) [5–8].

Previous reviews of IABP use have focused on physiology and practical issues of balloon use and timing [9, 10]. No thorough review of clinical outcomes associated with IABP use has been published despite more than 30 years of clinical use [6, 8]. Our objective was to review the use of the IABP in cardiac operations. In particular we focused on evidence for the indications, utilization, and efficacy relating to timing of IABP use. We also examined complications of the IABP, discussed current and future trends in use and suggest future directions for research.

Method of Review

A search of the MEDLINE database from 1966 to 2000 was undertaken using the keyword *intraaortic balloon pumping*, limited to human studies published in English. We excluded articles that were abstracts only, involved nonsurgical patients only, did not satisfactorily distinguish between surgical and nonsurgical patients, or included fewer than 30 patients. Additional references were obtained by direct communication with experts in the field. Manuscripts cited in the references retrieved were also reviewed. Studies' designs were documented as an indicator of the strength of evidence they represented. Where appropriate, evidence was classified and graded using the American College of Cardiology/American Heart Association guidelines [11]:

Class I: Conditions for which there is evidence for or general agreement that the procedure or treatment is useful and effective;
Class II: Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy;
Class IIb: Usefulness/efficacy is less well established by evidence/opinion;
Class III: Conditions for which there is evidence or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Levels of evidence were graded as follows: Level A = data derived from multiple randomized clinical trials; level B = data derived from single randomized trial or nonrandomized studies; and level C = case series or consensus opinion of experts.

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Table 1. Case Series of IABP Use and Outcomes

Reference	Years of Study	#IABPs	CABG/ All Cases	% Cases With IABP	Preop (% of cases, % survival)	Intraop (% of cases, % survival)	Postop (% of cases, % survival)	Overall Survival
Kantrowitz [14]	1967–1982	733[a]	NA	NA	NA, 83%	NA, 39%	NA, 48%	65%
Strum [49]	1972–1979	419	78%	NA	NA, NA	NA, NA	NA, NA	45%
Gunstensen [19]	1973–1975	147	74%	15%	11%, 83%	3%, 69%	0.9%, 44%	78%
Wantanabe [24]	1973–1976	123	NA	7.6%	2%, 74%	5%, 68%	0.6%, 50%	68%
Beckman [111]	1973–1976	228	NA	NA	NA, 77%	NA, 40%	NA, 30%	63%
Downing [13]	1973–1980	280[b]	27%	4.9%	0.3%, 60%	3.9%, 56%	0.8%, 51%	55%
Pennington [22]	1973–1982	316	61%	5.7%	1%, 58%	4.5%, 55%	1.3%, 44%	53%
Sanfelippo [110]	1973–1984	275	NA	5%	1.2%, 77%	3.8%, 44%		52%
Macoviak [27]	1974–1978	155	42%	6.5%	1.2%, 55%	4.3%, 35%	1%, 17%	36%
Golding [54]	1975–1978	197	100%	2.2%	0.7%, 82%	1%, 73%	0.4%, 57%	73%
Tobias [112]	1975–1978	32	31%	3.4%	0.1%, 100%	2.6%, 42%	0.7%, 57%	44%
McGee [44]	1975–1979	368	55%	2.6%	0.1%, NA	1.7%, NA	0.8%, NA	50%[c]
Kaplan [88]	1976–1977	63	NA	3.6%	1.2%, 81%	2.4%, 62%	0	68%
Makhoul [113]	1971–1985	431	78%	NA	NA, NA	NA, NA	NA, NA	71%[d]
Iverson [64]	1973–1986	395	NA	8%	2.4%, NA	4.5%, NA	1.2%, NA	53%
Corral [43]	1974–1985	313	70%	NA	NA, 75%	NA, 63%	NA, 41%	65%
Di Lello [87]	1974–1986	138	56%	2.3%	0	2%, 50%	0.3%, 40%	49%
Vigneswaran [26]	1976–1983	63	67%	1.5%	0.1%, 17%	1%, 33%	0.3%, 14%	27%
Lund [53]	1979–1986	90	18%	NA	NA, NA	NA, NA	NA, NA	37%
Torchiana [6]	1968–1995	3085[e]	NA	17%	11%, 86%	4%, 64%	1.5%, 64%	79%
Goldberger [25]	1980–1982	72	NA	NA	NA, 90%	NA, 54%	NA, 50%	63%
Arafa [16]	1980–1989	344	63%	5.9%	0.9%, NA	3.3%, NA	1.7%, NA	42%[f]
Naunheim [29]	1983–1990	580	NA	8.5%	1.6%, NA	6%, NA	0.8%, NA	56%
Christenson [50]	1984–1993	169	88%	4.7%	0.2%, NA	3%, NA	1.5%, NA	52%
Creswell [15]	1986–1991	672	53%	9.8%	3.5%, 80%	5%, 68%	1%, 59%	71%
Aksnes [42]	1988–1990	110	82%	8.8%	1.5%, NA	7.3%, NA		56%
Gol [60]	1988–1993	449	NA	6.5%	0.8%, NA	1.8%, NA	4%, NA	47%
Sirbu [58]	1988–1998	524	NA	5.2%	0.6%, NA	3%, NA	1.7%, NA	72%

All series include only cardiac surgical cases from each series unless otherwise specified. Survival to discharge cited unless otherwise specified.

[a] 238 clearly surgical patients, the rest are not specified. [b] 319 attempted IABP 280 actually received IABP. [c] Includes 42 nonsurgical cases. [d] Includes 5 nonsurgical cases. [e] surgical cases only. [f] Three-month survival.

CABG = coronary artery bypass grafting; IABP = intraaortic balloon pump; Intraop = intraoperative; NA = not available; Postop = postoperative; Preop = preoperative.

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Indications

The IABP exerts its effect by volume displacement. It has two principal effects; the first is to augment coronary blood flow, and thus myocardial oxygen supply, by increasing diastolic perfusion pressure. The blood displaced during balloon inflation reduces ventricular work by reducing afterload with rapid balloon deflation in systole, thus decreasing myocardial oxygen consumption [9]. This action enhances stroke volume and in conjunction with the favorable diastolic effects can increase cardiac output by 20% [10].

The currently accepted indications for IABP use have expanded to include [12]:

1. Ongoing unstable angina refractory to medical therapy
2. Acute myocardial ischemia/infarction associated with percutaneous transluminal angioplasty (PTCA)
3. Perioperative low cardiac output syndrome
4. Cardiogenic shock after myocardial infarction
5. Congestive heart failure
6. Bridge to heart transplant
7. Ischemic ventricular septal defect
8. Acute mitral valve insufficiency
9. Poorly controlled perioperative ventricular arrhythmias.

Although most surgeons accept many of these indications, the decision to use an IABP and the timing of its use are often not clear. No direct multicentered comparisons of use or outcomes with the IABP have been published, thus direct comparison is difficult due to the heterogeneity of patient populations and changes in practice patterns over time [13]. Intraaortic balloon pump use has shifted more toward ischemia rather than hemodynamic decompensation [6, 14, 15]. This change is likely the result of steady improvements in surgical and anesthetic techniques over this period, which have reduced the need for IABPs for early postoperative low cardiac output [8].

Evidence for Efficacy of Preoperative Intraaortic Balloon Pump Use

Case Series

A number of case series found that preoperative insertion of an IABP was associated with better outcomes than intra- or postoperative insertion [6, 15, 16]. In the mid-1970s, preoperative balloon pump use was found to be beneficial in high-risk surgical patients [17–20]. However its use remains highly variable and there is a lack of consensus for preoperative use, when the decision is most discretionary [13, 21–23].

Nearly all published studies have demonstrated that patients receiving IABPs preoperatively have better outcomes than those receiving IABPs intraoperatively or postoperatively (Table 1). This finding is a reflection of the fact that the IABPs are being inserted for different indications. Even in series reported in the 1970s and early 1980s, preoperative IABP use was associated with a 74% to 90% survival [24, 25]. The few series that reported poor survival with preoperative IABP use only rarely used the device preoperatively, and used it principally for shock [26, 27].

Observational Studies With Controls

We identified a total of six controlled observational studies of preoperative IABP use (Table 2). Feola and associates [28] reported in a small series of patients with low ejection fractions undergoing isolated coronary artery bypass grafting (CABG), that those receiving preoperative IABP support had significantly lower myocardial infarction rates and mortality compared with matched historical controls (Table 2). More recent reviews have also suggested the potential beneficial effects of preoperative IABP use, but have failed to consistently show a statistically significant difference in comparison with similar untreated patients [29, 30]. In a cohort of post-myocardial infarction patients undergoing CABG, Creswell and associates [30] demonstrated encouraging trends toward decreased mortality and morbidity in patients with preoperative IABP use operated on less than 14 days after acute myocardial infarction (Table 2). A cohort study by Dietl and associates [7] suggested a survival benefit with preoperative use of the IABP in patients with an ejection fraction of less than 0.25 (Table 2). In addition, they identified several predictors of the need for intra- and postoperative IABP support in these patients: reoperation, unstable angina, use of intravenous nitroglycerin, left main stenosis, acute myocardial infarction within 7 days, nonelective operation, and New York Heart Association class III–IV symptoms. These findings suggest that CABG patients with ejection fractions of less than 0.25 and one or more of these factors represent the subset of CABG patients who should be selected for preoperative IABP use.

The only published multicenter experience with the preoperative IABP is from Alabama (Table 2) [31]. Holman and associates [31] examined the use of what they termed *prophylactic IABPs* by excluding patients receiving preoperative IABP for hemodynamic instability, myocardial infarction within 3 days, or those undergoing emergency operation (not defined). They used propensity scores to match 550 patients with and 550 without preoperative IABP. No difference was noted for in-hospital mortality. Nonfatal events were not reported, presumably because of the reliance on administrative data that did not provide sufficiently detailed information.

Gutfinger and associates [32] examined a series of patients older than 70 years of age undergoing isolated CABG and having one of the following: left main stenosis ≥ 70%, medically refractory unstable angina, ejection fraction ≤ 0.40, failed PTCA, or reoperation (Table 2). Compared with a concurrent group of similarly aged patients, those receiving the preoperative IABP had sig-

Table 2. Preoperative IABP Use in Isolated CABG: Observational Studies With Controls

Reference	Years of Study	Design	Selection Criteria	Matched by	Number in IABP Group/"Control"	Intervention	Analysis	Outcomes (in-hospital mortality)	p^a
Feola [28]	1973–1976	Cohort (historical controls)	EF ≤ 0.30	EF	25/23	IABP 12 h preop	Univariate	8% vs 35%, MI 4% vs 30%	0.03 0.02
Dietl [7]	1991–1995	Cohort	EF ≤ 0.25	EF	37/126	IABP preop	Multivariate	2.7% vs 11.9%	0.004
Gutfinger [32]	1993–1996	Cohort	Age > 70 y & urgent with: LM > 70%, failed PTCA, UA, EF < 0.40, or emergent redo	Age	97/109	IABP ≤ 24 h preop	Univariate	6.2% vs 2.8%	0.3
Creswell [30]	1995	Cohort	Isolated CABG < 14 days post-MI	None	75/348	IABP preop	Univariate	5.3% vs 11.8% 1/3 controls IABP intra/post 18 controls VAD	0.1
Holman [31]	1995–1996	Cohort	Exclusion: MI < 3 days, shock	Age, Sex, CHF, DM	550/550	"Preincison"	Multivariate	5.5% vs. 6.1%	0.8
	1998		PTCA < 6 h, preop ventilation	redo, LM > 70%, CI, RI		IABP		1 y 11.5% vs 12%	0.8

[a] Fisher exact or χ^2.

CABG = coronary artery bypass grafting; CHF = congestive heart failure; CI = comorbidity index; DM = diabetes mellitus; EF = ejection fraction; IABP intraaortic balloon pump; LM = left main coronary artery; MI = myocardial infarction; preop = preoperatively; PTCA = percutaneous transluminal coronary angioplasty; RI = renal insufficiency; UA = unstable angina; VAD = ventricular assist device.

nificantly higher Parsonnet scores, lower ejection fractions, and twice the incidence of congestive heart failure and acute myocardial infarction. The 30-day crude mortality was not statistically significantly different (Table 2).

Randomized Controlled Trials

Recently, a series of reports by Christenson and associates [34–37] from Geneva described results of what appear to be subgroups of two prospective randomized controlled trials (conducted in a single institution). These reports concluded that preoperative IABP insertion in high-risk CABG patients decreased mortality and postoperative length of stay (Table 3) [5, 34–36]. High risk was defined as any two of the following: medically refractory unstable angina, ejection fraction ≤ 0.40, left main stenosis ≥ 70%, or redo surgery. Overall, 11 of 50 control patients died compared with 3 deaths among 62 receiving the IABP preoperatively ($p = 0.007$) [37].

The work by Christenson and associates represents an important contribution to the field. However, some major weaknesses with their reporting include the confusing presentation in several papers of what appears to be a single trial and a high mortality rate (20%) in the control patients.

Summary of Evidence for Preoperative Intraaortic Balloon Pump Use

The optimal use of the IABP in cardiac operations remains controversial, and poorly defined [25, 31]. Some of the controversy concerns the definition of a high-risk patient [38]. In some centers, fear over cost and complications of the IABP constrains use [39]. Others claim that preoperative IABP use in most patients is not necessary and that a femoral line could be inserted in the operating room to facilitate balloon introduction only if difficulties arise in weaning the patient from bypass [40]. However, much of the benefit derived from preoperative insertion and use of the IABP may be the result of improved myocardial perfusion and stability in the induction of anesthesia and the early operative period before commencing bypass [5, 32]. The difficulty lies in being able to identify those patients who are at risk of perioperative decompensation and thus would benefit most from a prophylactic IABP [31, 32].

In conclusion, there is class I level B evidence that preoperative IABP use in ischemic CABG patients is beneficial. There is class I level B evidence for preoperative IABP use in CABG patients with ejection fraction less than 0.25 who are undergoing nonelective operation or reoperation, or who have New York Heart Association class III–IV symptoms [7]. The evidence is less clear for those patients without ongoing ischemia, but who (in isolation) are undergoing reoperation, have low ejection fraction, have left main disease in isolation, or are undergoing procedures other than isolated CABG. There is class IIa level B evidence for preoperative IABP use in these patients.

Table 3. Preoperative IABP Use in Isolated CABG: Randomized Controlled Trials

Reference	Years of Study	Selection Criteria	Number in IABP Group/"Control"[a]	Intervention	Analysis	Outcomes (hospital mortality), IABP vs No IABP	p^a
Christenson [34]	1997	2 of: EF ≤ 0.40, LM ≥ 70%, redo, UA	32/20	IABP 24 h (13) IABP < 2 h (19)	Univariate	2/32 vs 5/20	<0.05
Christenson [35]	1997	EF ≤ 0.40 + LVH + HTN	19/14	IABP 2 h	Univariate	0/19 vs 3/14	<0.05
Christenson [5]	1997	Redo & 2 of: EF ≤ 0.40, UA, LM ≥ 70%	24/24	IABP 2 h	Univariate	0/24 vs 4/24	0.049
Christenson [36]	1999	2 of: EF ≤ 0.40, LM ≥ 70%, redo, UA	30/30	IABP 2 h (10) IABP 12 h (10) IABP 24 h (10)	Univariate	1/30 vs 6/30	0.05

[a] Fisher exact or χ^2.

CABG = coronary artery bypass grafting; EF = ejection fraction; HTN = hypertension; IABP = intraaortic balloon pump; LM = left main coronary artery; LVH = left ventricular hypertension; UA = unstable angina.

Evidence for Efficacy of Intraoperative and Postoperative Intraaortic Balloon Pump Use

Overall mortality in patients receiving IABPs intra- and postoperatively ranges from 21% to 73% (Table 1) [30, 41]. Patients receiving IABPs intra- and postoperatively differ from those receiving the device preoperatively. They may have been considered lower risk or were more stable preoperatively IABP than those receiving a preoperative IABP. The outcome of these patients may have been have been worse without the support of the IABP. Both intra- and postoperative IABP insertion and cardiogenic shock have been identified as independent predictors of mortality [6, 29, 42].

Intraaortic balloon pump use for weaning from cardiopulmonary bypass is well established, although the specific indications and the threshold for use are hard to analyze. Survival of patients requiring intraoperative IABP support is usually reported to be more than 50% (Table 1) [22, 43]. These patients likely would not have been separated from bypass without IABP assistance and would have died. However in a large series, 40% of the patients receiving an IABP intraoperatively ultimately required a ventricular assist device [44].

Intraoperative and postoperative IABP insertion is an indication of serious complications, which are often not correctable. As such, these patients face a high mortality. An IABP inserted for low cardiac output rather than ischemia is clearly associated with a poorer prognosis [6, 22, 43]. Not surprisingly, patients requiring intraoperative or postoperative IABP insertion have mortalities similar to those patients receiving an IABP for medical treatment of postmyocardial infarction shock [43, 45]. In addition the effect of the IABP on flow in bypass grafts is unclear and seems to be related at least in part to the graft used and its proximal origin [46, 47]. Thus in some cases IABP use may be of uncertain benefit [48].

Only one study [13] has reported outcomes of patients receiving intra- or postoperative IABP compared with any similar risk group. In a series of 319 patients, 280 received an IABP and 39 "controls" had failed attempts at balloon insertion [13]. Only 17 of the balloons were used preoperatively. In these similar risk groups a trend was noted toward decreased overall operative death, along with a significant benefit in those undergoing isolated CABG (33% vs 64% $p = 0.03$).

In conclusion, IABP use for weaning from bypass is well established although the evidence is hard to produce. There is class I level C evidence for the use of the IABP for weaning from bypass in CABG patients. There is class IIa level C evidence for postoperative IABP use in CABG patients. An important related issue that needs to be addressed is the appropriate use of a ventricular assist device in this setting.

Evidence for Efficacy of Intraaortic Balloon Pump Use in Cardiac Operations Other Than Isolated Coronary Artery Bypass Grafting

The type of operation and the timing of balloon pump use is a major determinant of survival [49]. The superior

Evidence for Efficacy of Intraaortic Balloon Pump Use in Cardiac Operations Other Than Isolated Coronary Artery Bypass Grafting

The type of operation and the timing of balloon pump use is a major determinant of survival [49]. The superior in-hospital and long-term survival of isolated CABG patients receiving IABPs, compared with patients undergoing other types of cardiac operative procedures, has been confirmed by many studies [15, 16, 27, 43, 50]. In a large series of IABP cases reported from Boston, Torchiana and coworkers [6] demonstrated that a procedure other than CABG was associated with a twofold increased risk of death. They also identified cardiogenic shock, heart failure, and mitral valve replacement as being independently associated with mortality. It is clear that patients with ongoing ischemia associated with shock do much better than those with shock and no ischemia [45]. In fact the superior survival in isolated CABG compared with valvular and other combined procedures persists regardless of timing of insertion [15]. No studies were identified in which non-CABG patients with and without an IABP were compared.

The higher mortality of patients with valvular disease and cardiogenic shock who receive an IABP is a reflection of the fact that the problem of ventricular dysfunction is either not reversible or only partially so. The IABP can improve cardiac output by only 10% to 20%, and thus is inadequate in cases requiring large doses of inotropic agents [10, 29]. Patients with profound hemodynamic compromise persisting after IABP insertion will likely survive only with a ventricular assist device [6, 51].

There is insufficient evidence to grade the use of the IABP in patients undergoing procedures other than isolated CABG.

Other Considerations

Long-Term Outcomes

It is recognized that the presence of an IABP defines a very high-risk group of patients [52]. Depending on the proportion of IABPs used preoperatively, 5-year survival is reported to be between 22% and 47% [15, 29, 53, 54]. Downing and associates [13] reported that 2-year actuarial survival was superior in those who received an IABP (45%) compared with those who did not (23%, $p = 0.006$). The best results appeared to be in transplant recipients (81%) and those undergoing isolated CABG (51%), whereas CABG with aortic valve replacement had the lowest actuarial survival of 34% at 5 years [15, 45].

A recent long-term study of 163 IABP patients who survived to hospital discharge demonstrated that those surviving to discharge have good long-term survival, comparable to that of patients with similar risk [16]. In a study of prophylactic IABP use in isolated CABG patients, no difference was found in hospital and early mortality [31]. At 3 years, however, a trend was noted toward better survival in the group receiving prophylactic IABPs [31].

In conclusion, IABP patients who survive to discharge appear to have good survival, which is determined by their disease and comorbidities. There is class IIb level B evidence that IABP use in CABG patients improves long-term survival.

Cost of Intraaortic Balloon Pump Use

In addition to a significant decrease in mortality and postoperative length of stay, Christenson and associates [37] reported that preoperative IABP use was associated with lower costs of in-hospital care and a shorter length of stay. They reported similar results in reoperative patients [5].

Dietl and associates [7] also reported a reduced length of stay with preoperative IABP use (10 vs 12 days). Mean hospital costs were also reduced by USD$4,000 per patient [7]. Using administrative data, Holman and associates [31] reported a decreased length of stay of 1 day in patients receiving prophylactic preoperative IABP compared with matched patients.

In conclusion, patients requiring IABPs by their nature are at high risk and thus will have longer hospital stays and spend more time in the intensive care unit. It appears that use of an IABP is unlikely to increase cost, and there is class I grade B evidence that preoperative insertion in selected CABG patients will decrease overall costs [31].

Complications of Intraaortic Balloon Pump Use

The use of IABPs is not without complications, which occur in 11% to 33% of cases (Table 4) [14, 55]. This range is largely a reflection of varied definitions of complications. The overall and ischemic complication rates do not appear to have changed substantially over time (Table 4). In a recent prospective study of 1,119 consecutive patients receiving IABPs, Cohen and associates [56] reported an overall complication rate of 15% with 46 patients requiring operation for their complications and only 5 deaths directly attributable to the use of an IABP.

Limb Ischemia and Vascular Injury

Limb ischemia is the most common complication of IABP use, reported in 8% to 42% of cases (Table 4). This variation is largely dependent on the definition of ischemia and the intensity of patient observation. In addition, a substantial proportion of injuries related to IABP use (perhaps as many as 80%) are not recognized clinically before death [57]. In all series, a substantial proportion of patients (usually more than 30%) who develop ischemia require surgical intervention (Table 4). A recent review from Germany found that those with ischemic complications had a significantly higher mortality rate (60% vs 30%, $p = 0.001$) [58]. Similar results have been confirmed by other series [59, 60].

Long-term follow-up of patients with lower limb ischemia as a result of IABP use revealed that 18% of patients had signs and symptoms of chronic limb ischemia [61]. Multivariate predictors of chronic ischemia include acute limb ischemia, cardiogenic shock, and smoking. This high rate of chronic ischemia has resulted in reluctance, on the part of some surgeons, to use the IABP [5, 39, 62, 63].

A number of investigators have examined risk factors for IABP-related vascular complications. Female sex, history of peripheral vascular disease, and diabetes have been consistently identified as independent risk factors for vascular complications [55, 56, 58, 59, 65–67]. Others have implicated duration of IABP use, smoking, and hypertension as risk factors [14, 68–71].

Aortic or iliac dissection or perforation are rare but usually fatal complications of IABP insertion, occurring in about 1% of cases (Table 4). If autopsy cases are included, the incidence of this complication can be has high as 5% to 9% [55]. Death as a direct result of IABP use is hard to quantify, except in the cases of dissection and perforation, but is reported to occur in 0.5% to 4% of cases [65, 72].

Other Complications

Other complications include bleeding, infection [55, 73], stroke, and other embolic complications including paraplegia [74, 75]; neuropathy and chronic pain occur less frequently (Table 4). Entrapment of the IABP has been reported only rarely and appears to be associated with balloon rupture and subsequent clot formation within the balloon [75, 76]. Some surgeons think that the benefits of prophylactic IABP use do not outweigh the risk of complications, and that use of the IABP should be restricted to life-threatening conditions only [64].

Insertion Technique

In 1980, percutaneous IABP insertion came into common usage. A number of studies have suggested that the percutaneous method has a higher complication rate than traditional surgical exposure of the femoral vessels and insertion under direct vision [55, 59, 77, 78]. A prospective, randomized controlled trial of 101 patients found that although percutaneous insertion was faster and technically easier, it was associated with a significantly higher vascular complication rate (11/51 vs 2/50 $p < 0.05$ [79]. Despite the related complications, percutaneous insertion has become the standard first method of insertion in most centers. This is partly because of the changing nature of use (now used more frequently by cardiologists than surgeons) [6] and the recognition that the differences in complications are partly due to physician experience with the technique [79]. In addition, percutaneous insertion avoids the mandatory need for reoperation to remove the IABP.

Alternative Routes of Intraaortic Balloon Pump Insertion

Alternate routes of IABP insertion can be used when occlusive aortoiliac disease or prior abdominal aortic or femoral artery operation prevents femoral artery insertion [80]. Insertion of the IABP through the ascending

Table 4. Complications of IABP Use

Reference	Years of Study	Number of Cases	Number of Surgical Insertions (Complication Rate)	Number of Percutaneous Insertions (Complication Rate)	Overall Complication Rate	IABP-Related Mortality	Ischemia[a]	Infection	Dissection/ Perforation	Bleeding	Stroke
Kantrowitz [14]	1967–1982	733	501	232	NA	NA	16%	22%	0.5%	15%	NA
Pennington [22]	1973–1982	378	201 (10%)	161 (15%)	12%	2%	7%	2%	2%	1%	NA
Makhoul [113]	1971–1985	431	365	66	11%	0.5%	9%	0.2%	0.5%	0.5%	NA
Iverson [64]	1973–1986	395	NA (32%)	NA (19%)	24%	NA	16%	0.5%	0.3%	0.3%	NA
Alpert [109]	1971–1978	332	332 (16%)	0	16%	NA	13%	2%	1%	NA	NA
Goldman [73]	1977–1979	389	299 (31%)	90 (17%)	28%	NA	10%	5.7%	2.3%	2%	NA
Grayzel [108]	1979–1980	722	0	722 (14%)	14%	NA	9%	NA	3%	NA	NA
Perler [104]	1968–1981	794	794[b]	0	11%	NA	9%	2%	1%	1%	NA
Scholz [69]	1977–1995	373[c]	23 (30%)	350 (12%)	13%	NA	11%	3%	NA	4%	NA
Todd [114]	1979–1981	102	0	102	22%	NA	12%	0%	NA	3%	1%
Curtis [78]	1976–1985	202	103 (14%)	99 (32%)	23%	0	24%	1%	NA	NA	NA
Beckman [111]	1973–1976	273	273 (14%)	0	14%	NA	6%	4%	4%	NA	NA
Gottlieb [107]	1980–1982	206[d]	101 (24%)	105 (30%)	27%	0.5%	16%	6%	4%	NA	2%
Arafa [16]	1980–1989	344	NA	NA	18%	0.6%	8%	8%	0.3%	3%	NA
Alvarez [63]	1980–1990	303	62 (11.3%)	262 (10.7%)	33%	2%	8%	2%	2%	3.3%	0.7%
Hedenmark [106]	1981–1985	90[e]	39 (27%)	49 (27%)	27%	NA	20%	2%	1%	7%	NA
Alderman [66]	1983–1986	103[f]	0	103	NA	NA	42%	NA	0%	0	0
Yuen [105]	1985–1989	93	15 (20%)	78 (19%)	19%	0	14%	1%	1%	2%	NA
Pelletier [77]	2 y[g]	85	42	43	24%	2.4%	18%	2%	1%	1%	NA
Alle [72]	1981–1991	90	56 (NA)	30 (NA)	33%	4%	14%	4%	2%	NA	1%
Barnett [65]	1983–1990	580	169	375	NA	0.5%	12%	NA	0.5%	NA	NA
Gol [60]	1988–1993	449	0	449	19%	NA	17%	0%	0.4%	5%	NA
Cohen [56]	1993–1997	1119	0	1119	15%	0.4%	3%	NA	0.09%	5%	0.01%
Shahian [71]	2 y[h]	87	41 (32%)	46 (33%)	32%	1.2%	18%	NA	2%	3%	NA
Busch [67]	1985–1995	472	293	170	31%	NA	27%	NA	NA	3%	NA
MacKenzie [68]	1988–1991	100	22 (NA)	77 (NA)	29%	NA	25%	NA	9%[i]	2%	NA
Sirbu [58]	1988–1998	524	178 (NA)	333 (NA)	31%	NA	27%	NA	0%	3.1%	NA
Miller [59]	1987–1989	404	92 (18%)	323 (39%)	18%	NA	6%	0.8%	0.3%	1%	1.4%

[a] Limb ischemia and thromboembolism (where available). [b] 75 nonsurgical cases, all femoral and thoracic IABPs excluded. [c] 55 surgical cases. [d] Includes 24 failed insertions. [e] 85 surgical. [f] 86 surgical. [g] Published 1986. [h] Published 1983. [i] At autopsy.

aorta, iliac, subclavian, and axillary arteries have all been reported [81–84].

Of these methods, transthoracic arch insertion is the most frequently used and has been reported in 1.9% to 6.2% of all IABP procedures [6, 29]. Transthoracic arch insertion of IABPs occurs intra- or postoperatively in patients in whom femoral insertion had failed; the mortality is similar to that reported overall for intra- and postoperative use in larger series (25% to 73%) [15, 22, 80, 85] (Table 1). Pinkard and associates [86] found in analyzing a series of 123 IABPs inserted for weaning from bypass in CABG patients (42 transthoracic and 81 femoral) that the increased mortality in the arch insertion group was a result of the greater comorbidities rather than the route of insertion. Additionally, no increase in complications was noted in the aortic insertion group, whereas the patients with femoral insertion had a higher incidence of leg complications. The largest reported series of transthoracic IABP insertion (n = 100) also demonstrated no increased mortality and complication rates similar to those of femoral insertion [85].

There is Class I level C evidence and general agreement that arch insertion is a good second choice if femoral insertion is not possible [80, 85, 86].

Intraaortic Balloon Pump Use

Overall use of the IABP in cardiac surgical patients varies from 1.5% to 17% of all cases (Table 1) [6, 26]. This marked variation in use remains high even after risk adjustment (7.8% to 20.8% of cases), indicating that in many centers the IABP is being either over- or underused [41]. Optimal use of the IABP in cardiac operation has not been clearly defined.

Over time, from the early 1970s through to the 1990s, the trend has been toward increased use (Table 1). In the largest published single-center experience with the IABP (The Massachusetts General Hospital), increasing usage has been associated with increasing risk of the patient population, and the introduction of the percutaneous method of insertion, which has broadened the availability and feasibility of balloon pump use [6, 79]. In addition, increased use of the IABP for ischemia rather than hemodynamic instability has contributed to the increased use [6, 15].

Use of the IABP in the preoperative period has also increased in many centers. This change is partly in response to recognition of the superior results of the IABP in ischemic patients [6, 8, 15, 29]. However, the variation between centers within the same time periods is substantial (Table 1). The proportion of IABPs used preoperatively ranges from 0% to 74% (Table 1) [19, 87]. Even recent series report the use of preoperative IABPs in only a minority of cases, as low as 4% to 12% of all IABPs [50, 60]. This wide variation reflects a lack of consensus over specific indications and a lack of widely accepted guidelines; in many respects the variation also represents differing philosophies of management [15, 88].

In summary, use of the IABP in cardiac operations appears to be center specific and inconsistent across centers.

Intraaortic Balloon Pump Use in Children

Use of the IABP in children has been limited, partly because of technical difficulties, although appropriate equipment has been developed [89–93]. Physiologic differences including greater compliance of the pediatric aorta, the large bronchial vessel in cyanotic diseases, and the higher heart rates in children, make augmentation difficult to achieve [91, 93]. Most importantly, children with congenital heart disease are more likely to have isolated right ventricular failure, biventricular failure, or pulmonary hypertension, which would require the use of extracorporeal membrane oxygenation or a ventricular assist device [89, 93].

Reported survival with IABP use in children ranges from 25% to 66%, but the largest series reported is only 29 patients [90, 94, 95]. These results are similar to those in adults receiving intra- or postoperative IABP support (Table 1). Results of extracorporeal membrane oxygenation support in children (61% to 71% survival) are better than IABP [96, 97]. Intraaortic balloon pumps appear to be most effective in older children, in whom augmentation is more reliably achieved [90, 91], and specifically in those with isolated left ventricular failure, such as those with anomalous coronary artery repairs, myocarditis, or Kawasaki's disease, or as a bridge to transplantation [92, 93, 95, 98]. There is class IIa grade C evidence for IABP use in hemodynamically unstable children.

Trends

Evidence suggests that the IABP can also be used to support primarily right ventricular failure, particular in the transplant population [99]. The IABP has also been found to be an effective adjuvant to off-pump CABG [100, 101]. Longer-term IABP use has been effectively used as a bridge to transplant, although its role in the era of long-term safe ventricular assist devices may be more limited [70]. Use of the balloon pump has been extended with good results to the increasing population of elderly [32, 102, 103].

Over the past 5 years, use of preoperative IABPs has increased in some centers [5, 6]. This increase has been associated with a decrease in mortality. It remains difficult to identify those patients who will benefit most from the IABP, while minimizing the device-related complications. The trend has been toward prophylactic use to avoid rather than treat ischemia [5, 31]. Use of preoperative IABPs will probably continue to increase as the criteria for use are better defined, and the population of patients presenting for cardiac operations becomes older and higher risk. Use of the IABP in high-risk angioplasty and primary angioplasty for acute myocardial infarction will also likely increase, as will its use for off-pump operations. Smaller catheter sizes will likely further re-

duce, although not eliminate, the incidence of vascular complications.

Future Research

Despite more than 30 years of clinical use and the large body of literature on IABPs, several critical questions remain to be answered. Appropriate and optimal use of the IABP, particularly preoperatively, remains to be clarified. The provocative results of a small but limited randomized controlled trial showing a survival benefit with the use of preoperative balloon support in high-risk cases needs to be validated, perhaps with a large series of observational data, and multi-institution comparisons. The role of the IABP for intraoperative and postoperative support relative to the use of ventricular assist devices needs to be defined, probably in the setting of a multicentered trial.

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REVIEW OF RECENT BOOKS

Mechanical Support for Cardiac and Respiratory Failure in Pediatric Patients
Edited by Brian W. Duncan, MD
2001, New York, New York, Marcel Dekker, Inc
369 pp, illustrated, $165.00
ISBN: 0-8247-0275-1

Reviewed by Joseph B. Zwischenberger, MD

This book attempts to "fill a void" in the current literature by concisely summarizing the state of the art of mechanical circulatory support in children. The textbook covers all areas from extracorporeal membrane oxygenation (ECMO) to a wide range of support devices including ventricular assist devices and intraaortic balloon pumps. The editor does a credible job bringing together older technology and experiences to the currently available technology. ECMO dominates the discussion and is a natural extension of the expertise gained from neonatal populations. The editor's forte is the application of ECMO for postoperative cardiac support, and the book reflects that expertise. The ECMO management section is detailed with a thorough explanation of the various components of an ECMO circuit. The book also provides insight into organizing a rapid deployment team for implementation of ECMO. Mechanical circulatory support is addressed separately and is contrasted to the technique of ECMO. Expertise is added to explain unique problems inherent to the pediatric population and discussing the differences between neonatal and adult populations.

Some aspects of the book were tedious. The first four chapters were very repetitive. Some of the figures and graphs in the book were not clear. Much of the data presented within the book did not reflect the experience of multiple centers collectively or the Extracorpeal Life Support Organization. Very little of the book was dedicated to respiratory failure, as the title might suggest, therefore the book would be of little benefit to a center that has a patient base of primary respiratory failure. Dr Duncan has obviously made an effort to retain a consistent philosophy throughout the book. He has gained experience as a pediatric cardiac surgeon utililizing ECMO for postoperative cardiac support, in this respect, his expertise is apparent. I should also comment that the book is relatively expensive in comparison to a literature search, which could yield much of the material contained within this book, or available materials from the Extracorpeal Life Support Organization.

Galveston, Texas

Fast-Track Anesthesia and Cardiac Surgery: A Retrospective Cohort Study of 7989 Patients

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BACKGROUND: Fast-track cardiac anesthesia (FTCA) has been widely implemented but its safety has not been evaluated in sufficiently powered studies.

METHODS: We compared outcomes of patients undergoing FTCA with a historical control group undergoing conventional high-dose opioid cardiac anesthesia (CCA). The primary outcome measure was the incidence of in-hospital mortality. Secondary outcome measures were the incidence of in-hospital acute myocardial infarction, renal failure, and stroke. We also compared duration of mechanical ventilation and length of hospitalization in the intensive care unit and postoperative ward.

RESULTS: The CCA group comprised 4020 patients and the FTCA Group 3969 patients. The patients in the FTCA group were slightly older, had more comorbidities, and were more likely to undergo valve surgery than the CCA group. The incidence of in-hospital mortality was 1.9% in the CCA group and 2.3% in the FTCA group. Compared with the CCA group, the crude odds ratio for mortality in the FTCA group was 1.20 (95% confidence interval 0.88–1.64, $P = 0.25$) and the adjusted odds ratio was 0.92 (95% confidence interval, 0.65–1.32, $P = 0.66$). The incidence of myocardial infarction and stroke in the CCA and FTCA groups were 5.2% and 5.5% ($P = 0.61$), and 0.9% and 1.3%, ($P = 0.06$), respectively, whereas the incidence of acute renal failure was similar in both groups (0.8%, $P = 0.84$). The duration of mechanical ventilation was shorter in the FTCA patients compared with the CCA group (6 vs 12 h, $P \leq 0.001$), but their median intensive care stay was 1 h longer (23 vs 22 h, $P \leq 0.001$). Although the median duration of hospitalization was 6.0 days in both groups, the 90th percentile of the hospitalization time was 13 days in the CCA group and 18 days in the FTCA group ($P \leq 0.001$).

CONCLUSIONS: These data from 7989 cardiac surgical patients showed no evidence of an increased risk of adverse outcomes in patients undergoing FTCA.

(Anesth Analg 2009;108:727–33)

High-dose opioid anesthesia (e.g., on fentanyl 25–100 μg/kg or sufentanil 2.5–10 μg/kg) was introduced into cardiac surgery almost 40 yr ago in an attempt to provide hemodynamic stability without myocardial depression in patients with compromised cardiac function.[1] It was also assumed that the prolonged intensive analgesia resulting from conventional cardiac anesthesia (CCA) would reduce postoperative myocardial ischemia.[2] Over the past decade, fast-track cardiac anesthesia (FTCA) has gained popularity because it facilitates early tracheal extubation that may lead to a decreased length of hospitalization in the intensive care unit (ICU) and postoperative ward.[3,4] FTCA is based on the administration of relatively small amounts of short-acting opioids, supplemented with either propofol or volatile anesthetics.[5,6] It has been reported that the risk of cardiovascular complications after FTCA is comparable with CCA.[7–9] Nonetheless, the safety of FTCA has not been thoroughly evaluated, because the studies performed to date enrolled too few patients to adequately assess the relative risk for low-frequency complications, such as mortality. The two largest studies comparing FTCA with CCA, in fact, comprised only 1012 and 404 patients[10,11] yielding results with limited statistical power. Meta-analyses evaluating FTCA included randomized trials with predominantly low-risk patients and may have been subjected to publication bias and other limitations inherent with this analytic approach.[12,13]

Thus, the aim of this study was to compare the incidence of mortality, myocardial infarction, stroke, and renal failure between cardiac surgical patients undergoing FTCA and historical controls undergoing CCA.

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METHODS

Design and Patients

The study was designed as a retrospective observational study. Because of the retrospective nature of the study, formal evaluation by the institution's ethical committee and informed consent were waived. Eligible patients were consecutive patients who underwent elective cardiac surgery at a single institution (Isala Clinics, Zwolle, The Netherlands). During the first period (January 2000 until May 2003) patients received CCA. In June and July 2003 our institution gradually introduced FTCA. Patients having surgery in these 2 mo were not analyzed. Patients undergoing surgery from August 2003 to December 2006 comprised the second group of patients receiving FTCA. Only patients operated on in June and July 2003, and patients undergoing emergency surgery, were excluded from the analyses.

Anesthesia Techniques

During the first period of study (CCA), patients were premedicated with midazolam 15 mg orally. Induction of anesthesia was with the combination of the opioid sufentanil 2–4 μg/kg and midazolam 0.05–0.1 mg/kg with pancuronium 0.1 mg/kg. Anesthesia was maintained with sufentanil 0.5–2.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and midazolam 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$.

After the introduction of FTCA, patients were premedicated with midazolam 7.5 mg orally. Induction of anesthesia was with remifentanil 1–3 μg/kg and propofol 1–2 mg/kg with the muscle relaxant pancuronium 0.1 mg/kg. Some patients also received a low dose of midazolam (up to 5 mg) at induction. Anesthesia was maintained with remifentanil 5–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and propofol 1–4 $mg \cdot kg^{-1} \cdot h^{-1}$ or sevoflurane (end-tidal concentration 0.5–1.5 volume percent). Upon completion of the operation, morphine 0.1–0.2 mg/kg was administered.

In the ICU after surgery, the CCA patients were sedated with midazolam 2–4 mg/h, and the FTCA patients with propofol 1–2 $mg \cdot kg^{-1} \cdot h^{-1}$. In both the FTCA and CCA groups, sedation was stopped when the patient was hemodynamically stable (no or minor inotropic support and urinary output >0.5 $mL \cdot kg^{-1} \cdot h^{-1}$), peripheral temperature >35°C, and arterial oxygen saturation ≥93% with an fractional inspired oxygen concentration of ≤40%. If a patient could not be weaned from the ventilator and the Ramsey score was >3, additional IV injections of midazolam or lorazepam were administered.

Senior anesthesiologists were responsible for the anesthetic management of the patients during their operations and their postoperative care in the ICU. There were no changes in the staff of senior anesthesiologists during the study period. Tracheal extubation criteria and ICU discharge criteria remained similar throughout the study period.

Surgical Procedures

All patients underwent surgery through a median sternotomy. In patients undergoing cardiac surgery using cardiopulmonary bypass (CPB), myocardial protection was achieved with antegrade blood or crystalloid cardioplegia. One surgeon used the combination of retrograde and antegrade crystalloid cardioplegia for aortic valve surgery. CPB was managed using nonpulsatile flow applied by centrifugal pump and with the α-stat principle. A 40-μM filter was placed in the arterial line. Heparin was given to maintain the activated clotting time >480 s throughout CPB. Nasopharyngeal temperature was monitored and body temperature reduced to 28°C–34°C during CPB, followed by rewarming to a rectal temperature of 36°C before separation from CPB. After weaning from CPB, protamine 300 U/kg was administered. At the conclusion of surgery, all patients were transported to the ICU.

Outcomes

The primary outcome measure was the incidence of mortality during hospitalization. Secondary outcome measures were the incidence of acute myocardial infarction, stroke, and renal failure, as well as duration of mechanical ventilation, length of hospitalization in the ICU, and total hospitalization.

In coronary artery bypass graft surgery patients, acute myocardial infarction was defined as myocardial specific creatine kinase (CKMB) >120 U/L (five times upper reference limit) plus a peak CKMB/CK ratio >10%, or pathological new Q waves on a postoperative electrocardiogram (ECG).[14] To avoid false-positive diagnoses after valve surgery, CKMB value ≥180 U/L (7.5 times upper reference limit) plus a peak CKMB/creatine kinase ratio >10% was used as the criteria to diagnose myocardial infarction. Preoperative CKMB was not measured, but CK and CKMB were measured in all patients shortly after arrival in the ICU and 4 h later. Measurements were repeated at 4 h intervals when a CKMB level was >50 U/L, the percentage was >10% of total CK, and when CKMB was increasing between the first and second measurement. These measurements were continued until the CKMB level was decreasing. In the ICU, all patients were continuously monitored with 12-lead ECG. Shortly after arrival, a 12-lead ECG was printed and examined by the attending physician. This was repeated before ICU discharge. Additional 12-lead ECGs were printed and examined if myocardial injury was suspected.

According to the second international consensus conference of the acute dialysis quality initiative group, acute renal failure was defined as an increase in postoperative serum creatinine of at least three times the preoperative value, or a serum creatinine >4 mg/dL associated with an acute increase of serum creatinine of at least 0.5 mg/dL.[15] Creatinine was

measured in all patients before surgery and at least once daily as long as they were in the ICU.

Stroke was defined as a new motor or sensory deficit of central origin or unexplained coma. The diagnosis of stroke was made after physical examination by a neurologist and usually confirmed by head computed tomography scan.

Data Collection

Clinical data for the patients were prospectively registered in a dedicated electronic research database from admission until hospital discharge. In the operating room, the attending anesthesiologist documented the patients' demographic data and intraoperative data on a dedicated form and also entered these variables in an electronic database (Microsoft Access). Although the patients were admitted to the ICU, relevant data (duration of ventilation, length of ICU stay, medication, complications, and routine laboratory measurements) were collected by the ICU medical staff on another dedicated data form. After transfer to the step-down ward, additional data (length of hospital stay, medication, and complications in the ward) were recorded by nurses from the research team. These research nurses subsequently entered the data from the dedicated forms into the electronic research database. Because the demographic and intraoperative data were already entered into the database by the attending anesthesiologist, the nurses did not reenter these data but only compared these electronic and written variables. After the patient's discharge from the hospital, all data collection forms were rechecked by another member of the research team to confirm accuracy of the data entry. The final data were transferred into an SPSS database, from which further analyses could be performed.

Statistical Analysis

The rates of mortality, myocardial infarction, stroke, and acute renal failure in the FTCA and CCA group were compared using the χ^2 test and are presented as odds ratio with 95% confidence interval (CI). Continuous outcome measures were compared using the two-sample *t*-test or the Mann–Whitney test, where appropriate, and are expressed as medians with 10th and 90th percentile. For binary outcome measures, multivariable logistic regression analysis was used to correct for baseline and intraoperative differences (confounders) between the two treatment groups. Based on the literature[16] and clinical expertise, we considered the following pre- and perioperative characteristics as potentially related to our study outcomes and thus as potential confounders of the association between FTCA and the study outcomes: age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, preoperative renal failure, preoperative neurological deficit, left ventricular ejection fraction (LVEF), use of cardiovascular drugs, type of surgery, number of anastomoses, duration of CPB, cross-clamp time, off-pump surgery, and additive (i.e., standard) Euroscore.[16] This approach was also used for studying the association with the secondary dichotomous outcomes. For the continuous secondary outcome variables (i.e., duration of mechanical ventilation and duration of hospitalization in the ICU, and total duration in hospital) we used linear regression. As these three duration outcomes were all nonnormally distributed, we first applied a natural log-transformation and compared the mean log(duration) between the FTCA and CCA group using univariable linear regression. Subsequently, for each of these outcomes, multivariable linear regression on the log(duration) was used to adjust this difference in mean log(duration) for the potential confounders.

Statistical analysis was performed with SPSS software version 13. Although very limited, some patients did have missing values for one or more covariates (confounders) ranging from 0.1% for age to 2.6% for LVEF (Table 1). Missing data seldom occur completely at random. Deleting subjects with a missing value does not only lead to loss of statistical power but also commonly leads to biased results. Therefore, imputing missing values is generally preferred to complete case analysis.[17–20] Missing covariate or confounder data were thus (single) imputed using a regression model (logistic regression for dichotomous covariates, linear regression for continuous covariates, and polytomous regression for categorical covariates) approach with addition of a random error component before conducting the analyses (S-PLUS, professional edition, version 6.2). The imputation model, i.e., the model to impute missing covariate data, included all other covariates including the outcome variables, as it has extensively been reported that imputation of missing covariate data should always be done with all available data including the outcome.[17–20] Missing outcome variables were not imputed.

RESULTS

The CCA group comprised 4020 patients and the FTCA Group 3969 patients. Baseline characteristics of the two groups are presented in Table 1. Although the median Euroscore was 5 in both groups, the 90th percentile of the Euroscore was 9 in the CCA group and 10 in the FTCA group, reflecting a higher risk profile in the FTCA group ($P < 0.001$). The FTCA group included more patients with hypertension, diabetes, renal failure, poor LVEF, and fewer patients using cardiovascular drugs preoperatively. Furthermore, the FTCA group had a median duration of CPB of 99 min vs 90 min in the CCA group ($P < 0.001$). There were no substantial differences between the two groups in age, gender, chronic obstructive pulmonary disease, peripheral vascular disease, or neurological disease. In the CCA group, 2655 (66.0%) patients underwent elective coronary artery bypass graft surgery versus 2360 (59.3%) in the FTCA group ($P < 0.001$).

Table 1. Baseline Characteristics and Intraoperative Data

	CCA group n=4020	FTCA group n=3969	P	Missing data (%)
Age, Median (10th; 90th) (yr)	67 (51–77)	68 (52–78)	≤0.001	0.1
Gender male (%)	70.5	70.5	0.98	0.2
Euroscore, median (10th; 90th)	5 (1–9)	5 (2–10)	≤0.001	0
COPD (%)	14.0	14.1	0.92	0
Hypertension (%)	42.3	49.6	≤0.001	0
Diabetes mellitus (%)	17.6	22.1	≤0.001	0
Peripheral vascular disease (%)	10.1	10.8	0.29	0
Renal failure (%)	1.2	1.8	0.04	0.3
Neurological disease (%)	8.1	8.8	0.23	0
LVEF <20 (%)	3.9	5.0	0.02	2.6
Preoperative medication use (%)				
Aspirin	63.1	59.6	≤0.001	0
Diuretics	23.2	22.7	0.56	0
Beta blockers	74.4	66.8	≤0.001	0
Calcium antagonists	33.3	21.5	≤0.001	0
Statins	29.3	34.3	≤0.001	0
ACE inhibitors	32.2	34.1	0.07	0
CABG (%)	66.0	59.3	≤0.001	0
CABG off pump (%)	9.0	8.1	0.18	0
Number of anastomoses, median (10th; 90th)	3 (0–5)	3 (0–5)	0.03	0
Aortic valve replacement (%)	22.8	27.5	≤0.001	0
Mitral valve replacement (%)	13.7	19.3	≤0.001	0
Other surgical procedure (%)	1.2	1.6	0.04	0
CPB time, median (10th; 90th) (min)	90 (45–196)	99 (49–215)	≤0.001	0
Aortic cross-clamp time, median (10th; 90th) (min)	61 (36–127)	68 (40–138)	≤0.001	0

Neurological disease is defined as history of stroke or other neurological dysfunction severely affecting ambulation or day-to-day functioning.

CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; ACE = angiotensin converting enzyme.

Table 2. Crude and Adjusted Odds Ratio for Mortality, FTCA Versus CCA Group

	Odds ratio	95% CI
Crude	1.20	0.88–.64
Adjusted for: age and female gender (1)	1.14	0.83–1.56
1 + diabetes mellitus (2)	1.13	0.82–1.54
2 + hypertension (3)	1.14	0.83–1.56
3 + LVEF (4)	1.11	0.80–1.54
4 + betablokkers (5)	1.05	0.76–1.46
5 + duration of CPB (6)	0.90	0.64–1.26
All confounders[a]	0.92	0.65–1.32

An odds ratio of >1.00 indicates an increased risk of mortality in the FTCA group.

CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia; CPB = cardiopulmonary bypass; CI = confidence interval.

[a] Adjusted for age, gender, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, preoperative renal failure, neurological disease, left ventricle ejection fraction (LVEF), use of cardiovascular drugs, type of surgery, number of anastomoses, duration of cardiopulmonary bypass, and off-pump surgery.

Outcomes

Crude and adjusted mortality for the CCA and FTCA groups are listed in Table 2. There was no difference in the incidence of in-hospital mortality between the CCA and FTCA groups (CCA group, 1.9% vs FTCA group, 2.3%, crude odds ratio, 1.20, 95% CI 0.88–1.64, P = 0.25). This lack of difference in mortality rate persisted after adjusting for confounding variables (odds ratio, 0.92; 95% CI, 0.65–1.32, P = 0.66). We also performed a stratified analysis based on preoperative risk. After stratifying the patients into three different risk groups (Euroscore 1–4, 5–9, and >10), the actual and predicted mortality were compared. Across the three strata, the predicted mortality was higher than the actual mortality in both the CCA and FTCA group, but there were no differences between the two groups (Fig. 1).

The frequency of myocardial infarction, stroke, and renal dysfunction for the CCA and FTCA groups are listed in Table 3. There was no difference between the two groups in the rates of these complications.

The duration of mechanical lung ventilation, hospitalization in the ICU and total hospitalization are listed in Table 4. The FTCA group had a significantly shorter duration of mechanical ventilation ($P \leq 0.001$) compared with the CCA group, as expressed by a ratio of geometric means significantly smaller than 1. For example, the ratio between the mean log (duration of mechanical ventilation) after adjustment for confounding was 0.53, implying that the mean log (mechanical ventilation) was 0.53 times shorter in the FTCA group. In contrast, the duration of hospitalization in the ICU ($P \leq 0.001$) and total duration of hospitalization was longer ($P \leq 0.001$) in the FTCA group compared with the CCA group, after adjustment for confounding.

DISCUSSION

In this study, we compared the hospital outcomes of 3969 patients undergoing FTCA with 4020 historical

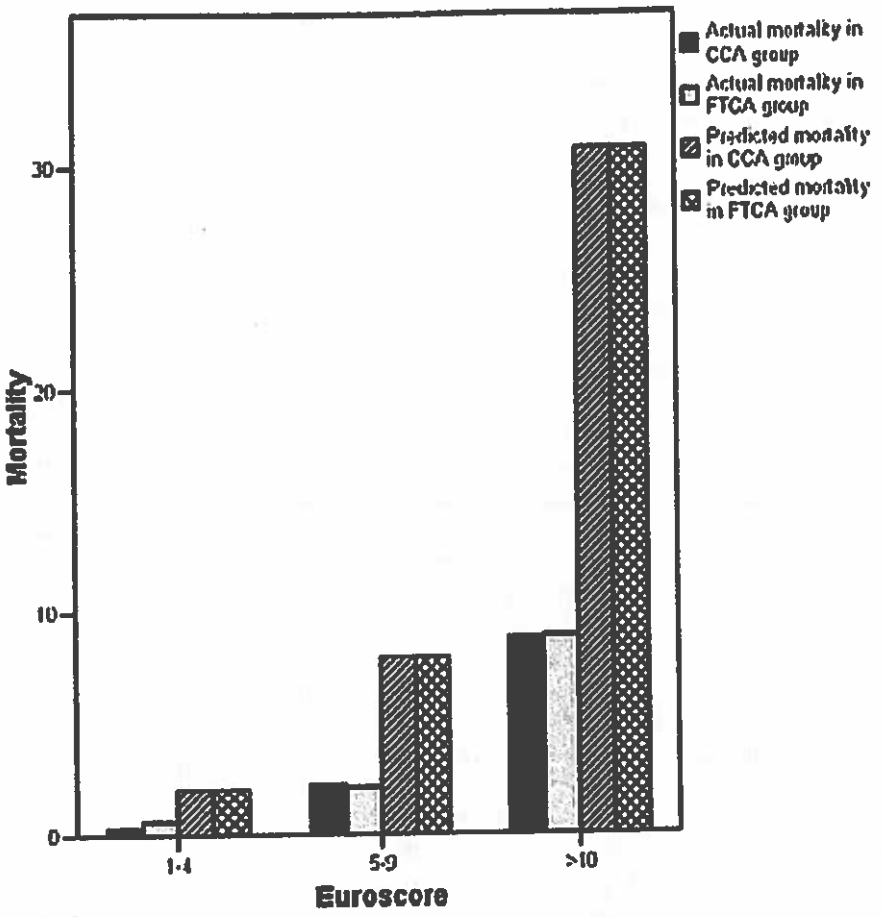

Figure 1. Predicted mortality (%) and actual mortality (%) in CCA and FTCA group, in three different risk strata. CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia. Because of the stratification according to risk, the predicted risks of mortality are similar in the CCA and FTCA group.

Table 3. The Frequency and Odds Ratios of Myocardial Infarction, Stroke, and Renal Failure Between the CCA and FTCA Groups

	CCA group n=4020	FTCA group n=3969	Crude odds ratio	95% CI	Adjusted odds ratio[a]	95% CI
Myocardial infarction	5.2%	5.5%	1.07	0.84–1.35	0.92	0.71–1.18
Stroke	0.9%	1.3%	1.52	0.98–2.35	1.38	0.86–2.20
Renal failure	0.8%	0.8%	0.95	0.59–1.54	0.64	0.37–1.12

An odds ratio of >1.00 indicates an increased risk in the FTCA group.

CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia; CI = confidence interval.

[a] Adjusted for age, gender, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, preoperative renal failure, neurological disease, left ventricular ejection fraction, use of cardiovascular drugs, type of surgery, number of anastomoses, duration of cardiopulmonary bypass, and off-pump surgery.

Table 4. The Duration of Mechanical Lung Ventilation, and Hospitalization in the Intensive Care Unit and Total Hospitalization for the CCA and FTCA Groups

	CCA group n=4020		FTCA group n=3969		Ratio of geometric means (95% CI)	
	Median (10th; 90th)	Geometric mean[a]	Median (10th; 90th)	Geometric mean[a]	Unadjusted[b]	Adjusted[c]
Duration of mechanical ventilation (h)	12 (7–19)	12.2	6 (3–16)	6.7	0.55 (0.53, 0.56)	0.53 (0.51, 0.54)
Duration of ICU hospitalizaton (h)	22 (18–71)	29.1	23 (18–95)	31.1	1.07 (1.03, 1.11)	1.15 (1.09, 1.21)
Duration of hospitalization (days)	6 (4–13)	6.6	6 (4–18)	7.3	1.10 (1.07, 1.14)	1.09 (1.07, 1.14)

The data are listed as median and geometric mean with estimated ratios of continuous outcomes.

CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia; ICU = intensive care unit; CI = confidence interval.

[a] Geometric mean = Exp (mean log duration time).

[b] Unadjusted (crude) ratio of geometric mean of FTCA and CCA using univariable linear regression analysis; $P < 0.001$ for all ratios (i.e., 1 was not included in any of the 95% CIs).

[c] Adjusted ratio of geometric mean of FTCA and CCA, adjusted for Euroscore, diabetes mellitus, use of cardiovascular drugs, number of anastomoses, duration of cardiopulmonary bypass and off-pump surgery, using multivariable linear regression analysis. $P < 0.001$ for all ratios. Additional adjustment for complications (mortality, myocardial infarction, stroke, and acute renal failure) yielded comparable results (data not presented).

control patients undergoing CCA. We found no differences in the frequency of hospital mortality or other major complications between patients receiving FTCA and patients receiving CCA.

Many cardiac surgical centers have embraced FTCA protocols to reduce ICU bed use and to reduce hospital costs associated with postoperative care.[9,10,21] It has been argued, however, that FTCA should not be adopted until further evidence of its safety is available, in particular because the prolonged intensive analgesia resulting from CCA is thought to reduce postoperative myocardial ischemia.[2] A number of randomized trials have indicated that FTCA is not associated with a higher risk for myocardial ischemia or other perioperative complications compared with conventional anesthetic methods.[5,6,10] However, the largest study to date included only 1012 patients, and thus did not contain enough statistical power to exclude a higher risk for mortality.[11] The authors of this article calculated that a sample size of 7844 patients would be needed to detect a possible difference in myocardial infarctions.[11] A meta-analysis of randomized trials evaluating FTCA included 10 trials with 1800 patients.[12] No differences were observed in 30-day mortality, myocardial infarction, or renal failure, but the authors recognized that even this meta-analysis was underpowered.[12] A later meta-analysis included 27 studies with 2821 patients.[13] Both meta-analyses predominantly included low-risk patients and were not designed to evaluate the safety of FTCA.

To our knowledge, the present cohort study is the first to evaluate the safety of FTCA in a large number of patients including all types of (elective) cardiac surgery. The results are in accordance with previous studies and meta-analyses,[12,13] insofar as we found no effect of FTCA on perioperative mortality or other major complications. The present analysis of almost 8000 patients has resulted in comparatively narrow 95% CIs, reflecting more precise estimates of the risks of FTCA. Because of its retrospective design, however, this study is liable to many more sources of bias than the smaller randomized studies.

As expected, the duration of mechanical ventilation was shorter in the patients receiving FTCA. Surprisingly, this did not result in a shorter ICU stay. An explanation could be that most FTCA patients had their tracheas extubated in the afternoon and early evening after surgery, meeting the ICU discharge criteria at a time when hospital procedures prevented transfer to the postoperative ward. Even so, patients in the FTCA group were discharged from the hospital later than CCA patients. We have no explanation for this finding, other than that the higher rates of comorbidity in the former group required more postoperative care, or that there was a higher rate of other complications not collected in this study in the FTCA group (e.g., postoperative atrial fibrillation).

The present study has several limitations, particularly its retrospective design. Moreover, the control subjects were operated on earlier than the FTCA subjects. This means that time effects and many other sources of bias could have influenced the results. The limited number of complications and processes of care collected for this study do not preclude that factors other than anesthetic technique might have confounded the results. More risk factors were present in the FTCA group, which reflects the gradual increase over time in age and comorbidity of cardiac surgery patients. We have corrected for a large number of possible confounders, but it is likely that other, unknown, confounders are still present. Because it is not possible to correct for differences in unknown risk factors, it is conceivable that the present analysis underestimates or overestimates the safety of FTCA.

In conclusion, the present retrospective study of 7989 cardiac surgical patients showed no evidence of an increased risk of adverse outcomes in patients undergoing FTCA.

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Intrahospital transport of critically ill patients

Christian Waydhas

Background: This review on the current literature of the intrahospital transport of critically ill patients addresses type and incidence of adverse effects, risk factors and risk assessment, and the available information on efficiency and cost-effectiveness of transferring such patients for diagnostic or therapeutic interventions within hospital. Methods and guidelines to prevent or reduce potential hazards and complications are provided.

Methods: A Medline search was performed using the terms 'critical illness', 'transport of patients', 'patient transfer', 'critical care', 'monitoring' and 'intrahospital transport', and all information concerning the intrahospital transport of patients was considered.

Results: Adverse effects may occur in up to 70% of transports. They include a change in heart rate, arterial hypotension and hypertension, increased intracranial pressure, arrhythmias, cardiac arrest and a change in respiratory rate, hypocapnia and hypercapnia, and significant hypoxaemia. No transport-related deaths have been reported. In up to one-third of cases mishaps during transport were equipment related. A long-term deterioration of respiratory function was observed in 12% of cases. Patient-related risk indicators were found to be a high Therapeutic Intervention Severity Score, mechanical ventilation, ventilation with positive end-expiratory pressure and high injury severity score. Patients' age, duration of transport, destination of transport, Acute Physiology and Chronic Health Evaluation II score, personnel accompanying the patient and other factors were not found to correlate with an increased rate of complications. Transports for diagnostic procedures resulted in a change in patient management in 40–50% of cases, indicating a good risk:benefit ratio.

Conclusions: To prevent adverse effects of intrahospital transports, guidelines concerning the organization of transports, the personnel, equipment and monitoring should be followed. In particular, the presence of a critical care physician during transport, proper equipment to monitor vital functions and to treat such disturbances immediately, and close control of the patient's ventilation appear to be of major importance. It appears useful to use specifically constructed carts including standard intensive care unit ventilators in a selected group of patients. To further reduce the rate of inadvertent mishaps resulting from transports, alternative diagnostic modalities or techniques and performing surgical procedures in the intensive care unit should be considered.

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Introduction

The safest place for the critically ill patient is stationary in the intensive care unit (ICU), connected to a sophisticated ventilator with all infusion pumps running smoothly, complete monitoring installed, and with a nurse present to care for the patient. Unless there are nursing, diagnostic or therapeutic procedures going on, the patient is in a more or less calm and controlled environment. In the case of an emergency, a team of well-trained nurses and physicians is available with all the necessary equipment at hand.

There may be situations when the patient has to leave these secure surroundings to be transported to the radiology department, the operating room or to some other department within the hospital, however. This transport may create an increased risk for mishaps and adverse events by disconnecting such critically ill individuals from the equipment in the ICU to some kind of transport gear, shifting them to another stretcher, and reducing the personal and the equipment around.

This article gives a review on the current literature of the intrahospital transport of critically ill patients. Its objective is to provide the reader with information about type and incidence of adverse effects, risk factors and assessment, and the efficiency and cost-effectiveness of

ICU = intensive care unit; pCO_2 = partial carbon dioxide tension; APACHE = Acute Physiology and Chronic Health Evaluation.

transferring such patients for diagnostic or therapeutic interventions within hospital. Furthermore, methods and guidelines to perform such transports safely are addressed, covering the personnel accompanying the patient, the equipment for monitoring the patient and treating complications, and the ventilator to be used.

A Medline search including the terms 'critical illness', 'transport of patients', 'patient transfer', 'critical care', 'monitoring' and 'intrahospital transport' was performed, and all information concerning the intrahospital transport of patients was considered, excluding review articles. Only studies published in the English or German language were used, however.

Adverse effects

Adverse effects may affect a variety of organ systems, may be related to the movement of the patient (dislocation of installations, drips, etc) or may be caused by equipment malfunctions. Furthermore, the reduced availability of personal, equipment and monitoring away from the ICU may be detrimental. These adverse effects may be of short-term or long-term duration, or require interventions.

The first indications that transport within hospital is a potentially dangerous undertaking were provided in the early 1970s, when arrhythmias were encountered in up to 84% of transports of patients with high-risk cardiac disease, which required emergency therapy in 44% of cases [1]. Significant complications such as bleeding and hypotension were observed in seven out of 33 transports of patients from the operating room to the ICU [2]. An early report compared the transport of postoperative patients from the operating room to the ICU with that of patients transferred from the ICU for diagnostic tests [3]. No complications or haemodynamic deteriorations were noted in the latter group, whereas the postoperative patients were subject to hypotension, hypertension or arrhythmias in 44% of the cases.

In more recent reports [4–9] the overall incidence of adverse effects during intrahospital transport was found to range from 6 to 71.1% (Table 1) [3–13]. An exact description of the severity of these complications is lacking in many studies and definitions differ in the others. However, major adverse effects with life-threatening disturbances that require interventions such as administration of vasoactive drugs, fluid boluses or even cardiopulmonary resuscitation, as well as those related to the disconnection of ventilatory, intravenous or intra-arterial lines, may be as high as 8% [4,6,9,10].

The majority of the studies were done with trauma and surgical patients, but medical patients and children were included in some. Although the highest rate of adverse events was noted in the one study with children [4], no clear relation of frequency and type of complication with the case-mix can be deduced. Neither the indication leading to the diagnostic evaluation nor the type of diagnostic procedure performed have been found to correlate with the type, number or severity of complications during transport [7,9]. In most of the studies the patient was accompanied by at least one nurse and one physician, who were sometimes supplemented with a respiratory therapist. The number of personnel involved in the transport was not found to influence the rate of complications [4]. Smith *et al* [6] observed a trend towards a reduced incidence of adverse effects if a physician was present during transport. In a recent study [11] a low rate of complications in 15.5% of patients was observed if a specially trained transport team accompanied the patient.

Cardiocirculatory adverse effects were noted in 0–47% of patients [7,9,12,13]. In particular, hypotension (a mean fall in systolic blood pressure of 40 mmHg or more) and arrhythmias were predominant in mechanically ventilated patients of a combined medical and surgical ICU [13]. Those events were closely related to periods of inadvertant hypoventilation or hyperventilation, with changes of the partial carbon dioxide tension (pCO_2) of up to 27 mmHg. In trauma patients transported for diagnostic studies, a change in blood pressure (of more than 20 mmHg) and in pulse rate (of more than 20 beats/min) was observed in 40 and 21% of the transports, respectively [7], which is quite similar to the findings of other investigators (Table 1) [8]. Although the overall incidence of complications was rather low in the study of Szem *et al* [9], they reported three cases of cardiac arrest and one case of pneumothorax that required chest tube placement. In medical patients electrocardiogram changes may occur that cannot be seen with standard electrocardiogram monitoring [14].

Respiratory complications were reported to occur in up to 29% of the transports, including a change in respiratory rate in 20% of the patients and a fall in arterial oxygen saturation in 2–17% of cases [7,8]. In one study [8] no change of pCO_2 and pH was found during transport.

In 125 transports of ventilated and nonventilated patients reported in another study [6], mishaps occurred in 34% of cases. Most of those problems were related to the equipment or the process of monitoring itself. Electrocardiogram lead disconnection (23%), monitor power failure (14%), a combination of those (10%), intravenous line or vasoactive drug infusion disconnection (9 and 5%, respectively), and disconnection from the ventilator (3%) were among the most frequent problems. Most mishaps were noted at the destination site either before or during the procedure, but not during the actual transport. Equipment-related mishaps occurred in 10% of transports in the study of Wallen *et al* [4]. These included malfunction of equipment, or loss of nasogastric or chest

Synopsis of investigations studying overall and specific complications during transport

Reference	No. of patients	No. of transports	Destination of transports	Rate of mishaps	Circulatory mishaps	Pulmonary mishaps	Equipment mishaps	Type of ventilation personnel
[3]	11 Postoperative	11	Radiol 11%	0%	0	NR	NR	Manual ventilation in 7 of 11, Personnel NR
[4]	139 Children	180	Radiol 30% OR 49% Others 21%	76.1%	HR 46.7% BP 21.1% Hypothermia 10%	RR 28.9% SaO_2 6.1%	10%	Manual ventilation Nurse and physician 82.2% Nurse only 17.8%
[5]	27 Head injured	35	Radiol 51% OR 49%	51%	Hypotension 9% Rise in ICP 23% Hypertension 14%	Hypoxia 9%	NR	Mechanical ventilator Personnel NR
[6]	NR (all critically ill)	127	Radiol 75% OR 25%	34%	NR	NR	34%	Type of ventilation NR Nurse and physician 45% Nurse and respiratory therapist 58%
[7]	56 Injured	103	Radiol 100%	68%	HR 21% BP 40%	RR 20% SaO_2 17%	0%	Mechanical ventilation Nurse and physician
[8]	83 Surgical/trauma	100	Radiol 100%	66%	HR 27% BP 36%	RR 20% SaO_2 2%	5%	Mechanical ventilation Nurse, physician and respiratory therapist
[9]	175 Surgical	203	Radiol 61% OR 39%	5.9%	Hypotension 1% Cardiac arrest 1.5%	Hypoxia 4%	NR	Mechanical or manual ventilation Physician and respiratory therapist
[10]	237 All critically ill	237	Radiol 100%	15.5%	NR	NR	NR	Specially trained nursing transport team
[11]	36 All critically ill	36	Radiol 100%	53%	Arrhythmia 5.5%	NR	11%	Mechanical ventilation
[12]	20 Medical/surgical	20	Radiol 100%	10%	0%	10%	0%	Manual ventilation Respiratory therapist
[13]	20 Medical/surgical	36	Radiol 100%	NR	Hypotension 19% Arrhythmia 5.5%	Change in pCO_2 56%	5.5%	Manual ventilation in 20 of 36 Nurse, physician and respiratory therapist

Not included are studies that compared specific transport protocols or equipment. BP, change in blood pressure; HR, change in heart rate; ICP, intracranial pressure; NR, not reported; OR, operation room; Radiol, radiology department; RR, change in respiratory rate; SaO_2, fall of arterial oxygen saturation.

tube, or were related to the endotracheal tube or the intravenous lines.

In a group of 27 patients with head injury (35 transports for diagnostic procedures or to the operating room) adverse effects were observed in 51% [5]. These included hypotension (systolic blood pressure below 90 mmHg in 8.6%), hypoxia (oxygen saturation below 90% in 5.7%) and increased intracranial pressure (42.9%, including 17% of cases with a pressure increase of more than 30 mmHg). Similar insults could be recorded in 60% of patients during the 4 h before transport and in 66% during the period after transport, however. It is important to note that, after transport, abnormal values that had not been present before were obtained in 17 patients.

Although much data has accumulated with respect to mishaps during the absence from the ICU, less is known about adverse long-term effects. In one prospective observation study [15] prolonged effects on respiratory function after intrahospital transports of critically ill patients were addressed. In 49 transports gas exchange had significantly decreased from a partial arterial oxygen tension : fractional inspired oxygen ratio of 267 at baseline to 220 1 h after transport. Even 24 h later a slight deterioration was still present. A fall in the partial oxygen tension : fractional inspired oxygen ratio of more than 20% from baseline was noted 1 and 24 h after transport in 42.8 and 12.2% of patients, respectively. Smith *et al* [6] reported that 24% of the patients of a study with 127 transports were considered, after having returned to the ICU, to be in worse condition than before the procedure. In a series of 273 mechanically ventilated patients who were transported from the ICU [16] the incidence of pneumonia was 24.4%, as compared to 4.4% in patients of similar severity of illness that had not been transported. This increased rate of complications could be attributed to the selection of patients that required transports to perform diagnostic (or therapeutic) interventions, however.

Whether the adverse effects observed are actually related to the transport itself or might be typical for critically ill patients irrespective of their location was assessed in only a few studies, and their findings are controversial. Wallen *et al* [4] compared patients over a period of 1–2 h before transport and during the consecutive transport to a diagnostic study. Although hypothermia (11.2%); change in heart rate (15.7%), blood pressure (21.3%) or in the respiratory rate of more than 20% (23.6%); or a change in oxygen saturation of more than 5% (5.6%) was observed in a significant number of transports, no such disturbances were noted during the observation period before transport. In contrast to these findings, Hurst *et al* [8] observed a similar rate of adverse events in a cohort of patients who were stationary in the ICU and matched for severity of illness [Acute Physiology and Chronic Health Evaluation (APACHE) II score] and age with the transport group (60 versus 66%). No difference was found with respect to number or type of physiologic changes.

Fatalities attributed to the transport were not reported in any of the communications reviewed.

Risk assessment and patient-related risk factors

To allow for a risk–benefit assessment, it would be helpful to identify patients with a high risk for the development of complications during or after transport.

In a study of 180 transports of critically ill children [4] it was shown that major corrective procedures during transport were necessary in 34.4% of mechanically ventilated patients, as opposed to 9.5% in nonventilated patients. Furthermore, the Therapeutic Intervention Severity Score and the duration of transport were significantly associated with the requirement for a major intervention or with any physiological deterioration (predominantly equipment related). The latter finding, however, could not be substantiated in several studies of adult patients [5–7,15]. For patients with severe head injuries the overall injury severity score was found to be the only predictor for the development of adverse effects during transport [5].

Not associated with the frequency of mishaps in a number of studies were the following: patients' age, diagnosis of the underlying disease, number of personnel accompanying the transport, duration of absence from the ICU, severity of illness (APACHE II), Glasgow Coma Score, number of lines in place, life-support modalities, destination of the transport (to the operation room versus to the radiology suite) and type of diagnostic procedure [6,7,9].

With regard to longer lasting detrimental effects on respiratory function, the only risk indicator was ventilatory support with positive end-expiratory pressure, whereas age, APACHE II score, duration of transport, destination of transport, pretransport gas exchange or peak airway pressure were not predictive of a respiratory deterioration [15].

Efficiency and cost-effectiveness

In a cohort of 103 consecutive transports for diagnostic evaluation in trauma patients, the results from these studies led to a change of therapy in 24% of the cases within 48 h after transport [7]. Changes in patient management resulting from a transport for a diagnostic procedure amounted to 39% in the experience of Hurst *et al.* [8], who studied surgical patients with trauma, and after major abdominal or vascular surgery. The main reasons for doing the diagnostic procedure were follow up (37%), identification of a septic focus (34%) and identification of the site of bleeding (14%). The examinations with the highest efficiency included angiography and abdominal computed

tomography, which resulted in therapeutic consequences in more than 50% of patients, whereas computed tomography of the head and the chest still resulted in a change of therapeutic management in 25%. In a study of 88 abdominal computed tomography examinations of critically ill surgical patients for reasons such as suspected abdominal focus (74%), acute necrotizing pancreatitis (12%) or suspected delayed intra-abdominal organ lesion after trauma (14%) [17] the results of the examination resulted in a change of therapy (operation or other invasive therapeutic intervention) in 43% of the patients. Similar studies of thoracic computed tomography in critically ill patients (predominantly trauma patients) to evaluate a potential pulmonary septic focus or a cause for a deterioration in gas exchange resulted in therapeutic consequences or a change in patient management in up to 70% of patients [18–20].

Thus, the overall yield of diagnostic procedures that require a transport of critically ill patients in terms of a direct and consecutive change of therapy is at least 25% and may be as high as 70%, provided that the decision to perform a specific procedure is based on criteria similar to the ones used in those studies. Unfortunately, little information was provided by investigators regarding why a specific procedure had been done and whether alternative methods would have been available. In summary, the efficiency of transports in trauma and surgical patients, and in search of a septic focus, a source of bleeding, or the identification and follow up of injuries appears to be moderate to fairly high, indicating a good risk:benefit ratio, as long as restrictive criteria are used to order those procedures. No such information is available for medical and pediatric patients. It can be assumed, however, that similar yields can be anticipated while looking for a focus of sepsis.

The cost of a transport was estimated to be $US465 in 1988 [7] and $US452 in 1992 [8]. No calculation of cost-effectiveness was reported in the literature reviewed.

Prevention of complications

Although patient-related risk factors are difficult to identify, equipment-related complications (which occur in up to one-third of transports) might be controlled more easily.

In 1993, guidelines for the transfer of critically ill patients were reported by a consensus committee that was formed by representatives from several major critical care societies [21]. They proposed requirements for the pretransport coordination and communication, for the personnel who accompany the patient, for the equipment needed and for the monitoring during transport.

It has been suggested [21] that a minimum of two people, one of them a critical care nurse, should accompany the patient. A physician is required for patients with unstable physiology who might need acute interventions. It is not clearly stated whether these latter conditions are met by mechanically ventilated patients. It appears justified that intubated patients are to be escorted by a medical doctor, however, on the basis of the large number of significant events that result in the necessity for an acute intervention in this group of patients. In those studies that reported on the personnel involved [4,6], at least two persons went with the patient but a physician was substituted by a respiratory therapist in 17.8–58% of transports. It should also be emphasized that personnel attending transports of critically ill patients may benefit from specific training [22].

Standard equipment includes the following [21]: a cardiac monitor with defibrillator; airway management equipment and a resuscitation bag (to allow for emergency intubation, coniotomy and manual ventilation via mask and tube); sufficient gas supplies; standard resuscitation drugs and intravenous fluids, as well as specific essential medications required by the patient transported (regulated by battery operated infusion pumps); and a portable ventilator for patients receiving mechanical ventilation.

The type of ventilation and the respirator to be used requires some discussion. One reason for the observed adverse effects on gas exchange could be the change from the ICU ventilator to a transport device, or even to manual ventilation. Although manual ventilation by a respiratory therapist has been said to result in a deterioration in blood gases in only 10% of transports [12], this positive experience was not shared by other investigators. Gervais *et al.* [23] compared blood gas variables during transport of 30 ventilator-dependent patients who were ventilated using either a manually operated ventilation bag with or without a volume meter at the exhalation valve of the bag, or a time-cycled, volume-constant, portable ventilator. Interestingly, patients with manual ventilation alone or the transport ventilator were significantly hyperventilated, as opposed to those in whom a volume meter was used to control manual ventilation. This finding was also reflected by an increase in pH in the former two groups. Arterial oxygen tension was not affected in a clinically significant way. In a follow-up study [24], the same group demonstrated that four out of five portable ventilators from different manufacturers produced either severe hyperventilation (particularly at low minute ventilation), or considerable hypoventilation under conditions of reduced compliance, as may be encountered in patients with acute respiratory failure or acute respiratory distress syndrome [24]. In 20 manually ventilated patients (not using a volume meter) mean changes in pCO_2 and pH of 9 mmHg and 0.08, respectively, were observed. Using a portable ventilator these blood gas changes could be significantly reduced to 4 mmHg and 0.05, respectively. Nevertheless, the complication rate in the mechanically ventilated patients was still 44% [13].

One possibility to reduce inadvertent ventilation problems might be the use of improved monitoring equipment, particularly of tidal or minute ventilation (see below). Bearing in mind the limitations of many portable ventilators, the use of sophisticated transport carts equipped with a standard ICU ventilator and the necessary gas supply should be considered [25–28]. Such carts could be hooked to the patient bed and moved fairly easily. Monitoring devices and infusion pumps can be implemented into the cart with its battery. Such equipment is widely used for interhospital transport of critically ill patients between institutions, and is being increasingly applied to intrahospital transport. Controlled studies showing a reduction in adverse events during and complications from transport using such equipment are still lacking, however, although one group did report zero unanticipated problems with such equipment [28]. Although it appears sensible to assume improved patient safety, the cost-effectiveness remains to be shown. Furthermore, suction devices should accompany the patient, as illustrated by a case report of a patient with acute airway obstruction from a mucus plug [29]. A pump-driven suction device appears to be preferable, however.

Minimum requirements for monitoring patients during transport should be continuous electrocardiography, pulse oxymetry and the intermittent measurement of blood pressure, respiratory rate and pulse rate [21]. In specific patients, capnometry, continuous blood pressure reading and further monitoring (such as of intracranial pressure, cardiac output and filling pressures) may be beneficial. Many of the complications reported during transport were caused by equipment not functioning correctly, however. The use of more equipment could result in a higher probability of equipment-related problems that might divert the attention of the personnel from the patient to the device. In one study of capnometry [30] more than 50% of the complications (four out of seven) were due to malfunction of the monitoring and not caused by actual physiologic disturbances.

Of particular importance appears the possibility of measuring the major ventilation parameters such as tidal volume or minute ventilation [23,31]. Unfortunately, this is not possible with most portable ventilators.

In some cases the hazards of transporting a patient could be prevented by performing diagnostic or therapeutic procedures within the ICU or choosing alternative (albeit equivalently effective) procedures that may render a transport of the patient unnecessary. Such interventions may comprise the following: use of chest ultrasound in detecting intrathoracic pathologies [32–34]; the introduction of new mobile computed tomography scanners that can be used in the ICU [35]; the application of conventional or dilatational percutaneous tracheostomy in the ICU, instead of transferring the patient to the operating room [36–38]; the placement of percutaneous endoscopic gastrostomy and of inferior vena cava filters [39]; fiberoptic intraparenchymal pressure monitoring instead of operative ventriculostomy [40–42]; scheduled reoperations for peritonitis with open abdomen in the ICU [43]; and many others [44].

Conclusion

Adverse effects during and after transport of critically ill patients are frequent. On the other hand, a change in patient management results from about half of the procedures that necessitate transport, indicating a good efficiency. Although a few patient-related risk factors can be identified, the rate of equipment-related adverse events may be as high as one-third of all transports. Thus, particular attention has to be focussed on the personnel, equipment and monitoring in use. Standard guidelines have been published. A potential weakness remains the mode of ventilation and the type of ventilator used during transport, as well as the extent of respiratory monitoring. In patients who require ventilation, it appears useful to use either portable ventilators that are equipped with a volume meter, or specifically constructed carts including standard ICU ventilators. To further reduce the rate of inadvertent mishaps from transports, alternative diagnostic modalities or techniques, and performing surgical procedures in the ICU should be considered.

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AHA Scientific Statement

Comparing On-Pump and Off-Pump Coronary Artery Bypass Grafting

Numerous Studies but Few Conclusions

A Scientific Statement From the American Heart Association Council on Cardiovascular Surgery and Anesthesia in Collaboration With the Interdisciplinary Working Group on Quality of Care and Outcomes Research

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Abstract—One of the most hotly debated and polarizing issues in cardiac surgery has been whether coronary artery bypass grafting (CABG) without the use of cardiopulmonary bypass or cardioplegia (off-pump CABG, or OPCAB) is superior to that performed with the heart-lung machine and the heart's being chemically arrested (standard CABG). Various clinical trials are reviewed comparing the 2 surgical strategies, including several large retrospective analyses, meta-analyses, and the randomized trials that address different aspects of standard CABG and OPCAB. Although definitive conclusions about the relative merits of standard CABG and OPCAB are difficult to reach from these varied randomized and nonrandomized studies, several generalizations may be possible. Patients may achieve an excellent outcome with either type of procedure, and individuals' outcomes likely depend more on factors other than whether they underwent standard CABG or OPCAB. Nevertheless, there appear to be trends in most studies. These trends include less blood loss and need for transfusion after OPCAB, less myocardial enzyme release after OPCAB up to 24 hours, less early neurocognitive dysfunction after OPCAB, and less renal insufficiency after OPCAB. Fewer grafts tend to be performed with OPCAB than with standard CABG. Length of hospital stay, mortality rate, and long-term neurological function and cardiac outcome appear to be similar in the 2 groups. To definitively answer the remaining questions of whether either strategy is superior and in which patients, a large-scale prospective randomized trial is required. (*Circulation*. 2005;111:2858-2864.)

Key Words: AHA Scientific Statements ■ grafting ■ trials ■ morbidity ■ mortality

One of the most hotly debated and polarizing issues in cardiac surgery has been whether coronary artery bypass grafting (CABG) without the use of cardiopulmonary bypass (CPB) or cardioplegia (off-pump CABG, or OPCAB) is superior to that performed with the heart-lung machine and the heart's being chemically arrested (standard CABG). Initial descriptive studies reported excellent to outstanding outcomes with OPCAB, with the suggestion in many studies of less use of resources, less blood loss, less morbidity, and a shortened length of hospital stay; however, these early studies tended to be nonrandomized clinical reports rather than rigorously controlled clinical studies. Since these early reports, several randomized trials have been completed. Nevertheless, it remains uncertain whether OPCAB is associated with a distinct advantage or whether the outcome with OPCAB is similar or identical to that achieved by CABG with CPB, which has been the "gold standard." Various clinical trials are reviewed comparing the 2 surgical strategies, including several large retrospective analyses, meta-analyses, and the randomized trials that address different aspects of standard CABG and OPCAB. Finally, we examine the various subtopics involving specific discussion criteria for

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these studies. Because of space constraints, this article cannot be an exhaustive review of studies that have compared the 2 strategies on clinical or physiological grounds. It is the purpose of this consensus article to briefly review selected clinical data comparing OPCAB with standard CABG and to summarize the relative merits of and indications for the 2 strategies for myocardial revascularization.

Retrospective Studies

Because techniques of OPCAB have markedly improved during the past several years and many surgeons have reached a plateau on the "learning curve," older studies may not be as useful for comparison. A retrospective study by Racz et al[1] analyzed >68 000 patients treated in New York state between 1997 and 2000. Of these patients, >9000 revascularizations were performed off pump. Of those patients undergoing OPCAB, there were higher proportions of older patients; women; and patients with low ejection fraction, previous CABG, stroke, peripheral vascular disease, left ventricular hypertrophy, congestive heart failure, calcified aortic disease, and renal failure. In the standard CABG group, a high number of patients had acute myocardial infarction (MI), shock, cardiopulmonary resuscitation, and left main disease, as well as more diseased arteries than in the OPCAB group. Thus, a comparison is difficult to make; however, risk-adjusted mortality was not different between the groups. In this study, no significant difference was found in the incidence of death, perioperative MI, wound infection, renal failure requiring dialysis, or respiratory failure. There were, however, significantly higher rates of stroke (2.0% versus 1.6%, $P=0.003$) and bleeding requiring reoperation (2.2% versus 1.6%, $P<0.001$) in the standard CABG group. A significantly higher risk of gastrointestinal complications (1.2% versus 0.9%, $P=0.003$) was observed in the OPCAB group. Hospital length of stay was longer in the standard CABG group by 1 day. At 3-year follow-up, patients in the standard CABG group had a higher survival rate (89.6% versus 88.8%, $P=0.022$) and need for repeat revascularization (percutaneous coronary intervention or CABG, 84.7% versus 82.1%, $P<0.0001$). In data from the last 2 years of the study (ie, excluding the first year), the survival benefit disappeared but the freedom from death and revascularization remained. The authors concluded that patients undergoing standard CABG with CPB have better rates of long-term survival and freedom from repeat revascularization.

In another retrospective nonrandomized study, Mack et al[2] reviewed 17 401 patients (7283 OPCAB) who underwent surgery between 1999 and 2001. The percentage of patients with congestive heart failure, chronic obstructive pulmonary disease, renal failure, stroke, peripheral vascular disease, and previous CABG was higher in the OPCAB group. The unadjusted mortality rate was 1.9% in the OPCAB group, versus 3.5% in the standard CABG group ($P<0.001$). Propensity matching was done in all patients with multivessel disease to minimize selection bias and to provide for similar predicted risks for multiple variables. In the propensity-matched groups, the mortality rate was 2.2% in the OPCAB group, versus 3.7% in the CPB group ($P<0.001$). The rate of complications was significantly lower in the OPCAB group, including overall number of complications, use of blood products, wound infection, reoperation for bleeding, atrial fibrillation, permanent stroke, gastrointestinal and respiratory complications, renal failure, MI, and multiorgan failure. Only transient stroke, reoperation for graft occlusion, and pulmonary embolus were not significantly different between the groups. These authors concluded that OPCAB is associated with less morbidity and mortality and that patients at high risk tend to yield the most benefit (ie, women, older adults, and patients undergoing reoperation).

The Cleveland Clinic reviewed a retrospective series of 812 propensity-matched patients (out of a total of 3712 patients undergoing isolated CABG during a 4-year period), with 406 patients in both the standard CABG and OPCAB groups.[3] Patients in both groups were well-matched with regard to multiple preoperative variables, except that peripheral vascular disease and previous stroke were more common in the OPCAB group and NYHA classification was higher in the standard CABG group. Standard CABG patients received a greater number of bypass grafts (3.5 ± 1.1 versus 2.8 ± 1.0, $P<0.001$) and had less incomplete revascularization (18% versus 31%, $P<0.001$) than did OPCAB patients as judged by the operating surgeon. Death, stroke, and MI were similar in both groups. OPCAB patients had less frequent renal failure requiring dialysis (1.5% versus 0%, $P=0.03$), red blood cell use (53% versus 42%, $P=0.002$), and sternal wound infections (2.0% versus 0.2%, $P=0.04$). The median follow-up period was 3.8 years for the standard CABG patients and 2.6 years for OPCAB patients. Rates of survival and freedom from MI and coronary reintervention were not significantly different, either alone or in combination, between groups. These authors concluded that mid-term outcomes with OPCAB and standard on-pump CABG were equivalent.

Meta-Analyses

This section briefly examines the results of the 2 strategies described in meta-analysis studies published between 1997 and 2003, in which large groups of patients from several institutions were reviewed. Reston et al[4] reviewed 53 studies, of which 10 were randomized control trials, 5 were prospective controlled trials, and 38 were retrospective controlled studies. The total review involved 46 621 patients. These authors found significantly less MI, stroke, reoperation for bleeding, renal failure, atrial fibrillation, and wound infection in the OPCAB group in the short term. In terms of mid-term outcome, the recurrence of angina was no different (odds ratio [OR]=1.28, $P=0.309$, confidence interval [CI]=0.79 to 2.05), but the risk of repeat intervention by percutaneous or open strategy (OR=3.63, $P=0.0001$, CI=1.91 to 6.78) or death was lower in the standard CABG group (OR=0.49, $P=0.008$, CI=0.29 to 0.82).

Parolari et al[5] reviewed 9 randomized trials reported in the literature from 1990 to 2002. Six of these studies were included in Reston and associates' article. The analysis involved 558 patients who had undergone standard CABG and 532 patients who had undergone OPCAB. The only studies reviewed were those in which the average number

of grafts was >2. The conclusions were that the composite end points of death, stroke, and MI within 30 days favored the OPCAB group but were not significantly different between the 2 groups (OR=0.48, P=0.08, CI=0.21 to 1.09).

Prospective Randomized Trials

The best of the large clinical trials remain those that are prospective, randomized, blinded studies. In this setting, however, such studies would be difficult to design because the surgeon performing the operation, anesthesiologist, nurses, and other personnel clearly know which patient received what type of operation, and thus there may be bias in the treatment of the patients during and after surgery.

A multicenter prospective randomized study was performed by Gerola and colleagues[6] in Brazil and involved 160 selected low-risk patients with 1- or 2-vessel coronary artery disease. The exclusion criteria included left ventricular dysfunction (ejection fraction <35%), renal failure, left circumflex territory lesions, urgent or emergent procedures, hemodynamic instability, concomitant significant carotid disease, age >70 years, and other comorbidities such as hepatitis, AIDS, and morbid obesity. No significant difference was seen in time to extubation, pulmonary complications (anything causing hypoxia), MI, postoperative blood loss, need for blood transfusions, wound infections, neurological dysfunction, or atrial fibrillation. Length of stay in the intensive care unit (ICU) was similar. Postoperative length of stay was not significantly different (8.0±3.1 days in the standard CABG group versus 7.6±3.4 days in the OPCAB group [P=0.75]). On the other hand, creatine kinase-MB levels were significantly higher in the standard CABG group at 0 (P=0.0001), 8 (P=0.0014), and 16 (P=0.0071) hours postoperatively, as compared with the respective levels in patients in the OPCAB group. Enzyme release was not different at 24 hours. The number of patients requiring vasoactive drugs in the postoperative period was higher in the standard CABG group (23.8% versus 8.8% patients, P=0.004). Mortality rate was not significantly different between groups (3.7% versus 1.2%, P=0.62). The authors concluded that in these groups of patients neither procedure was superior to the other.

A single institutional trial was undertaken by Straka and colleagues[7] in the Czech Republic. This study involved 400 consecutive, unselected patients randomized to standard CABG or OPCAB. The only exclusion criterion was the need for an emergency operation. There were no significant differences between groups in postoperative mortality, MI, stroke, atrial fibrillation, wound infections, or renal failure requiring dialysis. The number of distal anastomoses for patients was higher in the standard CABG group (2.7 versus 2.3, P<0.001). The total blood loss was higher in the standard CABG group (680 versus 560 mL, P<0.001), but the number of transfused patients and reoperations for bleeding was not significantly different. Creatine kinase-MB levels were higher at 6, 18, and 36 hours after surgery in the standard CABG group, as compared with the respective levels in the OPCAB group (P<0.001). The time to extubation, length of ICU stay, and total hospital length of stay were not significantly different between groups. The authors concluded that the OPCAB strategy can be applied widely to unselected patients and is as safe and effective as conventional standard CABG.

The results of a single institutional trial were reported from Emory University by Puskas and colleagues.[8] Two hundred patients were randomized to standard CABG or OPCAB. Candidate targets for revascularization were determined before randomization. The only exclusion criteria were the presence of cardiogenic shock or preoperative intra-aortic balloon pump. There were no significant differences between groups in terms of mortality, reoperation for bleeding, MI, arrhythmias, stroke, new renal failure and/or dialysis, wound infections, or operative time. The number of grafts for patients was 3.4±1.0 in the OPCAB group versus 3.4±1.1 in the standard CABG group (P=NS). Thus, in this study, the completeness of revascularization was not different between groups. Fewer patients required red cell transfusions postoperatively (26% versus 44%, P=0.007) in the OPCAB group than in the standard CABG group. Hematocrit on postoperative day 3 (29.3±4.16 versus 28.2±3.23, P=0.05) and at discharge (30.6±3.74 versus 29.5±3.30, P<0.05) was marginally higher in the OPCAB group than in the standard CABG group. Creatine kinase-MB and troponin I levels were significantly higher at 8, 16, and 24 hours postoperatively in the standard CABG group (P<0.001). The ICU length of stay was not significantly different (23.9±14.5 versus 26.8±24.9 hours, P=0.82). The postoperative hospital length of stay was 1 day shorter in the OPCAB group (5.1±6.5 versus 6.1±8.1 days, P=0.005). The authors' conclusions were that the OPCAB strategy provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay.

Recently, Puskas and colleagues reported additional results from the above study in a separate article.[9] They reported graft patency, clinical and quality-of-life outcomes, and cost among patients while in the hospital and at 1-year follow-up in the OPCAB and CABG groups. They found that graft patency was similar for the OPCAB versus the standard CABG group at 30 days (absolute difference, 1.3%; −0.66% to 3.31%; P=0.19) and at 1 year (absolute difference, −2.2%; −6.1% to 1.7%; P=0.27). There were no differences in the rates of death, stroke, MI, angina, or reintervention up to 1 year. The true generalizability of this study may be questionable because the pattern of referrals to this surgeon may favor patients who are suitable for OPCAB.

Another recent trial by Khan et al[10] was carried out at the Royal Brompton Hospital in London and involved 103 patients who required at least 3 grafts (as determined by preoperative angiography) and were randomized to standard CABG or OPCAB. Exclusion criteria included recent stroke or MI (6 months/3 months), age <30 or >80 years, carotid stenosis >70%, and a left ventricular ejection fraction <20%. The groups were similar with regard to preoperative variables, except that the number of planned grafts was higher in the standard CABG group than in the

OPCAB group. The authors emphasized that the patients were randomized after their angiograms had been reviewed and the need for >3 grafts per patient determined. The groups were similar with regard to completeness of revascularization, territories grafted, and subjective native vessel quality. There were no deaths in either group. The time to extubation and lengths of ICU stay and hospital stay were not significantly different. There were 2 reoperations for bleeding in the standard CABG group versus 0 in the OPCAB group ($P=0.13$). Whereas blood loss was not significantly different (898±434 mL in the standard CABG group versus 1031±552 mL in the OPCAB group; P=NS), more patients required transfusion of both packed red blood cells (32 versus 20 patients) and clotting factors (14 versus 2 patients) in the standard CABG group than in the OPCAB group. Troponin levels were higher in the standard CABG group at 6 ($P<0.001$) and 12 hours ($P<0.001$) but were not different at 24 hours. Of the 103 patients, 82 were reevaluated and underwent angiography at 3 months. There were no deaths, strokes, or MIs, and Canadian Cardiovascular Society/NYHA classes were similar at 3 months. The striking finding in this study was that graft patency was 98% in the standard CABG group and 88% in the OPCAB group ($P=0.002$). Graft patency of the left anterior descending graft was 100% in the standard CABG group and 92% in the OPCAB group ($P=0.07$). Circumflex graft patency was 95% in the CPB group and 87% in the OPCAB group ($P=0.25$). Right coronary artery graft patency was 100% in the standard CABG group and 84% in the OPCAB group ($P=0.01$). The left internal thoracic artery graft patency was 100% in the standard CABG group and 92% in the OPCAB group ($P=0.05$). The patency of the radial arteries operated on in this study was 100% in the standard CABG group and 76% in the OPCAB group ($P=0.01$). Saphenous vein graft patency was 95% in the standard CABG group and 91% in the OPCAB group ($P=0.42$). The authors concluded that OPCAB may not be widely applicable but may have a role in selected patients with good targets or serious comorbidities. The reduced graft patency at 3 months in the OPCAB group has been questioned by other investigators, and this study has been criticized because of the perceived inexperience of the surgeons and other issues.

Finally, Nathoe et al[11] performed a multicenter study involving 281 patients, 142 of whom underwent OPCAB. Patients in this study had predominantly 1- or 2-vessel coronary artery disease. Patients were excluded from this study if they required emergency surgery, had a recent MI, or had poor left ventricular function. The mean number of grafts was similar in both groups, with 2.6 in the standard CABG group and 2.4 in the OPCAB group. No significant difference was observed between groups in the primary composite end points of freedom from death, MI, stroke, and revascularization. No significant difference was observed between groups with regard to the secondary end points of freedom from angina and myocardial ischemia (as demonstrated by exercise stress test). Seventy patients (63.6%) underwent angiography at 1 year (42 on pump and 28 off pump). Unfortunately, 36.4% of patients declined to undergo angiography because of a lack of symptoms. In contrast to the prior study, no significant difference in graft patency was seen between the groups. Overall patency rates were 93% and 91%, respectively, in the CABG and OPCAB groups (absolute difference, 2.0%; CI=−6.5 to 10.4). Nathoe et al concluded that there was no significant difference in cardiac outcome between on-pump CABG and OPCAB.

The following sections discuss prospective randomized trials of patients at high risk of neurological morbidity, patients with poor left ventricular function, patients who are at high risk by virtue of multiple comorbidities, older adult patients, patients with an atheromatous aorta, and patients who have had a recent acute MI.

Patients With Neurological Morbidity

Multiple studies with transcranial Doppler have suggested higher rates of cerebral embolization in CPB patients than in OPCAB patients. Most studies that examine neurocognitive function show slightly more decline among standard CABG patients relative to OPCAB patients in the short term (<2 to 3 months) but fail to show significant differences at 1 year.[12] Quality-of-life assessments have not been shown to be significantly different at 1 year.[13–15]

Patients With Left Ventricular Dysfunction

Three recent studies have reviewed, in a retrospective nonrandomized fashion, the outcomes of patients with left ventricular ejection fractions <35% undergoing surgical revascularization. The OPCAB patients tended to have higher NYHA class scores, fewer recent MIs, and more type 1 diabetes mellitus but otherwise were well matched for other variables. In 2 of the 3 studies, standard CABG patients had significantly more grafts, with the third study showing a trend toward more grafts. There were no significant differences in MI, renal failure, reoperation for bleeding, wound infections, or stroke. Thirty-day mortality rates tended to be higher in the standard CABG patients than in the OPCAB group (14.1% versus 6.6%, $P=0.05$).[16] In one study, mid-term survival was slightly higher at 1 (92% versus 85%), 2 (90% versus 82%), and 3 (87% versus 73%) years, respectively, in the standard CABG group than in the OPCAB group, but the differences were not statistically significant.[16–18]

Patients With Multiple Comorbidities

Four recent studies reviewed, in a retrospective nonrandomized fashion, patients who were considered high risk because of the presence of multiple preoperative comorbid factors. These risk factors included recent MI, left main disease, left ventricular dysfunction, renal failure, previous stroke, unstable angina, heart failure, shock, chronic obstructive pulmonary disease, age >70 years, and urgent or emergent surgery.[19–22]

The mean age at the time of operation was significantly higher in the OPCAB group in one study[21] and tended to be higher in another.[22] More patients in the standard CABG group had unstable angina, severe heart failure symptoms, and 3-vessel disease. The OPCAB patients tended to have higher numbers of risk factors. There were no significant

differences for the majority of preoperative risk factors. In 2 studies, the number of grafts placed was greater in the standard CABG group than in the OPCAB group, but the numbers were similar in the other studies. Mortality was significantly higher in the standard CABG group in one study and not different in the other 3 studies. ICU and hospital length of stay were lower in the OPCAB group. In these reports, postoperative blood loss, need for transfusion, arrhythmias, and ventilation time were higher in the standard CABG group than in the OPCAB group. Perioperative MI was lower in the OPCAB group in one study but was not significantly different in the other 3 studies. Neurological, renal, and infectious complications were similar in all studies. Only one study looked at mid-term outcomes (mean follow-up, 16±9 months) and found that cardiac death (P=0.001), recurrent ischemia (P<0.0001), and graft dysfunction (P=0.05) all were significantly higher in the OPCAB group.[22]

Older Adult Patients

Two retrospective and nonrandomized studies reviewed the specific subgroup of older adult patients. In one study, patients >75 years old were examined, and in the other study, patients were >80 years old. Preoperative characteristics were similar in both studies. The number of grafts placed was higher in the standard CABG groups in both studies.[23,24] The incidence of stroke, prolonged respiratory failure, bleeding, transfusions, and ICU and hospital length of stay all were higher in the standard CABG groups than in the OPCAB group. Reoperation for bleeding, MI, renal failure, wound infections, and operative mortality were not significantly different. One study had mid-term follow-up data, and no significant difference between groups for overall survival and event-free survival was observed.

Patients With Atheromatous Aorta

Two retrospective and nonrandomized studies addressed the question of whether coronary revascularizations in patients with a severely atheromatous aorta should be performed off pump.[25,26] Both studies used propensity matching to identify an equal number of patients in the OPCAB and standard CABG groups with similar preoperative characteristics and intraoperative transesophageal echocardiography findings of severe ascending aortic atheromatous disease. Mortality and stroke were higher in the standard CABG groups in both studies. The first study by Sharony et al[25] reported an in-hospital mortality rate of 11.4% for standard CABG, versus 3.8% for OPCAB (P=0.003), and a stroke rate of 4.7% for standard CABG, versus 2.4% for the OPCAB group (P=0.08). In their second study 1 year later, they reported an in-hospital mortality rate of 11.4% for the standard group and 6.5% for OPCAB (P=0.058) and a stroke rate of 5.7% versus 1.6% (P=0.03).[26] Freedom from any complication was higher in the OPCAB group in both studies. Three-year follow-up was done in both studies, with one study showing increased survival in the OPCAB group and the other showing no significant difference.[25,26] It is thought that the decreased rate of complications in the OPCAB group is the result of the decreased clamping of the difficult aorta for that technique.

Findings Favoring On-Pump CABG or OPCAB

Findings favoring OPCAB
Probably less bleeding
Probably less renal dysfunction
Probably less short-term neurocognitive dysfunction, especially if aorta is calcified
Possibly shorter overall length of hospital stay
Findings favoring on-pump CABG
Less technically demanding
Shorter "learning curve"
Possibly better long-term graft patency
Easier to graft posterior (circumflex) bypass targets
Probably more bypass grafts constructed

Patients With Acute MI

A retrospective study from Israel reviewed 225 patients undergoing CABG soon after acute MI (106 CABGs were performed off pump),[27] and all patients had similar preoperative characteristics. All operations were performed on patients within 1 week of experiencing an acute MI. The OPCAB group had significantly more patients with 1 or 2 grafts, and standard CABG patients had significantly more patients with ≥3 grafts. The standard CABG patients had more bilateral internal thoracic artery grafts (58% versus 1.9%, P<0.001) and more circumflex grafts (90% versus 11.5%, P<0.001). The mortality rate was higher in the standard CABG group (12% versus 3.8%, P=0.027), but the majority of deaths occurred in patients undergoing standard CABG within 48 hours of MI. The mortality rate of patients operated on >48 hours after MI was not significantly different (5.8% versus 3.4%, P=0.44). Late mortality was lower and freedom from angina and reintervention was higher in the standard CABG group, with a follow-up of 2 to 9 years.[27]

Summary

Although definitive conclusions about the relative merits of standard CABG and OPCAB are difficult to reach from these varied randomized and nonrandomized studies, several generalizations may be warranted (Table). Patients may achieve an excellent outcome with either type of procedure, and individuals' outcomes likely depend more on factors other than whether they underwent standard CABG or OPCAB. Mortality rates vary between <1% to >6% in most databases, and thus the skill of the surgeon, quality of the institution, and systems approach play a much greater role in determining the outcome after surgical coronary revascularization.

There appear to be trends in most studies, however. These trends include less blood loss and need for transfusion after OPCAB, less myocardial enzyme release after OPCAB up to 24 hours, less early neurocognitive dysfunction after OPCAB, and less renal insufficiency after OPCAB. Of note, patients who require urgent or emergent conversion from off-pump to on-pump revascularization have a much greater risk of mortality, postoperative cardiac arrest, and multisystem organ failure than do patients initially undergoing on-pump CABG.[28,29] In addition, fewer grafts tend to be performed with OPCAB than

with standard CABG in many studies, and no study in the literature reports more grafts being placed with OPCAB. Length of hospital stay, mortality, and long-term neurological function and cardiac outcome appear to be similar in the 2 groups. A recent report from a prospective study suggested that graft patency may be significantly lower with OPCAB than with standard CABG,[10] but this needs to be verified or dismissed by additional prospective randomized studies. The greatest utility for OPCAB is probably the severely calcified or diseased aorta in which manipulation or clamping of the aorta can be associated with dire neurological consequences. To definitively answer whether either strategy is superior and in which patients, a large-scale prospective randomized trial will be required in which the surgeons and other physicians caring for the patient do not have prior knowledge of the operation the patient is to undergo. Also, optimally, the surgeon should not know the revascularization strategy until just before entering the operating room, and subsequent caregivers in the ICU should remain blinded after surgery. Finally, the surgeons should be equally skilled with either type of procedure. Surgeons who perform either OPCAB or standard CABG almost exclusively should not be part of such a study. Criticism has been aimed at Khan et al with regard to the relative inexperience of the surgeons in their study in performing off-pump surgery.[10] On the other side, there is the question of a randomized study performed by a single surgeon whose referral pattern may reflect those cases more easily amenable to OPCAB. Such a trial will be difficult to design and execute. The need for such a large prospective trial was suggested at a recent NIH working group composed of cardiac surgeons and other clinicians. The Department of Veterans Affairs currently is enrolling patients into a large prospective trial. Ultimately, whether a patient benefits more from standard on-pump CABG or OPCAB may depend more on the familiarity, comfort, and skill of the individual surgeon with either procedure than on an intrinsic benefit. Both the OPCAB and standard CABG procedures usually result in excellent outcomes, and neither should be judged to be inferior to the other.

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Minimally Invasive Direct Coronary Artery Bypass and Off-Pump Coronary Artery Bypass Surgery: Anesthetic Considerations

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The use of beating heart techniques for cardiac surgery is not new, and was first introduced in the 1950s in an attempt to offer hope to patients suffering from cardiac disease at a time when extracorporeal circulation was in its infancy. Coronary artery disease (CAD) had not yet exploded into the epidemic it would later become in the 1970s, and so most surgery focused on the more significant issue of valvular lesions, at that time still a common result of rheumatic heart disease. A sweeping change took place in cardiac surgery in the 1950s and 1960s, and it emerged in the 1970s in a form similar to today's: extracorporeal circulation (ECC)-assisted arrested heart surgery, focusing primarily on coronary artery bypass surgery, in response to the explosion in CAD. Although refinements have been made to cardiac surgical techniques, such as the use of membrane oxygenators instead of bubble oxygenators and the use of arterial grafts in place of venous grafts, the procedure itself has remained essentially unchanged.

So why did off-pump beating heart surgery and minimally invasive direct coronary artery bypass (MIDCAB) techniques develop? The search for a better way to perform coronary artery bypass graft (CABG) surgery was driven by two forces: (1) the realization that conventional heart surgery

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carried a burden of significant morbidity and mortality, and (2) by competing pressure from interventional cardiologists whose own specialty had itself undergone a radical transformation over the last 20 years. ECC is associated with many adverse outcomes, including stroke, atrial fibrillation, and blood product transfusions. The circuit itself is known to cause systemic inflammation and systemic coagulation factor and platelet activation. As the evidence mounted demonstrating that ECC was not without risk despite ongoing improvements in circuit design, new developments in the field of interventional cardiology were giving patients and physicians a choice for treatment of CAD. Although to this day no study has demonstrated a superior outcome in patients undergoing percutaneous coronary intervention (PCI) over cardiac surgery, and in many cases the results have been shown to be inferior, the rates of PCI have exploded, whereas those of CABG surgery are in slow decline. One cause may be that the "gatekeepers," cardiologists who can choose to refer patients to either another cardiologist (or themselves) or a cardiac surgeon, often choose to refer to themselves or within the specialty. Another large reason behind the increase in PCI is the patients' desire to have the procedure with the least amount of risk, even if the long-term results are less favorable. This phenomenon, known as immediacy, is commonly encountered when people make choices between two potentially risky procedures, with distant risk not being weighted as heavily as more immediate risk.

In an attempt, therefore, to reduce the risk associated with conventional ECC-assisted CABG, many cardiac surgeons began to explore the feasibility of performing CABG surgery without ECC, off-pump coronary artery bypass surgery (OPCAB), and some looked at the use of OPCAB with only a small thoracotomy or hemisternotomy for isolated left internal mammary artery (LIMA) to left anterior descending artery surgery (LAD), the MIDCAB technique. This line of investigation has also led to the development of robotic bypass techniques using port access, as well as the development of minimally invasive mitral valve and aortic valve replacement techniques. Both of these are beyond the scope of this article, which focuses on the surgical and anesthetic consideration for OPCAB and MIDCAB surgery. The final section reviews outcomes of these surgical procedures.

Surgical considerations for off-pump coronary artery bypass surgery/ minimally invasive direct coronary artery bypass surgery techniques

The MIDCAB technique was developed to specifically address the patient who has an isolated high grade lesion of the LAD (Fig. 1). It essentially involves a right mini-thoracotomy through which both the harvesting of the LIMA and anastomosis of the LIMA to LAD is performed. The patient thus avoids both a sternotomy and cardiopulmonary bypass.

OPCAB can be thought of as a more generalized approach to patients who have CAD. Unlike MIDCAB, it is not limited to patients who have isolated LAD disease, and four and five vessel bypasses can be performed with

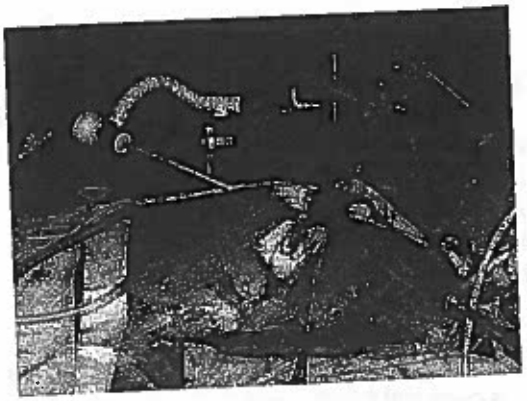

Fig. 1. MIDCAB technique showing the small (5–7 cm) incision, along with the stabilizer.

this technique. OPCAB surgery is performed through a midline sternotomy. The harvesting of the conduits proceeds in a similar fashion to conventional surgery. To permit anastomosis, the heart is positioned in the desired location. This is usually facilitated through the use of pericardial sutures behind the heart to lift the heart out of the chest, followed by the application of a positioning device that exposes the diseased coronary artery in a manner that permits anastomosis of the conduit. Two sutures are then placed through the myocardium in a fashion that allows control of the proximal and distal aspects of the vessel to be bypassed. After this a stabilizer is placed to reduce motion around the vessel of interest (Fig. 2). Before opening the vessel the sutures are tightened, thus preventing both antegrade and retrograde bleeding of the vessels. Following incision into the coronary artery, a shunt is often placed to allow distal perfusion during anastomosis. The anastomosis is then performed, the shunt removed before completing the anastomosis, and

Fig. 2. OPCAB technique showing the Octopus (Medtronic, Minneapolis, Minnesota) suction stabilizer system.

finally the sutures and stabilizer are removed upon completion. Some surgeons complete all distal anastomosises before starting the proximals, whereas some prefer to attach each distally grafted vessel to the aorta before continuing with the next vessel. Although this latter approach ensures an increase in blood flow to the myocardium with each successive graft, it requires multiple aortic cross clamps, which may not be ideal in patients who have diseased aortas. Likewise some surgeons perform the LIMA-LAD graft first to improve coronary flow to the myocardium.

Patient selection

There remains much debate and controversy over the ideal candidate for OPCAB or MIDCAB surgery. Theoretically, the ideal candidate is one who has good cardiac function (ejection fraction [EF] >40%), with isolated disease of the ascending/arch of the aorta, and who is thus at risk for postoperative neurologic complications. Anyone who has a small body habitus may also be a good candidate for OPCAB surgery, because it avoids hemodilution from the pump prime. Unfortunately, these patient populations typically have poor distal anastomotic targets, which is a relative contraindication to bypass. For the same reason, intramyocardial targets often are difficult to bypass with the OPCAB or MIDCAB techniques, and often force a surgeon to convert to conventional cardiac surgery.

Some surgeons feel that poor left ventricular (LV) function is a good indication for OPCAB surgery because it avoids cardioplegic arrest and the possibility of a difficult wean from bypass [1]. Others feel that the risk of eventual adverse outcomes associated with conversions is too high, and that therefore poor LV function is a relative contraindication. Overall, the evidence supporting the benefit of beating heart surgery in subpopulations of cardiac surgical patients is poor. Generally there appear to be two groups of surgeons: those who will perform OPCAB only in poor surgical candidates (age and associated comorbidites) who have good distal targets, and those who will try OPCAB on most patients they are referred unless it is not indicated (poor distal sites).

Demographics of off-pump coronary artery bypass surgery/minimally invasive direct coronary artery bypass surgery

In the era of drug-eluting stents (DES), the use of MIDCAB techniques appears to be in decline, with many cardiologists preferring to stent the LIMA to LAD. OPCAB is still commonly used at some institutions; however, at some it is rarely used. There is little published information on current trends in OPCAB surgery as a percentage of overall CABG procedures. In the province of Ontario, Canada during the year 2000/2001, out of a total CABG population of 15,172, only 1660 OPCAB procedures were performed (11%) [2]. A study from Duke university for the period 1998 to 2003 also

had a rate of 11% (641 OPCAB procedures, 5667 total CABG surgery) [3]. Rates in Japan for 2005, however, have been reported at 60% [4]. The reasons for these discrepancies, and for the relative low implementation of OPCAB techniques, are unclear. It may be the belief by some surgeons that it offers no advantage over ECC-assisted CABG. It also must be said that it is a technique that is difficult to master, and that many surgeons have simply stopped performing OPCAB surgery as a result.

Anesthesia for minimally invasive direct coronary artery bypass surgery and off-pump coronary artery bypass surgery

The overall goals for OPCAB and MIDCAB surgery are similar to those of conventional CABG. These include the placement of monitoring lines, an arterial line and central venous line, the induction of general anesthesia, endotracheal intubation, and the maintenance, throughout the surgery, of hemodynamic stability. Monitoring for ischemia is done in a similar manner, using both a five-lead ECG and transesophageal echocardiography (TEE). There are, however, some key differences at various points in the surgical procedure. These differences include: (1) the use of regional techniques, before induction, for postoperative pain control; (2) the use of double lumen tubes for one lung anesthesia during MIDCAB IMA harvesting; (3) the use of vassopressor support during positioning and stabilization of the myocardium; and finally (4) monitoring of patients during coronary occlusion.

Regional techniques are often employed in patients undergoing MIDCAB procedures, and may be employed in patients for OPCAB surgery also. The use of regional techniques remains controversial in conventional CABG surgery, mainly out of a concern for an increased risk of epidural hematoma [5,6]. It is more widely used, however, in both OPCAB and MIDCAB surgery, because the risk is theoretically lower owing to the avoidance of ECC. In addition, MIDCAB techniques can be managed with unilateral nerve blocks such as paravertebral blockade, which reduces the risk of epidural hematoma. Possible techniques for peripheral or central neuraxial block include intercostal block (local anesthesia, cryotherapy [7]), wound infiltration, interpleural block, thoracic epidural analgesia, continuous paravertebral blocks, or intrathecal morphine. Although the smaller incision of a thoracotomy is often thought less painful than full sternotomy, Diegeler and colleagues [8] reported that a lateral thoracotomy is actually more painful than conventional sternotomy during the first 48 hours after surgery. Management of pain during minimally invasive cardiac surgery (MICS) is usually the first step in the anesthetic technique, and so early consideration should be given to the potential benefits and risks with these procedures.

Hemodynamic changes during off-pump coronary artery bypass surgery and minimally invasive direct coronary artery bypass surgery

Positioning

OPCAB and to a lesser extent MIDCAB surgery are associated with hemodynamic changes as a result of positioning and stabilization of the heart during distal anastomosis. In addition, the vessel occlusion associated with distal anastomosis may cause ischemia, which may add to the hemodynamic changes.

Devices that immobilize the heart can be divided into two groups: (1) those that use suction and suspend the heart (Octopus, Medtronic, Minneapolis, Minnesota), and (2) those that use compression (CoroNeo retractors, CoroNeo, Montreal, Canada). The hemodynamic changes vary according to the type of stabilizer used, surgical technique, use of intracardiac shunt, location of target vessel (LAD, circumflex or right coronary artery), use of Trendelenberg position, and the inotropes employed to treat hemodynamic changes. The degree and cause of hemodynamic changes during heart positioning have been well-documented in animal models. Elevation of the heart resulted in a drop in mean arterial pressure by 26%, a reduction in cardiac output by 37%, and a decrease in stroke volume by 44% [9,10]. This was associated with a decrease in coronary flow of 25% to 50% [11]. Trendelenberg position restored hemodynamic and coronary blood flow. On echocardiography, LV filling normalized with Trendelenberg, but the right ventricle (RV) remained underfilled, a result of compression of the RV [12]. Isolated RV bypass restored hemodynamic parameters, whereas isolated LV bypass did not [12]. An overview of human studies on hemodynamic changes occurring during OPCAB is presented in Table 1 [13–20]. These are all observational studies employing only one surgical technique, usually looking at a homogeneous population.

OPCAB is consistently associated with falls in systemic pressures and increase in pulmonary artery pressures,. Pulmonary capillary wedge pressures and central venous/right atrial pressures also increase. This likely reflects a change in compliance of the ventricles and not an increase in preload, because echocardiography has demonstrated smaller ventricular volumes, especially on the right side. Finally, positioning of the heart is associated with a decrease in cardiac output. Most studies employed the Trendelenberg position, and some inotrope or vassopressor, accounting for the consistent decrease in MAP of only 1% to 15%. Again, studies in humans have supported the benefit of right heart assist devices in relieving hemodynamic compromise, suggesting that the RV is the cause of the drop in systemic arterial pressure and fall in cardiac output. The most likely cause for this is RV compression, facilitated in part by the low intraventricular pressures and thin free wall. One randomized trial [21] did compare deep pericardial suture to apical stabilizer and found that the use of apical stabilizer was superior;

Table 1
Hemodynamic changes and OPCAB surgery

	LAD anastomosis					Circumflex/OM anastomosis					Posterior descending anastomosis				
	SAP	PAP	PCWP	RAP/CVP	CO/CI	SAP	PAP	PCWP	RAP/CVP	CO/CI	SAP	PAP	PCWP	RAP/CVP	CO/CI
Suction	−2 (−1 to −5)	4 (−10 to 41)	33 (6 to 70)	21 (0 to 43)	−7 (−18 to −4)	−6 (−22 to −2)	0 (−11 to 22)	38 (14 to 50)	28 (−35 to 166)	−14 (−11 to −32)	−3 (−10 to −1)	6 (0 to 23)	31 (7 to 55)	36 (0 to 149)	−8 (−4 to −25)
Compression	−7 (−9 to −3)	19 (9 to 24)	7 —	3 —	−13 (−9 to −15)	−11 (−15 to −4)	16 (12 to 24)	13 —	18 —	−15 (−25 to −9)	−12 (−15 to −6)	13 (12 to 14)	9 —	15 —	−9 (−20 to −3)

Abbreviations: CI, cardiac index; CO, cardiac output; CVP, central venous pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SAP, systemic arterial pressure.

however, both methods resulted in reductions in CO and systemic pressure. In another study [22], the hemodynamic effects of OPCAB in patients who had ejection fractions of 30% were compared with those having EF of 50%, and no significant difference in hemodynamic changes were seen except for an increase in LV volume during positioning in the hearts of patients who had a poor EF, compared with a decrease in volume in those who had normal EF. An excellent review of the mechanisms of hemodynamic changes and causation has been previously published [23].

Ischemia, mitral regurgitation, and bradycardia

The hemodynamic changes that occur with displacement and stabilization of the heart often occur within seconds and stabilize within 5 minutes, so that late hemodynamic changes as a result of positioning tend not to occur [17]; however, progressive decreases in systemic pressure may occur from ischemia during distal anastomosis. Typically some degree of new-onset ST segment elevation or depression occurs. Not surprisingly, ECG axes and voltages change during cardiac manipulation, and so may make ST segment interpretation difficult. TEE may be helpful, and usually demonstrates new-onset wall motion abnormalities in the ischemic patient; however, this must be interpreted cautiously because the stabilizer itself may induce a regional defect. Ischemia, positioning, or both may lead to mitral regurgitation, most often an increase in an already leaky valve, which may additionally contribute to hemodynamic compromise. This is usually readily apparent on TEE [24,25].

Bradycardia often occurs during right coronary artery (RCA) grafting, a result of ischemia to the SA or AV nodes. It seems to occur most frequently during anastomosis of a low grade lesion (70% occlusion), likely because low-grade lesions rarely have collateral circulation. Bradycardia is readily apparent on ECG, is easy to anticipate based on lesion anatomy and site of grafting, and is easily treatable with ventricular pacing. Many surgeons place pacemaker leads before distal RCA grafting to minimize hemodynamic compromise if heart block should occur.

Treatment of hemodynamic changes

There are several possible methods of treating hemodynamic changes during OPCAB surgery. Volume loading to increase the preload is common, with target central venous pressure (CVP) of 10 to 12 in the supine patient. Trendelenberg positioning to 20° to 30° head down is also helpful both in increasing preload and in assisting cardiac displacement, especially during posterior descending artery (PDA) grafting. The use of inotropes/vassopressors during grafting is common; Levophed (norepinephrine bitartrate) is widely used, although some institutions prefer phenylephrine or epinephrine. If hemodynamic deterioration persists despite the use of inotropes,

volume loading, and positioning, then a cause must be sought. Ischemia should be ruled out by observing for ST segment changes on the ECG. The appearance of new ischemic wall motion changes is also suggestive of ischemia. Neither ECG nor TEE monitoring is 100% specific during OPCAB surgery, and positioning or stabilization can themselves lead to false positives [26]. As well, positioning may result in areas of myocardium that go undetected because of poor visualization on TEE. Ischemia, if suspected, may be treated with nitroglycerin. Surgical use of coronary shunts may also improve ischemia. If surgical anastomosis has not yet begun, then releasing of the ligatures around the coronary artery may also restore coronary perfusion.

If mitral regurgitation (MR) is the cause of hemodynamic changes, then an increase in the degree of MR should be readily apparent on TEE. Although MR may be secondary to ischemia, it is usually caused by myocardial positioning, and so repositioning of the heart is the usual treatment if worsening MR is suspected.

If hemodynamic deterioration persists, then a final surgical maneuver is to incise the right pericardium/pleura to allow the right heart to "herniate" slightly into the right chest cavity. As mentioned previously, right heart compression is felt to be the cause of hemodynamic deterioration during OPCAB surgery. Releasing the pleura reduces right heart compression and improves hemodynamic parameters.

Assist devices for hemodynamic support during off-pump coronary artery bypass surgery

Although the main goal of OPCAB surgery is to avoid conventional ECC, the use of right heart assist devices has been explored as a "bridge" or hybrid technique between conventional cardiac surgery and pure OPCAB techniques. Right heart bypass does not require an oxygenator, avoids cannulation of the aorta (and therefore cerebral emboli), and should support the right heart, which is the main ventricle affected by positioning during OPCAB. Several studies have examined the use of right heart support devices during OPCAB and have shown minimal effects on hemodynamic changes during positioning with these devices [27–31].

Intra-aortic balloon pumps (IABP) have also been inserted in patients undergoing OPCAB surgery to either reduce hemodynamic changes or, more commonly, to reduce ischemia during OPCAB surgery [32–34]. IABP devices tend to be inserted into patients who have left main disease as a method of reducing ischemia during grafting. Some investigators have also placed the devices in patients who have poor EF or in the elderly. Usually these devices are placed before positioning for OPCAB surgery, in anticipation of hemodynamic changes or ischemic changes, and are not used as a salvage for the prevention of conversion to conventional ECC-assisted cardiac surgery.

Conversions to conventional bypass grafting

Patients who require emergency conversion to conventional ECC do worse than patients treated with successful OPCAB or those operated on with conventional bypass. Several studies have shown that compared with OPCAB surgery, the mortality rate is increased two to six times (absolute rates of 5%–12%) [35,36]. It is unclear whether this is a result of patient factors (sicker patients are more likely to convert) or surgical factors in patients who are converted being exposed to the hemodynamic changes of OPCAB and to the bypass pump. It may also be that surgeons and anesthesiologists wait until the last possible moment to convert, resulting in prolonged hypotension for the patient along with a hurried conversion to conventional bypass. Common sense suggests that the patient is much better served by abandoning the procedure when the patient is still relatively stable, allowing the heart to recover and the surgical team to prepare for ECC in an unhurried atmosphere. However the surgical team decides to proceed, conversion to conventional bypass should be anticipated, and all the necessary equipment must be immediately available in the event of emergency conversion.

Early extubation and fast-track management

OPCAB and MIDCAB surgical patients are often ideal candidates for fast-track programs, and can be rapidly extubated following surgery. Some centers have even proposed an "ultra" fast-track program, in which OPCAB and MIDCAB patients are extubated within the operating room (OR) [37–39]. This is especially appealing in MIDCAB surgery, because some form of lung isolation is often used, usually a double lumen tube, and extubation within the OR avoids the need to reintubate the patients with a single lumen tube. As with conventional bypass surgery, the maintenance of both hematological and hemodynamic homeostasis is necessary before extubating patients. Hematological homeostasis is usually easy to achieve because the bypass pump is avoided. Lower total doses of heparin are also administered, often via a continuous infusion to avoid dramatic swings in activated clotting times (ACT). The ideal ACT is still unclear, with many reporting ACTs over 380 as being acceptable. As with conventional bypass, most centers completely reverse the effects of heparin with the administration of protamine and then administer acetylsalicylic acid (ASA) in the early postoperative period to avoid graft thrombosis. In addition to coagulopathy, careful consideration must be given to patient temperature. If active warming is not performed during surgery, with forced air warmer for example, the patient's temperature often drifts to 35°C or lower. This may contribute to bleed loss, prolong the duration of narcotics and muscle relaxants, and make early extubation more difficult. Often warming blankets, fluid warmers, or an increase in ambient room temperature are used to avoid hypothermia.

Outcomes and off-pump coronary artery bypass surgery/minimally invasive direct coronary artery bypass surgery

The hope of any change in practice is that it will result in an improvement in care of patients, with a resultant improvement in outcomes. It is important with any new advance to demonstrate, with randomized trials, that these improvements do indeed occur, and that patients will benefit from the widespread adoption of this technology. OPCAB is often compared with conventional bypass grafting, a logical comparison. MIDCAB with grafting of a single vessel has been compared with conventional bypass, but is probably best compared with PCI as a suitable alternative. The remainder of this article therefore examines outcomes of OPCAB versus conventional bypass and MIDCAB versus PCI.

Off-pump coronary artery bypass surgery versus conventional bypass surgery

Many surgeons heralded the reinvention of OPCAB surgery as a way to prevent stroke and neurologic dysfunction by avoiding aortic cannulation and conventional ECC. Unfortunately, few randomized trials were conducted, and most relied on evidence from observational studies, often using historical controls. Fortunately, over the last 5 to 8 years a number of randomized trials were conducted examining the efficacy of OPCAB versus conventional bypass. Most of these trials included relatively healthy patients who were suitable for either conventional cardiac surgery or OPCAB surgery. Most trials were limited because they were not designed to specify, before randomization, which targets were to be grafted. As a result, most patients randomized to OPCAB treatment arms received fewer grafts in total than the conventional groups. Many trials also did not follow intention-to-treat analysis. This is especially important considering the increased risk in patients converted from OPCAB surgery to conventional bypass. In most trials these conversions were excluded from analysis.

A meta-analysis of randomized trials conducted by the authors' group has aided in elucidating the benefits of OPCAB surgery compared with conventional bypass grafting. Although it was widely believed that the rates of stroke and neurocognitive dysfunction would be lower in the OPCAB group, the review found no difference between OPCAB patients and conventional coronary artery bypass (CCAB) patients. Although the neurocognitive dysfunction was statistically significantly improved at 2 to 6 months, there was no difference at 30 days or at 1 to 2 years. A more recent meta-analysis of 811 patients drew similar conclusions [40]. Another recent meta-analysis of stroke in OPCAB versus CCAB trials concluded that stroke rates were reduced in OPCAB surgery [41]. The rates of death, myocardial infarction, and renal failure were not statistically different in either study. Patients who undergo OPCAB surgery do benefit from a reduction in the incidence

of atrial fibrillation, blood transfusion, respiratory infections, and inotrope use. Resource use is also reduced in OPCAB surgery (Box 1).

The issue of graft patency has been raised as a concern by some surgeons following an article by Khan and colleagues [42] in the *New England Journal of Medicine* that suggested that graft patency may be compromised in OPCAB patients. There was no difference in the rates of angina recurrence or reintervention (at 30 days or at 1–2 years) from the authors' review, suggesting, at least clinically, that graft patency was similar. Three additional papers reporting on graft patency found no difference in OCAB versus CCAB groups [43–45].

Overall outcomes are improved in patients undergoing OPCAB surgery; however, most randomized trials were performed on low-risk groups, and so generalizing to higher-risk subgroups is difficult. Specific subgroups that still require more study include elderly patients and those who have poor LV function [46].

Minimally invasive direct coronary artery bypass versus percutaneous coronary intervention

There have been a number of studies comparing MIDCAB surgery with conventional percutaneous intervention. A recently published meta-analysis reviewed these trials [47]. Most of the trials employed a MIDCAB surgical approach for revascularization; however, some trials did perform sternotomy. Most trials were single LIMA to LAD grafting or stent to LAD, depending on the trial arm. The results demonstrated no significant differences in the rates of death, acute myocardial infarction, or stroke between the two groups. Angina recurrence in hospital, reintervention rates at 1 to 5 years, major adverse coronary events (MACE) at 6 months and 1 to 5 years, and event-free survival at 6months and 1 to 5 years were all higher in the PCI-randomized patients. This suggests that for treatment of LAD disease OPCAB surgery remains superior (Box 2). Many of the trials used

Box 1. Benefits of off-pump coronary artery bypass surgery over conventional coronary artery bypass surgery

Decreased rates of stroke
Decreased rates of atrial fibrillation
Decreased rates of blood transfusion
Decreased rates of respiratory infections
Decreased use of inotropes
Decreased hospital length of stay
Decreased ICU length of stay
Decreased ventilation time

Box 2. Benefits of minimally invasive direct coronary artery bypass surgery

Angina recurrence in hospital
Reintervention rates at 1 to 5 years
MACE at 6 months and 1 to 5 years
Event free survival at 6 months and 1 to 5 years

bare metal stents (BMS), which may not be reflective of current practice. The one trial that employed DES placed patients on clopidogrel for only 6 months [48]. These may all result in lower long-term morbidity if patients receive DES; however, studies of real-world experience of stenting versus surgery support the inferiority of stenting and PCI for the management of CAD. In addition, there has been much concern expressed about the need to take clopidogrel for at least 1 year following DES implantation to avoid acute stent thrombosis, which carries a high mortality [49]. The assumption therefore that the newer DES stents are inherently superior to the BMS needs to questioned until adequately powered long-term studies are completed.

In patients who have isolated LAD disease therefore, OPCAB/MIDCAB techniques are superior to PCI for treatment. The choice, however, is ultimately affected by patient preference and choice based on fully informed consent.

Summary

Many new technologies are being developed, refined, and ultimately implemented for the treatment of patients, with the overall aim at improving outcomes. One common feature of many new technologies is that they offer a safer approach to previous techniques. Indeed, perhaps one of the greatest driving forces for change over the last 30 years is risk reduction. From the removal of lead in paint to the addition of seatbelts, then airbags, in cars, the concept of mitigating risk has become immensely important today. Although cardiac surgery has evolved to reduce risks incrementally, risks have been effectively undercut by percutaneous based procedures that have offered dramatic reductions in risk—at least in the short term. Beating heart techniques, whether OPCAB, MDCAB, or in other forms such as percutaneous valve replacement, are likely to dramatically increase over the next decade. What role OPCAB and MIDCAB techniques will play in this new era is anyone's guess.

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The version of the article by Drs Warkentin and Greinacher, originally published in the August 2003 issue of *The Annals of Thoracic Surgery* (76:638–48) was inadvertently printed without the corrections the authors made in proof. The correct article appears here. *The Annals* regrets the error that occurred.

Heparin-Induced Thrombocytopenia and Cardiac Surgery

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Unfractionated heparin given during cardiopulmonary bypass is remarkably immunogenic, as 25% to 50% of postcardiac surgery patients develop heparin-dependent antibodies during the next 5 to 10 days. Sometimes, these antibodies strongly activate platelets and coagulation, thereby causing the prothrombotic disorder, heparin-induced thrombocytopenia. The risk of heparin-induced thrombocytopenia is 1% to 3% if unfractionated heparin is continued beyond the first postoperative week. When cardiac surgery is urgently needed for a patient with acute or subacute heparin-induced thrombocytopenia, options include an alternative anticoagulant (bivalirudin, lepirudin, or danaparoid) or combining unfractionated heparin with a platelet antagonist (epoprostenol or tirofiban). As heparin-induced thrombocytopenia antibodies are transient, unfractionated heparin alone is appropriate in a patient with previous heparin-induced thrombocytopenia whose antibodies have disappeared.

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Physicians caring for cardiac surgery patients require an understanding of heparin-induced thrombocytopenia (HIT), as this patient population is at relatively high risk for this antibody-mediated, prothrombotic adverse effect of heparin. Indeed, monitoring of the platelet count for HIT is a standard feature of postcardiac surgical care [1]. Nevertheless, only a small minority of thrombocytopenic postcardiac surgery patients actually have HIT, illustrating the need to view HIT as a clinicopathologic syndrome, ie, the diagnosis should be based on both clinical and serologic grounds [1]. The occasional need to perform urgent cardiac surgery in a patient with acute HIT presents the challenge of choosing an appropriate anticoagulant approach among several available options [2]. Our aim is to review HIT in the context of the cardiac surgical patient, and to combine our North American and European perspectives in providing treatment recommendations.

Currently, three anticoagulants are approved for treatment of HIT (United States: lepirudin [3] and argatroban [4]; European Union: danaparoid [5] and lepirudin; Canada: all three agents). However, neither these nor other available nonheparin anticoagulants (bivalirudin [6]) are approved for use during cardiopulmonary bypass (CPB), necessitating off-label use under exceptional circumstances. The appendix summarizes our review.

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Pathogenesis

Heparin-induced thrombocytopenia is an immune-mediated disorder resulting when immunoglobulin G antibodies are produced that recognize a self protein, platelet factor 4, when platelet factor 4 has formed complexes with heparin [7, 8]. Multimolecular complexes of heparin, platelet factor 4, and immunoglobulin G form on platelet surfaces, and occupancy of the platelet Fc receptors by HIT–immunoglobulin G produces platelet activation. Heparin chains bind in relation to their chain length to platelet factor 4, perhaps explaining why unfractionated heparin (UFH) is more likely to cause HIT than low-molecular-weight heparin (LMWH) [9–12]. Platelet activation in HIT leads also to activation of coagulation. Once these procoagulant events are triggered, the prothrombotic risk remains for days to weeks, even after heparin has been stopped [13].

Clinical Picture

Timing of Thrombocytopenia

Most often, HIT presents as an unexpected platelet count fall beginning 5 to 10 days after heart surgery (Fig 1A) [14, 15]. Sometimes, HIT presents as an abrupt fall in the platelet count when heparin is administered (Fig 1B). Invariably, such patients have received heparin within the past 100 days (usually within the past 3 weeks). The reason for this temporal association is that the heparin antibodies triggered by the recent heparin exposure are remarkably transient [14]. Rarely, HIT presents several

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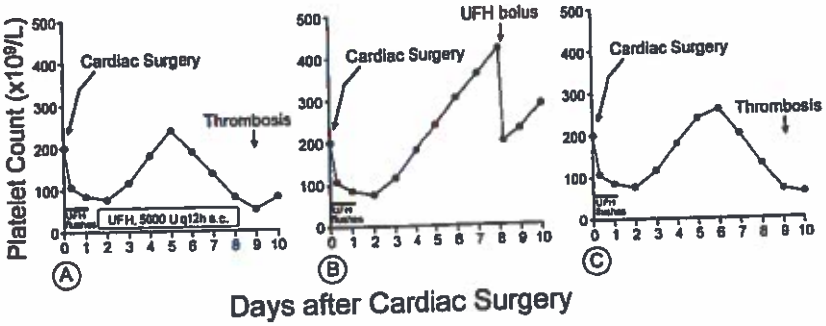

Fig 1. Temporal profiles of onset of heparin-induced thrombocytopenia after cardiac surgery. (A) Typical-onset heparin-induced thrombocytopenia. (B) Rapid-onset heparin-induced thrombocytopenia. (C) Delayed-onset heparin-induced thrombocytopenia. (UFH = unfractionated heparin.)

days or even a few weeks after discharge from the hospital (delayed-onset HIT; Fig 1C) [16, 17]. This syndrome is associated with high-titer HIT antibodies that activate platelets even in the absence of pharmacologic heparin.

Severity of Thrombocytopenia

Thrombocytopenia in HIT is usually of moderate severity: 80% of patients have platelet count nadirs between 20 and 150 × 10^9/L (median, 60 × 10^9/L) [8]. Only 10% have platelet counts below 20 × 10^9/L, but even these patients do not have signs of thrombocytopenic bleeding (petechiae). The remaining 10% of patients whose platelet count never falls below 150 × 10^9/L are recognized either because of substantial platelet count falls (>50%) [18] or because of clinical events (thrombosis or skin lesions) suggesting HIT [17]. Using a proportional fall in platelet count such as more than 50% is appropriate because HIT usually occurs in the background of a rising postoperative platelet count (Fig 1) [11, 18, 19].

Thrombosis and Other Sequelae of Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is strongly associated with thrombosis (odds ratio, 17 to 37) [9, 18, 20]. Approximately 40% to 75% of patients develop thrombosis, with predominance of venous over arterial thrombosis (ratio, 2:1 to 4:1) [13, 17]. Although postcardiac surgery patients with HIT develop similar rates of thrombosis (38% to 81%), arterial thrombi predominate [21–24], likely reflecting additional risk factors (arteriosclerosis, intravascular catheter use) in this patient population. Heparin-induced thrombocytopenia–associated mortality was 28% in the largest study of cardiac surgery patients [21].

Arterial thrombosis most often affects large lower-limb arteries, with thrombotic strokes and myocardial infarction less often seen (ie, the converse of usual localization of atherothrombosis) [17]. Rarely, arterial thrombi affect mesenteric, brachial, renal, or spinal arteries. HIT after coronary bypass grafting is associated with saphenous vein graft occlusion(s) [25]. Venous thromboembolism (deep-vein thrombosis [DVT], pulmonary embolism) is also common. Upper-limb DVT in HIT is strongly associated with use of a central venous catheter [20]. Sometimes, intraatrial or intraventricular thrombosis occurs. Rarely, thrombosis of adrenal veins leads to bilateral adrenal hemorrhagic necrosis and acute adrenal insufficiency.

About 10% to 20% of patients who develop HIT during subcutaneous heparin therapy develop skin lesions at the injection sites ranging from painful erythematous plaques to skin necrosis [17]. Some patients who develop rapid-onset HIT after intravenous bolus heparin evince an acute systemic reaction that can be inflammatory (fever or chills, flushing), cardiorespiratory (dyspnea, hypertension, cardiorespiratory arrest), gastrointestinal (vomiting, diarrhea), or neurologic (transient global amnesia) [17].

Although increased thrombin generation is universal in HIT, overt (decompensated) disseminated intravascular coagulation leading to hypofibrinogenemia or increased prothrombin time is seen in only 5% to 10% of patients with HIT [7].

Differential Diagnosis

Thrombocytopenia secondary to hemodilution and platelet consumption occurs during cardiac surgery, with the lowest platelet counts (40% to 60% decline) usually seen on postoperative days 2 to 3, followed by thrombocytosis (peaking at two to three times baseline at about day 14), with subsequent return to preoperative baseline by 1 month after surgery. Thrombocytopenia during the first four postoperative days is only rarely attributable to HIT [26]. This is because heparin administered during CPB does not lead to clinically significant levels of HIT antibodies until postoperative day 5 or later, and because clinically significant levels of HIT antibodies are not commonly produced by *pre*operative heparin given during heart catheterization or for treating acute coronary syndromes.

However, a platelet count fall that begins 5 to 10 days after cardiac surgery (Fig 1A, 1C) or that occurs abruptly after starting heparin in a patient previously exposed to heparin within the past 100 days (Fig 1B), is very suggestive of HIT. However, other complications can produce thrombocytopenia during this time period, both common (septicemia, multiorgan system failure) and rare (post-transfusion purpura [27]).

Laboratory Testing for Heparin-Induced Thrombocytopenia Antibodies

Two commercial enzyme immunoassays (EIAs) are available that are very sensitive for detecting platelet factor 4–reactive HIT antibodies. Platelet activation assays that use washed platelets (eg, platelet serotonin release assay,

heparin-induced platelet activation assay) have similar sensitivity as the EIAs for detecting clinically significant HIT antibodies, but with greater diagnostic specificity [28]. As reference laboratories usually perform these assays, delays in obtaining test results are common. Conventional platelet aggregation assays have limited sensitivity and specificity for detecting HIT antibodies [1, 7].

The high sensitivity of EIAs and washed platelet activation assays means that a negative result usually rules out HIT (high negative predictive value) [29]. However, the high frequency of subclinical HIT antibody seroconversion after cardiac surgery (discussed subsequently) means that a positive assay result does not necessarily prove HIT to be the diagnosis (moderate positive predictive value), particularly if the pretest probability for HIT is low, or the test result is only weakly positive [29].

Frequency of Heparin-Induced Thrombocytopenia After Cardiac Surgery

Several prospective studies have evaluated the frequency of HIT in postoperative cardiac surgical patients who also received postoperative antithrombotic prophylaxis with UFH [11, 28, 30]. Pooling the data, the frequency of HIT was 2.4% (10 of 414 patients). This frequency is consistent with retrospective studies [21–24] that observed an overall frequency of about 2%.

Prospective studies [11, 28, 30–33] have found that 27% to 50% of postcardiac surgical patients form HIT antibodies detectable by EIA; however, only 7% to 40% [11, 28, 31] of these seroconversion events include high-titer immunoglobulin G antibodies that activate platelets in vitro. The observed frequency of HIT after cardiac surgery (1% to 3%) despite much higher seroconversion rates (27% to 50%) indicate that only a small minority (<10%) of antibody-positive patients actually develop thrombocytopenia even when heparin is continued through the postoperative period. In general, patients with the strongest antibody test results are most likely to develop HIT (eg, >90% serotonin release corresponds to a likelihood ratio for HIT of 20) [29].

Francis and colleagues [33] found a higher frequency of HIT antibody formation when UFH of beef lung origin was used for cardiac surgery, rather than UFH derived from porcine gut (49.5% versus 35.2%; $p = 0.037$). This study is consistent with previous comparisons of these two UFH preparations for treatment of DVT, in which beef lung heparin was more likely to cause HIT [12, 34].

Heparin Anticoagulation After Cardiac Surgery

Despite the common practice of giving UFH for antithrombotic prophylaxis after cardiac surgery, we are unaware of studies establishing its efficacy in this situation, particularly vis-a-vis its potential to cause HIT-associated thrombosis. A nonrandomized comparison of LMWH and UFH administered after cardiac surgery found a lower risk of HIT with LMWH: 1 of 370 patients (0.3%) versus 9 of 263 patients (3.4%) [11], consistent with studies in postorthopedic surgery patients [9, 12]. However, LMWH has not been well studied in cardiac surgical patients, and lacks regulatory approval for this indication. We recommend that if UFH or LMWH is given after cardiac surgery (either in therapeutic, prophylactic, or flush doses), appropriate platelet count monitoring for HIT be performed [1].

Management of Heparin-Induced Thrombocytopenia After Cardiac Surgery

The probability of HIT is high if a more than 50% fall in the platelet count begins between postoperative days 5 and 10 and occurs in the absence of alternative explanations, eg, infection. In such patients with high clinical suspicion for HIT, there is emerging consensus that heparin should be stopped, and an alternative, nonheparin anticoagulant substituted. This recommendation is based on the unfavorable natural history of HIT managed by heparin cessation alone (with or without warfarin): 25% to 50% thrombosis at 30- to 37-day follow-up (5% fatal thrombosis) [8, 13]. Further, lower limbs should be routinely screened for venous thrombosis, as clinically silent DVT is common in HIT patients [8]. Heparin-induced thrombocytopenia should also be suspected whenever a patient develops thrombosis while receiving heparin, or if the patient returns to the hospital with thrombocytopenia and thrombosis within the first 2 weeks after cardiac surgery (delayed-onset HIT). The next section summarizes briefly the treatment of HIT, which is discussed in detail elsewhere [7, 8, 35].

Treatment of Thrombosis Complicating Heparin-Induced Thrombocytopenia

The principles of treating thrombosis complicating HIT are (1) stop all heparin, including small doses of UFH used to flush invasive catheters, as well as LMWH; (2) give a rapidly acting, nonheparin anticoagulant, eg, a direct thrombin inhibitor such as argatroban, lepirudin, or bivalirudin, or danaparoid (factor Xa-inhibiting heparinoid); (3) avoid prophylactic platelet transfusions; (4) avoid warfarin until substantial resolution of thrombocytopenia has occurred; and (5) consider adjunctive therapies in specific situations, eg, surgical thromboembolectomy for limb-threatening arterial thrombosis.

The choice of alternative anticoagulant (Table 1) depends on patient-specific factors. Argatroban and lepirudin are excreted through hepatobiliary and renal routes, respectively; thus, argatroban is more suited for patients with renal insufficiency, whereas lepirudin is preferred if the patient has hepatic dysfunction. Bivalirudin predominantly undergoes enzymic degradation in the plasma (80%), with minor renal excretion (20%). Lepirudin is immunogenic, and during repeat courses a bolus should be avoided, as the risk of anaphylaxis is estimated at 0.16% [36]. The direct thrombin inhibitors have short half-lives (lepirudin, 80 minutes; argatroban, 40 to 50 minutes; bivalirudin, 25 minutes), which is useful when dose interruptions are anticipated, eg, for an impending invasive procedure.

Warfarin and other oral anticoagulants should be avoided during acute HIT because they can lead to limb

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Table 1. Three Direct Thrombin Inhibitors for Treatment of Heparin-Induced Thrombocytopenia

Anticoagulant	Dosing Protocol for HIT-Associated Thrombosis[a]	Anticoagulant Monitoring[b]	Metabolism	Half-life	Comment
Lepirudin	(± Bolus, 0.4 mg/kg); initial infusion rate, 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$ [a]	1.5–2.5 × baseline aPTT	Renal	80 min	Relatively contraindicated in renal failure;[c] risk of anaphylaxis, especially on reexposure; minor prolongation of INR
Bivalirudin	No bolus; initial infusion rate, 0.15–0.20 $mg \cdot kg^{-1} \cdot h^{-1}$	1.5–2.5 × baseline aPTT	Enzymic (80%); Renal (20%)	25 min	Small experience in treating HIT; minor prolongation of INR
Argatroban	No bolus: initial infusion rate, 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.5–3.0 × baseline aPTT	Hepatobiliary	40–50 min	Initial dose 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in hepatic insufficiency; moderate to marked prolongation of INR (complicates warfarin overlap)

[a] Identical protocols are generally used for isolated HIT, except for lepirudin (no initial bolus; initial infusion rate, 0.10 $mg \cdot kg^{-1} \cdot h^{-1}$ adjusted to aPTT 1.5–2.5 × baseline aPTT). However, in contrast to the package insert, and in order to avoid overdosing (especially in elderly patients with unrecognized renal dysfunction), we recommend omitting the lepirudin bolus unless there is life threatening thrombosis. [b] Generally, the patient's baseline aPTT should be used (when applicable) for calculating target range, when appropriate; otherwise, the mean of the laboratory normal range can be used. [c] Substantial dose-reduction in renal insufficiency is required.

aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio.

necrosis resulting from microvascular thrombosis caused by depletion of the vitamin K-dependent natural anticoagulant, protein C [37, 38]. This complication, which may occur in 5% to 10% of patients with HIT-associated DVT receiving oral anticoagulants, is usually seen when the international normalized ratio rises above 3.5, as this represents a surrogate marker for protein C depletion. After platelet count recovery, if longer-term anticoagulation is needed, then warfarin anticoagulation is commenced that should overlap at least 5 days with the heparin alternative being used. For unknown reasons, argatroban prolongs the international normalized ratio much more than does lepirudin or bivalirudin, complicating monitoring of warfarin during overlapping anticoagulation. In contrast, the long half-life of danaparoid (25 hours) and lack of interference with the international normalized ratio makes it well-suited for treating venous thromboembolism when subsequent overlap with oral anticoagulants is required.

Treatment of Isolated Heparin-Induced Thrombocytopenia

Isolated HIT indicates when HIT is suspected because of a fall in platelet count alone without a HIT-associated thrombosis having occurred (yet) [12]. Previously, it was assumed that stopping heparin avoided subsequent thrombosis in isolated HIT. However, studies indicate that 25% to 50% of patients managed with heparin cessation develop thrombosis [8, 13]. Thus, in most situations, patients strongly suspected as having isolated HIT should receive a rapidly acting, nonheparin anticoagulant [35].

Anticoagulation During Cardiac Surgery in Patients With Previous or (Sub)Acute Heparin-Induced Thrombocytopenia

Activation of coagulation by contact of blood with the artificial surfaces of the CPB apparatus, as well as the reinfusion of tissue factor–enriched blood from the operative field, mandates high-dose anticoagulation. Well-known advantages of UFH during CPB include (1) its high efficacy for preventing thrombosis of the CPB circuit; (2) rapid and simple intraoperative monitoring by activated clotting time; and (3) neutralization of heparin by protamine sulfate. No other agent meets these requirements; further, minimal experience with nonheparin anticoagulation during CPB exists. Thus, situations in which UFH is truly contraindicated must be well defined, so as to avoid potentially greater risks of nonheparin

Table 2. Options for Anticoagulation During Cardiac Surgery

A. Acute HIT
   1. Postpone cardiac surgery for several weeks (then go to C)
   2. Bivalirudin (preferably, if ecarin clotting time monitoring available)
   3. Lepirudin (if ecarin clotting time monitoring available and normal renal function)
   4. Epoprostenol plus heparin
   5. Tirofiban plus heparin
   6. Danaparoid (if drug and anti-factor Xa monitoring available)

B. Subacute HIT[a]
   1. Postpone cardiac surgery for several weeks (then go to C)
   2. Off-pump technique[b] using bivalirudin, lepirudin, or danaparoid
   3. Heparin (if washed platelet activation assay for HIT antibodies is negative or enzyme immunoassay negative or weakly positive)
   4. See options listed under A

C. Previous HIT[c]
   1. Heparin

Each of the numbered items above indicates a separate option for consideration, with options we favor listed first.

[a] Subacute heparin-induced thrombocytopenia (HIT) indicates a patient with recent HIT who has detectable HIT antibodies despite resolution of thrombocytopenia. [b] Off-pump surgery requires only about one half to one third the level of anticoagulation compared with cardiopulmonary bypass. [c] Previous HIT indicates that HIT antibodies no longer are detectable.

agents in this setting. Table 2 summarizes various approaches for managing CPB in patients with previous or (sub)acute HIT.

Cardiac Surgery in Patients With Previous Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia antibodies are transient and usually decline to nondetectable levels by 100 days (median, 50 days) using washed platelet activation assays; by EIA, the time to antibody disappearance is somewhat longer (median, 80 days) [14]. If heparin is administered to a patient with previous HIT whose antibodies are no longer detectable, several days are required for B lymphocytes to regenerate antibodies, if they are made at all. Indeed, recent studies [14, 15, 39] indicate that HIT antibody formation does *not* recur more quickly or more often in a patient with previous HIT who is reexposed to heparin, ie, there is no anamnestic (immune memory) response against HIT antigens.

Therefore, UFH is the drug of choice for anticoagulation during CPB in patients with a history of HIT who no longer have circulating HIT antibodies using one or more sensitive assays. We [14, 40] and others [39, 41, 42] have performed this strategy without producing HIT-related complications. When planning a reexposure, it is prudent to avoid preoperative heparin completely, so as to avoid restimulating antibodies, eg, by performing heart catheterization using either argatroban [43], bivalirudin [44], lepirudin [3], or danaparoid [45]. After surgery, nonheparin anticoagulants should be given if antithrombotic prophylaxis is needed, eg, warfarin, danaparoid 750 U twice or thrice daily subcutaneously, or hirudin 15 mg subcutaneously twice daily (see Table 1 if therapeutic-dose anticoagulation is required).

In our opinion, it is also reasonable to use UFH for CPB in a patient with recent HIT who tests weakly positive by EIA if a sensitive washed platelet activation assay is negative. This is because HIT antibodies detectable by activation assays correlate more closely with clinical HIT [28]. One of us (A.G.) has used UFH for CPB in this situation in 2 patients, with no adverse HIT-associated events.

For patients with previous HIT who require urgent heart surgery, there may be no opportunity to perform repeat testing for HIT antibodies. In this situation, we recommend using UFH if HIT occurred more than 100 days earlier. Both of us have used this approach with success when faced with this situation [40]. For patients whose episode of HIT occurred more recently, the decision to use standard UFH depends on the likelihood that significant antibody levels persist and the center's capacity to organize quickly an alternative anticoagulant approach.

Cardiac Surgery in Patients With Acute or Subacute Heparin-Induced Thrombocytopenia

Subacute (or latent) HIT refers to a patient with a recent episode of HIT who continues to have detectable HIT antibodies [8]. Such a patient can develop rapid-onset HIT if heparin is administered again [14, 15]. The precise risk of giving high-dose UFH for CPB in this situation is not well defined, and anecdotal success using UFH has been reported [46]. Sometimes, cardiac surgery can be avoided, eg, low-dose thrombolysis (tissue-type plasminogen activator, 2 mg/h) plus lepirudin to treat HIT-associated intracardiac thrombosis [47].

For patients with acute or subacute HIT in whom heart surgery cannot be postponed, and for whom standard UFH anticoagulation is considered contraindicated, several off-label approaches exist (Table 2). No single method is appropriate in all circumstances, given patient-dependent factors (eg, renal failure), differences in jurisdictional availability of the nonheparin anticoagulants, accessibility and turnaround time of specialized laboratory monitoring, and prior physician experiences and preferences. Moreover, a team approach involving cooperation among surgeon, cardiologist, cardiac anesthesiologist, critical care physician, hematologist, and laboratory personnel is necessary. When a heparin-free approach is chosen, it is important not to administer heparin accidentally, eg, by heparin-coated intrapulmonary catheters, heparin-coated arterial filters or tubing within the CPB apparatus, or intravascular heparin flushes.

Particularly for patients with subacute HIT, use of an off-pump technique should be considered, as only one third to one half of the usual dose of danaparoid or lepirudin, respectively, than required for CPB is needed, potentially reducing bleeding [48, 49]. Bivalirudin has also been used successfully for off-pump cardiac surgery in HIT patients [50], with similar dosing as that under investigation for non-HIT patients undergoing off-pump surgery (bolus, 0.75 mg/kg, then 1.75 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion to maintain activated clotting time > 300 seconds) [51]. (This is the same bivalirudin dosing used in percutaneous coronary interventions [52].)

Recombinant Hirudin

Hirudin is an anticoagulant naturally produced by the salivary gland of the medicinal leech [3]. Two preparations are available by recombinant technology: lepirudin (Refludan, Berlex Laboratories, Montville, NJ) has been studied more extensively for HIT than desirudin (Revasc) [3, 38]. Hirudin is a single-chain 65-amino acid polypeptide (7,000 Da) that forms an irreversible 1:1 complex with thrombin. Hirudin interacts with both the fibrinogen-binding and catalytic sites of thrombin, completely inhibiting all procoagulant actions of thrombin. Unlike heparin, hirudin also inhibits clot-bound thrombin, including thrombin on fibrin lining the CPB circuit. The half-life of hirudin greatly depends on renal function, ranging from 80 minutes (normal kidneys) to more than 200 hours (anephric patient). No antidote exists.

In animal studies, hirudin in fixed doses provided effective CPB anticoagulation. However, in humans undergoing CPB, individualized dosing adjusted by intraoperative laboratory monitoring is required (Table 3). Unfortunately, although the activated partial thromboplastin time is adequate to monitor hirudin when treating thrombosis, the activated partial thromboplastin time–

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Table 3. Treatment Protocol for Hirudin (Lepirudin) Anticoagulation During Cardiopulmonary Bypass (modified from [42])

Initial lepirudin dosing (pre-CPB)	
Initial intravenous (iv) lepirudin bolus:	0.25 mg/kg body weight
and initiate continuous iv infusion:[a]	30 mL/h (0.5 mg/min)
Lepirudin added to pump circuit volume:	0.2 mg/kg body weight
Target lepirudin plasma level:[b]	>2.5 μg/mL before start of CPB
	If <2.5 μg/mL, give additional bolus (10 mg)
Lepirudin dosing and monitoring while on CPB	
Continue iv infusion (adjusted as below):	30 mL/h (0.5 mg/min)
Frequency of lepirudin level monitoring:	Every 15 min using ecarin clotting time
Intraoperative dose adjustments, based on ecarin clotting time	
Lepirudin plasma level[b]	Dosing modification
>4.5 μg/mL	Reduce infusion rate by 10 mL/h
3.5–4.5 μg/mL	No change in infusion rate
<3.5 μg/mL	Increase infusion rate by 10 mL/h
Special steps toward end of CPB	
Stop lepirudin infusion 15 min before anticipated end of CPB	
After separation from CPB, administer 5 mg lepirudin to the pump circuit to prevent clot formation	

[a] 50 mg of lepirudin is dissolved in 50 mL of 0.9% sodium chloride. [b] The target lepirudin level pre-CPB (>2.5 μg/mL) is lower than the level sought during CPB (3.5–4.5 μg/mL) because of the addition of lepirudin to the pump circuit volume (0.2 mg/kg body weight).

CPB = cardiopulmonary bypass.

hirudin relation flattens at the high concentrations needed during CPB. Further, the activated clotting time does not correlate well with hirudin levels, although it has been used for this purpose [53]. Reliable ($r^2 > 0.90$) results at this time are only obtained using the ecarin clotting time, which can be measured rapidly using whole blood [54]. However, as accuracy of the ecarin clotting time requires normal (at least 70%) prothrombin levels [55], and because hemodilution during CPB can cause hypoprothrombinemia, supplementation of normal human plasma (1 part normal plasma to 1 part patient whole blood) is recommended for a reliable test [53, 56].

In the United States and Canada, there is the additional option to use a commercial ecarin clotting time method available from PharmaNetics (Morrisville, NC) by way of a humanitarian device exemption (H990012) for the specific situation of CPB when heparin is contraindicated because of HIT [57]. The assay is performed using a point-of-care methodology (Thrombolytic Assessment System; manufactured by PharmaNetics; and marketed as Rapidpoint Coag by Bayer Diagnostics, Toronto, Ontario, and Tarrytown, NY). Practical issues include the time required for obtaining the indemnification agreement and institutional review board approval (United States) or patient-specific regulatory approval (Canada).

Clot formation can occur at hirudin concentrations less than 2 μg/mL [58, 59], and the goal is to achieve stable intraoperative hirudin levels at approximately 4 μg/mL [42, 54]. With normal renal function, hirudin levels decline quickly after stopping the infusion. In renal impairment, drug accumulation can cause severe bleeding [40], and ultrafiltration during (or modified ultrafiltration immediately after) CPB or hemofiltration or hemodialysis after surgery may be required (using filters appropriate for removing lepirudin) [60]. After discontinuation of CPB, the blood in the reservoir must be anticoagulated with an additional bolus of lepirudin (Table 3); if this blood is to be reinfused, a cell saving device should be used to wash out the drug. In patients who have received hirudin for several days before CPB, hirudin will have saturated the extravascular compartment, thus contributing to greater hirudin levels after CPB as hirudin redistributes back into the intravascular space (80% of lepirudin distributes in the extravascular space). From experience to date, major bleeding is a frequent problem in HIT patients who receive lepirudin for CPB.

Bivalirudin

Bivalirudin (Angiomax, The Medicines Company, Parsippany, NJ) is a 20-amino acid synthetic peptide modeled after hirudin, which consists of two peptide fragments (connected by a tetraglycine spacer) that respectively recognize the fibrinogen binding site (exosite I) and catalytic site of thrombin. Unlike lepirudin, this bivalent interaction with thrombin is reversible once plasma enzymes (including thrombin itself) cleave the arg3–pro4 bond on bivalirudin. Its short half-life (25 minutes) and predominant enzymic elimination are advantageous for use in CPB. As with lepirudin, the ecarin clotting time is recommended for intraoperative monitoring during CPB [61], although anecdotal success (and some failure) using activated clotting time monitoring exists. For off-pump procedures (at lower bivalirudin concentrations) the activated clotting time can be used [51]. Extracorporeal hemoconcentration can remove up to 70% of circulating bivalirudin and can be applied after discontinuation of the infusion either routinely or specifically in the patient with renal dysfunction [62].

Bivalirudin has been used successfully off-label for anticoagulation during both off-pump [50] and on-pump [61, 63, 64] cardiac surgery in patients with acute or

Table 4. Treatment Protocol for Bivalirudin Anticoagulation During Cardiopulmonary Bypass (Under Investigation[a])

Initial bivalirudin dosing (pre-CPB)	
Initial intravenous (iv) bivalirudin bolus:	1.5 mg/kg body weight
and initiate continuous iv infusion:	2.5 mg · kg^{-1} · h^{-1} (42 μg · kg^{-1} · min^{-1})
Bivalirudin added to pump circuit volume:	50 mg
Target bivalirudin plasma level:	>10 μg/mL before start of CPB
	If <10 μg/mL, give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg · kg^{-1} · h^{-1}
Bivalirudin dosing and monitoring while on CPB	
Continue iv infusion (adjusted as below):	2.5 mg · kg^{-1} · h^{-1} or greater (as above)
Frequency of bivalirudin level monitoring:	Every 30 min using ecarin clotting time
Intraoperative dose adjustments, based on ecarin clotting time (ECT)	
Bivalirudin plasma level (ECT)[b]	*Dosing modification*
>15 μg/mL (>500 s)	Reduce infusion rate by 0.25 mg · kg^{-1} · h^{-1}
10–15 μg/mL (400–500 s)	No change in infusion rate
<10 μg/mL (<400 s)	Give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg · kg^{-1} · h^{-1}
Special steps at end of CPB	
Stop bivalirudin infusion at end of CPB, then either:	
(A) Within 10 min of stopping bivalirudin infusion: First, reinfuse appropriate portion of pump volume to patient, and then give 50-mg bivalirudin bolus to the circuit to prevent clotting; start an infusion of 50 mg · h^{-1} into the circuit only, and continue to recirculate; any subsequent reinfusion of remaining pump volume to patient should be processed through a cell saving device (which removes >90% of bivalirudin); or	
(B) Promptly empty remaining pump volume into cell saving device (replacing the pump contents with crystalloid), thus avoiding need for postseparation bivalirudin boluses to circuit; process blood for reinfusion with cell saving device to remove bivalirudin	

[a] Up-to-date information on protocol amendments are available from the manufacturer of bivalirudin. [b] The target bivalirudin concentration (10–15 μg/mL) corresponds to an ecarin clotting time (ECT) of 400–500 s using the RapidPoint Coag (Bayer); with other ECT methods, the bivalirudin concentration should be determined using a calibration curve.

CPB = cardiopulmonary bypass.

previous HIT. In addition, bivalirudin compared favorably in a randomized trial against heparin in non-HIT patients undergoing off-pump surgery [51]. Bivalirudin was therefore evaluated in a 20-patient pilot study (on-pump, non-HIT), and is currently under investigation in a phase 3 multicenter pivotal trial comparing bivalirudin (Table 4) with UFH for on- and off-pump cardiac surgery in patients with and without HIT.

The enzymic metabolism of bivalirudin presents certain practical issues. Surgical techniques that allow blood to lie stagnant should be avoided, as local bivalirudin levels will decrease owing to its metabolism by proteases (including thrombin) produced in blood exposed to wound or foreign surfaces, leading to local clot formation. As a caveat related to this issue, the presence of visible thrombus in an area of pooled blood, such as in the pericardial cavity, should not be interpreted by the surgeon as indicative of the need for additional anticoagulation, as this may only reflect local bivalirudin metabolism and not correlate with intravascular levels. If blood cardioplegia is used, the blood should be directly sourced from the circuit, and (after mixing with the cardioplegia solution) immediately reinfused into the coronary system. For the same reason, assessment of graft blood flow and testing for leakage should preferably be performed with albumin and saline solutions or, alternatively, using blood taken directly from the patient and used immediately for this assessment. Because hypothermia somewhat reduces the proteolysis of bivalirudin, the patient's core temperature should be maintained at close to 37°C following coming off CPB or completion of the final anastomoses in off-pump procedures, and care should be taken to maintain body temperature during the early postoperative period by active measures.

After separation from CPB, the risk that the circuit may clot rapidly may be even higher than with lepirudin due to bivalirudin's shorter half-life and ongoing metabolism owing to continuing bivalirudin proteolysis. Thus, provision to continue to recirculate pump blood after separation from bypass is made by adding a cross-limb in the bypass circuit at the time of setup, which remains clamped until coming off bypass. After clamping of the venous line, this limb is opened and the contents are recirculated. Within 10 minutes of separation from bypass, should the patient potentially need to return to bypass support, a 50-mg bolus of bivalirudin should be added to the circuit to prevent clotting, and a 50 mg · h^{-1} infusion into the bypass circuit should also be started and continued until such time as it is clear the patient will not require urgent return to CPB. Once postseparation bivalirudin dosing to the circuit has commenced, any remaining pump volume contents intended for reinfusion to the patient should first be processed using a cell saving device, thus washing away most of the bivalirudin. An-

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other approach is simply to drain rapidly the contents of the pump into a cell saving device after separation from bypass (replacing the pump contents with crystalloid) and washing the blood, thus avoiding the possibility of pump clotting without the need to administer additional bivalirudin into the pump.

Danaparoid

Danaparoid sodium (Orgaran; Organon, Oss, the Netherlands) is a mixture of anticoagulant glycosaminoglycans with predominant anti-factor Xa activity and low risk for in vivo cross-reactivity with HIT antibodies [45]. The absence of an acceptable linear correlation between the activated clotting time or activated partial thromboplastin time and the high plasma danaparoid levels required for CPB means that anti-factor Xa levels are required for monitoring [65]. Danaparoid was recently withdrawn from the U.S. market (April 2002), but continues to be available in Canada, continental Europe, Australia, New Zealand, and Japan.

The efficacy of danaparoid for CPB anticoagulation was first shown in dogs before human use for HIT [45, 66]. The largest series [67] describes 53 patients who underwent CPB using a fixed-dose regimen (most without laboratory monitoring). Severe postoperative bleeding (>20 U of blood products required) occurred in 11 (20%) patients; clots in the operative field occurred in 18 (34%) patients. Subsequently, two revised protocols based on patient weight were developed [42, 67], one also recommending intraoperative dose adjustments using a target anti-factor Xa level of 1.5 ± 0.3 U/mL (about twice the usual therapeutic range). However, postoperative bleeding as a result of the long half-life of and lack of antidote for danaparoid remains a problem.

Heparin Plus Antiplatelet Therapy

During the 1980s, CPB in patients with acute or subacute HIT was sometimes accomplished by giving standard-dose UFH once platelet inhibition was achieved using the potent antiplatelet agent, iloprost [68]. An analog of prostacyclin, iloprost inhibits platelet activation by stimulating adenylate cyclase, thus raising platelet adenosine monophosphate levels. Recently, this approach has experienced a revival with epoprostenol sodium (Flolan), a freeze-dried preparation of prostacyclin itself [69, 70]. Epoprostenol is approved for use in patients with primary pulmonary hypertension. Its very short half-life (6 minutes) means that continuous intravenous infusion is necessary.

Complete inhibition of heparin-dependent platelet aggregation by HIT antibodies is generally achieved by doses ranging from 15 to 30 $ng \cdot kg^{-1} \cdot min^{-1}$. Thus, one protocol [69] that aims to avoid intraoperative monitoring of platelet aggregation gradually increases epoprostenol infusion (in 5 $ng \cdot kg^{-1} \cdot min^{-1}$ increments made at 5-minute intervals) until the target rate (30 $ng \cdot kg^{-1} \cdot min^{-1}$) is reached, whereupon standard-dose UFH anticoagulation is given. The infusion is continued until 15 minutes after protamine. The major adverse effect is vasodilation, leading to severe hypotension that requires intraoperative vasopressors.

Conventional antiplatelet agents (aspirin, dipyridamole) do not reliably inhibit HIT antibody–induced platelet aggregation. However, inhibition of the platelet fibrinogen receptor using an anti-glycoprotein IIb/IIIa agent, such as tirofiban (Aggrastat) or abciximab (ReoPro), can block platelet aggregation (though not platelet activation) by HIT antibodies. Using the short-acting agent, tirofiban, Koster and colleagues [71] reported success (44 of 47 patients discharged on schedule from the hospital). Tirofiban is given 10 minutes before standard-dose UFH as a 10-μg/kg bolus followed by 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ continuous infusion, before stopping tirofiban 1 hour before the end of surgery. Unfractionated heparin is neutralized with protamine, and postoperative anticoagulation is achieved using lepirudin. However, in patients with severe renal impairment, tirofiban persists in the circulation and can cause major bleeding refractory to platelet transfusions: three such cases led the manufacturer (MSD Sharp & Dohme, Haar, Germany) to discourage use of this off-label protocol (letter to German cardiac surgeons, 2002). In such patients, extracorporeal elimination of tirofiban (eg, ultrafiltration at the end of CPB or modified zero-balanced ultrafiltration after CPB) might be required.

Miscellaneous

Low-molecular-weight heparin has been used for CPB in some patients with HIT. However, as proper dose-finding studies are lacking, only partial neutralization (60%) is achieved using protamine, and as LMWH can precipitate acute HIT in patients with circulating antibodies, we do not recommend LMWH for anticoagulation during CPB.

Although the direct thrombin inhibitor argatroban has been used successfully for CPB anticoagulation in dogs, experience with its use in humans is limited to cardiovascular procedures not requiring CPB [72]. Thus, it cannot be recommended for use in CPB.

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Appendix

Heparin-Induced Thrombocytopenia and the Cardiac Surgeon, Cardiologist, and Cardiac Anesthesiologist: Summary of Key Points

Definition of Immune Heparin-Induced Thrombocytopenia

1. Heparin-induced thrombocytopenia is defined as thrombocytopenia (see number 3) or thrombosis plus one or more positive tests for HIT antibodies (see also number 5).

Monitoring for Heparin-Induced Thrombocytopenia After Heart Surgery

2. Platelet count monitoring for HIT (as part of a complete blood count) is indicated after cardiac surgery as long as the patient is receiving heparin (either in therapeutic, prophylactic, or flush doses), at least every other day until hospital discharge or postoperative day 14 (whichever occurs sooner).

3. A platelet count fall of 50% or greater from baseline or any thrombosis that occurs 5 to 14 days after cardiac surgery is suggestive of HIT, even when heparin is not being given in the postoperative period (delayed-onset HIT). (The appropriate baseline platelet count is *not* the preoperative platelet count, but rather the highest platelet count in the postoperative period.)

Laboratory Testing for Heparin-Induced Thrombocytopenia

4. Commercially available EIAs and washed platelet activation assays (eg, platelet serotonin release assay or the heparin-induced platelet activation test) are very sensitive for detecting HIT antibodies; thus, with rare exception, a negative test with one of these assays rules out HIT (high negative predictive value).

5. Heparin-induced thrombocytopenia antibody seroconversion of no clinical consequence is common after heart surgery (about 25% to 50% by EIA), and thus the presence of HIT antibodies in the absence of an otherwise unexplained platelet count fall or clinical sequelae such as thrombosis does not indicate HIT.

6. Serum or plasma from patients with acute HIT usually has strong positive HIT antibody results (eg, serotonin release > 80%; EIA optical density > 1.0). In general, the greater the magnitude of a positive HIT antibody test result, the greater the likelihood the patient has HIT.

7. Heparin-induced thrombocytopenia antibodies are transient, and so acute serum or plasma should be tested to investigate a putative episode of HIT.

Frequency of Heparin-Induced Thrombocytopenia and Heparin-Induced Thrombocytopenia-Associated Thrombosis After Heart Surgery

8. In patients receiving unfractionated heparin after cardiac surgery, the frequency of HIT is 1% to 3% by postoperative days 7 to 14.

9. At least 50% of patients with HIT develop arterial or venous thrombotic complications, often beginning after heparin has been stopped because of suspicion of HIT.

Management of Heparin-Induced Thrombocytopenia After Cardiac Surgery

10. Discontinue all heparin if there is a high suspicion of HIT, including heparin administered by intravascular catheter flushes, and consider removing heparin-coated devices.

11. In general, HIT-associated thrombosis should be treated with one of the following alternative anticoagulants: lepirudin (United States, Canada, European Union, Australia, New Zealand), argatroban (United States, Canada), danaparoid (Canada, European Union, Australia, New Zealand), or bivalirudin (United States, Canada, New Zealand).

12. Warfarin and other oral anticoagulants are contraindicated during acute HIT, as acute protein C depletion can lead to microvascular thrombosis causing venous limb gangrene. Oral anticoagulants should be delayed pending substantial recovery of the platelet count (to at least 100×10^9/L), started in low initial doses (maximum, 5 mg) and during concomitant anticoagulation with an agent such as lepirudin, argatroban, or danaparoid. The alternative anticoagulant should be stopped (after a minimum 5-day overlap) only when platelet count recovery is complete and therapeutic oral anticoagulation is achieved.

13. Low-molecular-weight heparin is contraindicated for treatment of HIT.

14. Prophylactic platelet transfusions should be avoided when HIT is strongly suspected, as platelets theoretically may increase thrombotic risk and spontaneous bleeding is uncommon in patients with HIT.

15. For patients strongly suspected of having HIT but without clinical evidence of thrombosis (isolated HIT), an alternative anticoagulant in therapeutic doses is recommended because of the high risk of developing thrombosis. It is also recommended that noninvasive imaging for lower-limb thrombosis be performed because of the high frequency of DVT in patients with HIT.

Cardiac Surgery in a Patient With Previous or Acute Heparin-Induced Thrombocytopenia

16. Standard anticoagulation with UFH is recommended for cardiac surgery in patients with previous HIT in whom HIT antibodies are no longer detectable, or only weakly detectable, by EIA.

Cardiac Surgery in a Patient With Acute or Subacute Heparin-Induced Thrombocytopenia

17. Two general approaches are available for patients in whom standard UFH anticoagulation is contraindicated because of acute or subacute HIT: (1) give an alternative anticoagulant for CPB (eg, bivalirudin, lepirudin, danaparoid), being careful to avoid all intraoperative and postoperative heparin exposure (eg, by means of heparin-bonded arterial filters in the CPB apparatus, heparin-coated pulmonary artery catheters, heparin flushes, and so forth); or (2) give standard heparin anticoagulation together with a platelet antagonist (eg, epoprostenol or tirofiban).

(Subacute HIT indicates that the patient's platelet count has recovered from acute HIT, but HIT antibodies remain detectable, and so there is the potential for rapid-onset HIT if heparin is administered.)

18. No single option listed in number 17 can be generally recommended, given the absence of prospective comparative studies, as well as important differences in jurisdictional approval and availability of the various agents and in appropriate laboratory monitoring and prior physician experience, as well as patient-dependent factors such as renal insufficiency, all of which influence choice of anticoagulant approach.

Reducing Risk of Heparin-Induced Thrombocytopenia After Heart Surgery

19. Unfractionated heparin derived from porcine intestinal mucosa is preferred over heparin obtained from bovine lung, as the risk of HIT antibody formation is less, and porcine heparin has been associated with a lower risk of HIT in other patient populations.

20. There is evidence that LMWH may be less likely than UFH to cause HIT when administered for postoperative antithrombotic prophylaxis. However, LMWH is not well studied in postcardiac surgery patients.

Patients with a History of Type II Heparin-Induced Thrombocytopenia with Thrombosis Requiring Cardiac Surgery with Cardiopulmonary Bypass: A Prospective Observational Case Series

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Heparin-induced thrombocytopenia with thrombosis (HITT) type II is a life-threatening complication of heparin therapy that most often occurs after 5–10 days of exposure to heparin. Anticoagulation is a significant concern for patients with HITT type II being prepared for cardiac surgery requiring cardiopulmonary bypass (CPB). We report a case series of 12 patients with a history HITT type II who underwent CPB and cardiac surgery. Six patients did not express the antibody that mediates HITT type II immediately before surgery. Heparin was used as the anticoagulant for the duration of CPB only, and all these patients did well without thrombotic complications. Six patients expressed the antibody that mediates HITT type II immediately before surgery. Hirudin was used as the anticoagulant for CPB in these patients. The ecarin clotting time was used to guide hirudin therapy during CPB. The patients receiving hirudin did well, but they had a large amount of bleeding, required transfusions of multiple allogeneic blood products, and had a frequent rate of reexploration of the mediastinum after CPB.

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Heparin-induced thrombocytopenia with thrombosis (HITT) type II is an often overlooked but life-threatening complication of heparin therapy. This disorder most often occurs after 5–10 days of heparin exposure (1). HITT is a paradoxical prothrombotic syndrome produced by an antibody against heparin-platelet factor 4 (PF4) complex. Bound to heparin, PF4 partially unfolds exposing a neo-epitope against which an antibody forms. These antibodies bind to the heparin-PF4 to form an immune complex that engages the platelet Fc γ RIIA-receptors, inducing strong platelet activation and aggregation (2). These antibodies can also bind to PF4 on endothelial cell proteoglycans, thereby promoting endothelial injury. These combined events can lead to a precipitous reduction in circulating platelet counts, frequently to $<30 \times 10^9$/L, and life-threatening venous and arterial thrombosis, which can result in limb and organ ischemia (3,4). The profound thrombocytopenia usually resolves once heparin exposure has ceased. Even small doses of heparin, such as prophylactic doses, flush solutions, and heparin-bonded catheters can induce HITT type II (4,5).

Anticoagulation is a significant concern for patients with HITT type II being prepared for cardiac surgery with or without cardiopulmonary bypass (CPB). We report our experience with 12 patients clinically diagnosed with HITT type II presenting for cardiac surgery requiring CPB.

Methods

After IRB approval and written informed consent, we prospectively studied 12 cardiac surgical patients undergoing CPB with a previous clinical diagnosis of HITT type II. The patients were enrolled in a standardized protocol of care secondary to the humane device exemption (HDE) (h9900012) status of the Ecarin Clotting Time (ECT) coagulation test device over 3 yr.

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All of the patients had been diagnosed with HITT type II using clinical criteria. Each patient had a decrease in platelet count to $<100 \times 10^9$/L associated with heparin administration, which increased after heparin cessation. Two patients had thrombotic episodes associated with thrombocytopenia. Because HITT type II is an antibody-mediated disorder, the antibody may resolve over time. Therefore, a patient with a history of HITT type II may no longer have measurable amounts of the antiheparin antibody (6). Each patient had the presence of the HITT type II antibodies determined by enzyme-linked immunosorbent assay (ELISA) for heparin-PF4 complex using goat antihuman antibody that directly detects the heparin-induced antibodies before surgery. Six of 12 patients had a positive ELISA for the heparin-PF4 complex antibodies immediately before surgery. The other six patients had a negative ELISA for the heparin-PF4 complex antibodies immediately before surgery.

All patients received a moderate-dose opioid-based anesthetic, supplemented with benzodiazepines, muscle relaxants, and inhaled anesthetics. A Terumo 5 × 25-membrane oxygenator (Terumo Cardiovascular Systems, Elkton, MD) was used in a Sarns 9000 CPB machine (Sarns Inc, Ann Arbor, MI) at a flow of 2.4 $L \cdot min^{-1} \cdot m^2$. The CPB circuit was primed with 1.5 L of plasmalyte, 10 mEq of sodium bicarbonate ($NaHCO_3$), and 0.5 g/kg of mannitol. All patients had arterial and nonheparin-bonded pulmonary artery catheters placed before CPB, and all flushing solutions were free of heparin. In all patients, antifibrinolytic therapy was administered using either full-dose aprotinin (2×10^6 kallikrein inhibitory units [KIU] [280 mg] followed by a maintenance infusion of 500,000 KIU/h (70 mg/h), with a bypass prime of 2×10^6 KIU [280 mg]) or tranexamic acid (10-mg/kg load followed by 1 $mg \cdot kg^{-1} \cdot h^{-1}$). Our practice for antifibrinolytic use is aprotinin for repeat sternotomies and complex procedures and tranexamic acid for primary procedures. Allogeneic red blood cells were transfused when the hemoglobin concentration became <8 g/dL after discontinuation of CPB and <7 g/dL during CPB. Transfusion of allogeneic fresh frozen plasma, platelets, or cryoprecipitate was based on clinical evidence of bleeding and supporting laboratory studies (thromboelastography [TEG®; Haemoscope Co, Skokie, IL] maximum amplitude <48 mm, platelet count $<102{,}000 \times 10^9$/L, prothrombin time >16.6 s, activated partial thromboplastin time [aPTT] >57 s, or fibrinogen level <144 mg/dL) (7).

Patients who were negative for the HITT type II antibodies underwent cardiac surgery with CPB, and heparin was only administered for anticoagulation during CPB. No heparin or heparin flush was administered after CPB. Porcine heparin was administered to patients as an initial bolus of 300 U/kg and 10,000 U in the priming volume of the oxygenator. Additional heparin (5000 U) was administered when the activated clotting time (ACT) was <450 s in patients not receiving aprotinin. For patients receiving aprotinin, additional heparin was administered when the kaolin ACT was <450 s or the celite ACT was <750 s. After discontinuation of CPB, the initial protamine sulfate dose was 0.013 mg/U of heparin administered. Heparin neutralization was regarded as adequate if the postprotamine ACT value was within 10% of the preheparin ACT value. Additional protamine (20–50 mg) was added at the discretion of the attending anesthesiologist if the ACT had not returned to this range. Intraoperative blood salvage and reinfusion of shed mediastinal blood was used in all cases. Ultrafiltration was not used with any of these patients.

If those patients who had HITT type II antibodies confirmed by ELISA were unable to have their cardiac surgery delayed until the antibodies disappeared, recombinant hirudin (r-hirudin or Lepirudin) was used as the anticoagulant during CPB. The r-hirudin concentration was monitored by measurement of the ECT on the Thrombolytic Assessment System (TAS) point-of-care analyzer (PharmaNetics Inc, Morrisville, NC). Before surgery, a sample of blood was collected in 3.2% sodium citrate tubes, and an *in vitro* titration of r-hirudin was performed to develop an individual patient calibration curve for the ECT. In those patients already on r-hirudin before surgery, when possible, the patient's r-hirudin was discontinued for a 24-h period to collect the *in vitro* titration sample without previous r-hirudin contamination of the sample. To minimize the effects of hemodilution and depletion of procoagulant through contact activation of the CPB circuit, the citrated whole-blood samples were supplemented 1:1 with standard human plasma. This ensures adequate prothrombin and fibrinogen concentrations for precise ECT measurements when the r-hirudin concentrations are larger than 2 μg/mL. All measurements were performed in duplicate.

The dose of r-hirudin was a 0.25 mg/kg bolus before CPB, 0.20 mg/kg in CPB pump prime, and a continuous infusion of 0.5 mg/min after the bolus and throughout CPB (8). The bolus and infusion of hirudin were administered early enough to insure an adequate hirudin concentration of more than 3.5 μg/mL per ECT monitoring (8). Supplemental bolus doses of hirudin and increases in the hirudin infusion occurred to maintain hirudin concentrations larger than 3.5 μg/mL per ECT. The ECT was performed every 15–30 min throughout CPB. There is no Food and Drug Administration (FDA) approved antagonist to hirudin. The r-hirudin infusion was discontinued 15–30 min before termination of CPB. Because r-hirudin has a molecular weight (6980 Da) that is small enough to be effectively hemofiltered with certain large

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flux hemodialyzers, hemofiltration (Hemoconcentrator HC05, 0.5 m (2), cutoff point 65,000 Da; Terumo Cardiovascular Systems) and forced diuresis with furosemide and mannitol were performed on rewarming or near the termination of CPB to assist in the rapid removal of circulating r-hirudin (9). Fresh frozen plasma was also transfused to antagonize hirudins' anticoagulant effect after CPB if bleeding and laboratory tests supported this intervention. Perioperative blood salvage (cell saver) was not used in these patients because of the concern of re-transfusing blood with hirudin.

Results

Demographic information, preoperative anticoagulation, and coexisting diseases for the 12 patients are listed in Table 1. The patients with a positive ELISA for the heparin-PF4 complex antibodies immediately before surgery were considered too unstable from the standpoint of their cardiovascular disease to delay surgery until the ELISA became negative. For all 12 patients, the type of surgery performed, the intraoperative anticoagulant used, duration of CPB, the perioperative hirudin concentrations or ACT values, and the amount of allogeneic blood products administered during surgery are listed in Table 2. Postoperative blood use, blood loss, and need for surgical reoperation of the mediastinum for the 12 patients are listed in Table 3. The patients who received hirudin anticoagulation tended to receive much larger volumes of allogeneic blood products and had more blood loss than the patients who received anticoagulation with heparin. All of the patients survived the surgery, and thrombotic or embolic complications were not detected.

An *in vitro* titration of hirudin was performed on the patient's blood before the cardiac surgical procedure. Each individual patient's titration curve had r^2 values more than 0.98. The titration curves for all six patients combined are shown in Figure 1. The r^2 was 0.94.

Discussion

Patients with HITT and who require CPB present a significant challenge. Cooperation between hematologists (to aid in diagnosis of HITT), laboratory medicine specialists (to correctly perform the ECT), cardiac surgeons, perfusionists, and anesthesiologists (to care for the patient) is required to provide best results. Our prospective observational study has demonstrated that for those patients without heparin-PF4 complex antibodies by ELISA immediately before surgery, it is possible to receive heparin for a brief period encompassing the duration of CPB without thrombotic or embolic episodes. Further, patients who continue to have heparin-PF4 complex antibodies by ELISA immediately before cardiac surgery can successfully undergo CPB using hirudin as the anticoagulant in conjunction with ECT monitoring.

HITT type II is a clinical diagnosis that is supported by laboratory tests (4). HITT type II is identified by the following clinical criteria: a massive decrease in platelet count with exposure to heparin, thromboembolism, resolution of thrombocytopenia after cessation of heparin exposure, and detection of heparin-dependent antibodies. Various laboratory tests can be used to verify the diagnosis of HITT type II (5,10). The two most common tests are the heparin-induced platelet aggregation assay (HIPAA) by platelet-rich plasma aggregometry and ELISA for heparin-PF4 complex using goat antihuman antibody that directly detects the heparin-induced antibodies.

Although the prevalence of antibodies to the heparin-PF4 complex by ELISA may be as frequent as 61% at five days after cardiac surgery, the incidence of clinical HITT type II in cardiac surgery patients is estimated to be 1.3% (11,12). Yet, if HITT develops in this setting, both the morbidity and mortality can be frequent. Walls et al. (11) reported a 51% incidence of thromboembolic complications with an accompanying mortality of 37% in patients with HITT after CPB. Therefore, heparin administration in any form should be avoided if possible in patients with documented HITT type II antibodies. However, heparin is the preferred anticoagulant for CPB. Therefore, in patients with circulating heparin-PF4 antibodies, the urgent or emergent necessity for cardiac surgery remains problematic. The FDA has approved the use of r-hirudin for anticoagulation in patients with documented HITT type II. Hirudin is a highly selective thrombin inhibitor that does not inhibit other serine proteases. It was originally derived from the saliva of leaches. Although hirudin is available as an anticoagulant for CPB, appropriate dosing and anticoagulation monitoring are not fully standardized. The following dosing regimen for hirudin administration during CPB has been shown to be effective (1,8): 0.25-mg/kg hirudin bolus before CPB, 0.20 mg/kg in CPB pump prime, and continuous infusion 0.5 mg/min after bolus and throughout CPB.

With the use of hirudin instead of heparin, which is the conventional method of anticoagulation monitoring, the ACT is not applicable. Instead, there is an effective point-of-care test to measure hirudin levels during CPB based upon the FDA approved coagulation device called the "TAS." The test cartridge for the TAS that measures hirudin levels is the ECT (1). The mechanism by which the ECT measures hirudin concentrations is by ecarin, derived from snake venom, converting prothrombin to meizothrombin. Because hirudin inhibits meizothrombin's conversion of fibrinogen to fibrin, the time it takes for clot formation to

Table 1. Patient Demographics

Patient number	Age (yr)	Sex	Weight (kg)	Height (cm)	Preoperative creatinine	Preoperative	Coexisting diseases
ELISA +							
1	14	M	59	170	0.7	—	Two previous Tetralogy of Follot repairs, right ventricular outflow obstruction from endocarditis, and continuing septic pulmonary emboli
2	76	M	79.5	180	1.6	Hirudin	Coronary artery disease; acute pulmonary edema; severe left ventricular dysfunction (LVEF 15%–20%), left-cerebral vascular accident; hyperlipidemia
3	74	M	91.4	166	2.2	—	Coronary artery disease; renal insufficiency; type II diabetes mellitus; hypertension; hyperlipidemia
4	69	F	67.6	160	0.7	Hirudin	Aortic stenosis; renal failure on dialysis; hepatic insufficiency secondary to extreme aortic stenosis, hyperglycemia; atrial fibrillation; asthma
5	80	F	73.6	145	1.2	Warfarin	Severe aortic stenosis
6	83	F	92.1	163	1.9	Warfarin; hirudin	Right atrial mass; bilateral pulmonary fibrosis; renal failure on dialysis; diabetes mellitus
ELISA −							
1	74	M	104	173	1.3	—	Coronary artery disease; hypertension; hyperlipidemia, deep venous thrombosis and pulmonary embolism with previous HITT episode, atrial fibrillation
2	33	F	57.6	151	1.3	—	Severe mitral stenosis; systemic lupus erythematosus; h/o antiphospholipid syndrome; h/o severe pulmonary hypertension
3	68	F	57.7	155	0.9	Warfarin	Severe aortic stenosis; rheumatic heart valve disease; type II diabetes mellitus
4	59	F	65	177	1.1	Warfarin	Severe chronic thromboembolic pulmonary hypertension with suprasystemic pulmonary artery pressures; severe RV dysfunction; polycythemia vera
5	75	F	87.3	165	1.2	—	Coronary artery disease; patent foramen ovale; noninsulin dependent diabetes mellitus
6	74	M	105.8	186.6	1.9	ASA	Coronary artery disease; hypertension; smoking history

ELISA = enzyme-linked immunosorbent assay; RV = right ventricular; ASA = aspirin; HITT = heparin-induced thrombocytopenia with thrombosis.

occur is directly related to the hirudin concentration in the plasma. Previous investigations have maintained hirudin concentrations more than 3.5 μg/mL throughout the duration of CPB. The ECT cartridge has recently received a HDE from the FDA (HDE-h9900012), and a compassionate use IRB approval or a research protocol is required for its use. Before CPB, an *in vitro* titration of hirudin using the patient's blood is required to develop a titration curve for the ECT test's response to various hirudin concentrations.

The previous studies of hirudin use for CPB, from which we derived our clinical care protocol, have been retrospective studies performed primarily in Germany (1,8). These studies have demonstrated good success with the use of hirudin anticoagulation during CPB with ECT guidance in larger numbers of patients. Because hirudin is eliminated primarily through renal excretion, we also augmented hirudin elimination through the use of ultrafiltration and forced diuresis, as reported in the previous studies.

It is now recognized that HITT type II is a transient immune response to the conformationally altered PF4 heparin complex triggered by heparin administration that results in thrombocytopenia in addition to a prothrombotic state and thromboembolic events (6). The immune response begins to wane after eliminating further heparin exposure, and the antibodies that mediate HITT type II often are no longer detectable after several months (6). Therefore, a patient with a very significant history of HITT type II may no longer have the PF4 complex antibody after several months. Six of the 12 patients with clinical histories of HITT type II did not have detectable anti-PF4 antibodies by ELISA. Brief exposure to heparin was used for CPB

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Table 2. Intraoperative Information

ELISA+	Procedure	CPB duration (min)	Anticoagulant	Hirudin concentration (μg/mL) 1st on CPB	Last on CPB	Last Post-CPB	OR blood products (mL or units) RBCs	IAT	FFP	Plt	Cryo
1	RVOT reconstruction	82	Hirudin	2.6	2.7		10 u	0	10 u	16 u	10 u
2	CABG ×3	53	Hirudin	0.96	3.8	2.4	2 u	0	3 u	6 u	0 u
3	CABG ×3	70	Hirudin	6.5	5.4	0.6	4 u	0	9 u	6 u	0 u
4	AV replacement	71	Hirudin	3.2	3.0	0.3	16 u	0	26 u	3 u	10 u
5	AV replacement	71	Hirudin	4.4	4.2	1.7	5 u	0	7 u	0 u	0 u
6	Excision right atrial mass	29	Hirudin	6.4	3.4	0.9	14 u	0	21 u	6 u	0 u

ELISA−	Procedure		Anticoagulant	ACT test (s) 1st on CPB	Last on CPB	Postprotamine	OR blood products (mL or units) RBCs	IAT	FFP	Plt	Cryo
1	Redo CABG ×3	Off pump	Heparin	383	—	124	0 u	225	0 u	0 u	0 u
2	MV replacement	68	Heparin	1500	711	119	3 u	1125	0 u	18 u	0 u
3	AV replacement	61	Heparin	861	1340	132	2 u	675	0 u	0 u	0 u
4	Pulmonary embolectomy	339	Heparin	750	381	149	4 u	900	8 u	12 u	10 u
5	CABG ×3 PFO closure	78	Heparin	615	540	150	2 u	675	0 u	0 u	0 u
6	CABG ×3	119	Heparin	559	538	149	0 u	500	0 u	0 u	0 u

The second ELISA + patient started as an off-pump CABG with one-half of the standard hirudin dose administered. He emergently needed to be placed on cardiopulmonary bypass (CPB) secondary to hemodynamic instability, and the standard hirudin dose for CPB was administered before CPB. His ecarin clotting time (ECT) was low and more hirudin given. No patients who received heparin, received aprotinin.

RBC = red blood cells; IAT = intraoperative autotransfusion; FFP = fresh frozen plasma; Plt = platelets; Cryo = cryoprecipitate; RVOT = right ventricular outflow tract; CABG = coronary artery bypass grafting; AV = aortic valve; MV = mitral valve; PFO = patent foramen; ACT = celite activated clotting time; OR = operating room; ELISA = enzyme-linked immunosorbent assay.

and reversed after CPB with protamine because of the absence of antibodies. No further heparin was administered after that time, and heparin was excluded from the flush systems for any invasive catheters to prevent any heparin from being in the patient, should anti-PF4 antibodies redevelop in response to heparinization during CPB. None of these patients developed detectable thromboembolic phenomenon after surgery. The blood loss and transfusion requirements in these patients were consistent with our general population of cardiac surgical patients.

Because the kidney removes hirudin, patients with renal failure or insufficiency may benefit from the use of an alternative anticoagulant. Koster et al. (13,14) recently reported on the use of the combination of the short acting platelet glycoprotein IIb/IIIa inhibitor tirofiban (load 10 μg/kg followed by an infusion of 0.15 $\mu g \cdot kg^{-1} \cdot h^{-1}$), followed with standard-dose unfractionated heparin to accomplish CPB in 10 patients who had renal impairment. The patients were placed on hirudin infusions upon arrival to the intensive care unit adjusted to an aPTT of 40–60 seconds. There were no thrombotic complications, and the patients had very little bleeding and allogeneic blood transfusion requirements. A new FDA-approved specific thrombin inhibitor, bivalirudin, is less dependent on renal function for drug clearance (normal renal function, $t1/2$ = 25 minutes; severe renal impairment, $t1/2$ = 57 minutes)[1] than hirudin. This drug could also be used in the same way as hirudin for anticoagulation in patients with or without renal insufficiency who require CPB, although there are no published studies using this drug in CPB (15,16).

There are limitations to our case series. The diagnosis of HITT type II is based on both clinical and pathologic criteria. The most common clinical abnormality is thrombocytopenia, which is often complicated by thrombosis. Only one of our ELISA negative patients had a previous positive ELISA with the initial diagnosis of HITT. Therefore, a possibility is that those patients with a negative ELISA may never have had HITT, and the clinical diagnosis was incorrect. The accuracy of the confirmatory tests for HITT type II is not perfect. In our protocol, we chose to use the ELISA for the heparin-PF4 complex antibodies immediately before surgery as the determinant for whether to use heparin as the anticoagulant during CPB. The ELISA is very sensitive but has a frequent false-positive rate (12). There have been reports of false negatives with this assay also. An alternative assay that is popular in

[1] Package insert: Angiomax® (bivalirudin) for injection manufactured by Ben Venue Laboratories, Bedford, Ohio.

Table 3. Postoperative Information

Patient number	ICU blood products (ml or units)					ICU blood loss			Reoperate	Reason for reop
	RBCs	IAT	FFP	Plt	Cryo	4 h (mL)	12 h (mL)	24 h (mL)		
ELISA+										
1	0 u	0	3 u	6 u	0 u	300	560	1040	no	—
2	8 u	0	10 u	6 u	10 u	460	2460	3445	yes	bleeding
3	4 u	0	5 u	12 u	10 u	820	2350	2780	yes	bleeding
4	9 u	0	12 u	12 u	0 u	1050	1890	2415	yes	bleeding
5	2 u	0	0 u	0 u	0 u	240	340	460	no	—
6	3 u	0	5 u	6 u	0 u	210	545	740	no	—
ELISA−										
1	0 u	0	0 u	0 u	0 u	70	130	260	no	—
2[a]	0 u	0	0 u	0 u	0 u	60	215	450	no	—
3	0 u	0	0 u	0 u	0 u	90	170	260	no	—
4	0 u	450	8 u	1 u	20 u				yes	bleeding and tamponade
5	0 u	0	0 u	0 u	0 u	70	329	424	no	—
6	0 u	0	0 u	0 u	0 u	90	430	607	no	—

RBC = red blood cells; IAT = intraoperative autotransfusion; FFP = fresh frozen plasma; Plt = platelets; Cryo = cryoprecipitate; ELISA = enzyme-linked immunosorbent assay.

[a] Blood loss data on the 4th ELISA− patient who had a pulmonary thromboembolectomy lost secondary to need for urgent reoperation for cardiac tamponade.

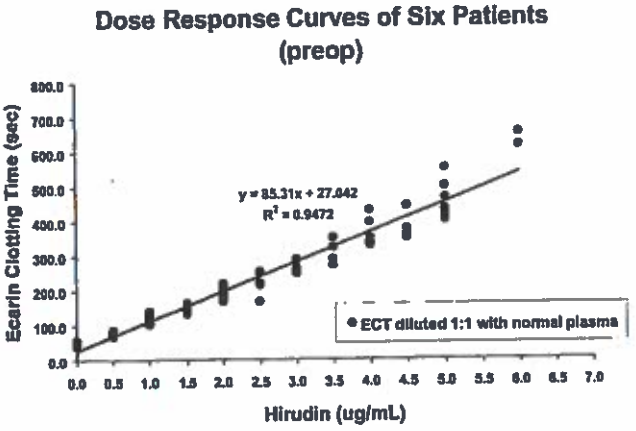

Figure 1. The dose response of the ecarin clotting time (ECT) to *in vitro* titration of hirudin in six patients with the patient's blood being diluted 1:1 with pooled normal plasma. Each dot represents the results from one patient, and many data points overlap.

Europe is a functional assay based on the platelet activating properties of the HITT antibody in platelet-rich plasma aggregometry or HIPAA. The HIPAA is difficult to perform and user dependent. It also has a frequent false-positive rate. Another limitation of our study is that a large number of our patients had impaired renal function. As a result, hirudin clearance was impaired, and these patients had large blood loss and allogeneic transfusion requirements. Use of the newer alternative anticoagulants listed above would be beneficial in this population. We also had a much larger amount of bleeding and transfusion than previously reported by Koster et al (13,14). The patients described in this manuscript were very sick (many with hepatic and renal insufficiency), and this may have resulted in the large amount of bleeding and blood transfusion. Another cause for the large blood loss and allogeneic transfusion requirements in the hirudin treated patients may be that intraoperative auto infusion was not used in these patients. Use of intraoperative auto infusion has been shown to reduce allogeneic blood use (17).

In conclusion, patients with HITT type II who require cardiac surgery and CPB constitute a significant challenge. Cooperation between multiple specialties is critical to successfully manage these patients. This is a case series of patients who, because of FDA requirements, were cared for under a defined protocol of care. With the proper anticoagulation and monitoring, this population can successfully undergo cardiac surgery and CPB.

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Hematologic Aspects of Cardiac Surgery

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Introduction

Patients with cardiovascular disease have a host of underlying hemostatic derangements that predispose to thrombotic disorders. Recent literature indicates that many of the risk factors for thrombosis in cardiovascular disease are inherited and include disorders of major platelet receptors, dysfunctional fibrinolysis, and defects in anticoagulant feedback mechanisms.

When patients with cardiovascular disease undergo "open-heart" surgery utilizing cardiopulmonary bypass (CPB), the hemostatic system is impaired leading to bleeding and the frequent need for transfusion of allogeneic blood products. This occurs as a result of hemodilution of the patient's platelets and coagulation factors by the extracorporeal circuit priming solution and the induction of microvascular coagulation by contact of blood with the synthetic surfaces. This microvascular coagulation leads to thrombin formation and to subsequent fibrinolysis, platelet activation, and platelet dysfunction. Because of the multifactorial etiology of the CPB-induced hemostatic defect, a multimodal approach to blood conservation and hemostasis must be employed throughout the entire perioperative period.

Preoperative Preparation

The population presenting for cardiac surgery is frequently unable to donate autologous blood preoperatively due to concomitant illnesses, preoperative anemia, and the need to maintain oxygen carrying capacity. In addition, the acute nature of cardiac surgery makes the 4-6 week time period for autologous donation rarely possible.

Recombinant erythropoietin (Epogen®, Amgen, Thousand Oaks, CA) was first used clinically to treat the anemia of chronic renal failure. Use in the perioperative patient has distinct potential advantages such as an increase in preoperative hematocrit, an increase in the volume and rate of autologous blood withdrawal, a reduction in the need for allogeneic blood transfusions, and an improvement in erythrocyte recovery indices postoperatively. The first studies in cardiac surgical patients documented increases in the volume of preoperative autologous blood donation, and maintenance of perioperative hemoglobin in patients receiving intravenous or subcutaneous erythropoietin for up to two preoperative weeks.[1] Subcutaneous doses range from 100-600 U/kg weekly for 2-3 weeks.

Platelet Sequestration Prior to CPB

Platelets can be sequestered prior to the insult of cardiopulmonary bypass (CPB) by pre-bypass harvest of either fresh whole blood or platelet-rich plasmapheresis. Subsequent reinfusion after CPB ensures that the platelets have not been exposed to the evil humors of the bypass procedure. The former technique has been associated with improved hemostasis in children and adults but is highly dependent on preoperative hematocrit allowing for withdrawal of blood prior to surgery.[2,3] The harvest of platelet-rich plasma is a potentially valuable procedure in that the patient's red blood cell count is preserved and changes in intravascular volume are minor if a highly effective technique of sequestration is utilized. Many randomized controlled trials in high risk patients cast doubt on the efficacy and safety [4] of preoperative platelet pheresis.[5,6] The success of this technique rests on a high platelet yield of approximately 3.5×10^{11} platelets (approximately 30% of circulating platelets) and may be augmented with concomitant use of other blood conservation techniques.

Heparin and Protamine

Surgical procedures requiring cardiopulmonary bypass (CPB) have been successfully conducted for decades as a result of systemic anticoagulation using heparin. Heparin is ideal in that its activity is rapid in onset, it is readily reversed with protamine sulfate, and it is conveniently measured using the activated clotting time (ACT), which increases linearly with heparin dose. Heparins are heterogeneous carbohydrates that vary in molecular weight and in biological activity. Individual responses to heparin vary greatly among patients and are dependent on such factors as patient age, sex, body surface area, heparin source (bovine vs. porcine), and prior heparin exposure.

Protamine administration has been associated with histamine-related hypotension, mild to severe anaphylactoid reactions, frank allergy, and catastrophic pulmonary arterial hypertension. Protamine has anticoagulant and anti-platelet effects when given alone or in excess of heparin; thus its dose should be carefully calculated. Furthermore, only the higher molecular weight heparins are specifically susceptible to protamine antagonism.

There is a paucity of research confirming that an ACT $\geq$ 400sec is safe in inhibiting thrombin formation during CPB. The optimal amount of heparin for adequate anticoagulation for CPB remains controversial as is the optimal dose of the protamine required to reverse heparin-induced anticoagulation. A number of different heparin and protamine management strategies have been reported to result in reduced perioperative bleeding. Both heparin and protamine have adverse effects on the hemostatic, immunologic, and cardiovascular systems, thus administration of the minimal effective dose would seem to be advantageous. Higher heparin concentrations have been associated with increased mediastinal tube bleeding postoperatively[7] possibly due to heparin rebound or to platelet dysfunction.[8] Conversely, some investigators postulate that higher heparin levels blunt the consumptive coagulopathy that occurs with CPB and lead to reduced bleeding.[9] Lower protamine doses have been successfully used to neutralize heparin after CPB and have been associated with reduced bleeding and transfusion requirements. This combination of higher heparin and lower protamine doses has been recommended as beneficial in reducing postoperative bleeding.[10]

Although ACT is the most commonly used test to ensure adequate heparin anti-coagulation, ACT is criticized for its propensity to overestimate the anticoagulant response under conditions of hypothermia, hemodilution, or aprotinin therapy. Using ACT alone, patients may be potentially susceptible to a consumptive coagulopathy. For this reason, point of care assays that strive to maintain a therapeutic heparin effect based on the individual patient's sensitivity to heparin have been advocated.[10-12]

Patients on preoperative heparin therapy traditionally require larger heparin doses to achieve a given level of anticoagulation when that anticoagulation is measured by the ACT. Presumably this "heparin resistance" is due to deficiencies in the level or activity of antithrombin III (ATIII).[13] Other possible etiologies include enhanced factor VIII activity and platelet dysfunction causing a decrease in ACT response to heparin.[14] Montes and Levy have shown that the in vitro addition of ATIII enhances the ACT response to heparin.[15] ATIII concentrate is now available and represents a reasonable method of treating patients with documented ATIII deficiency.

Platelet Function

The hemostatic defect of CPB is multifactorial in etiology. The most frequently implicated post-CPB hemostasis abnormality is platelet dysfunction. The temporal course of post-CPB bleeding correlates most closely with abnormalities of tests of platelet function, not those of platelet number. The heterogeneity of the platelet function defect of CPB (hypothermia, drugs, fibrinolysis, receptor defect, contact activation),[16,17] partly explains the difficulty investigators have had in diagnosing and consistently measuring it.[18,19] Platelet function testing has become an important focus of hemostasis monitoring in cardiac surgical patients.

Many patients present to the operating room having been recently exposed to drugs that significantly impair platelet function. These include the GPIIbIIIa antagonists abciximab, eptifibatide, and tirofiban and the thienopyridine ADP receptor antagonists ticlopidine and clopidogrel. These drugs are certain to become even more prevalent in clinical practice because they have been shown to be effective in reducing ischemic complications in patients who have vascular disease, have had an interventional cardiology procedure, or have had cardiac surgery.[20,21] Baseline platelet function and the magnitude of impairment during CPB are important to ascertain. Point-of-care platelet function monitors that may be advantageous in monitoring the post-CPB patient with a bleeding disorder include thromboelastography, Hemostatus (Medtronic, MN), PlateletWorks (Helena, TX), and the Ultegra (Accumetrics, CA).[22-24]

Off-Pump Cardiac Surgery

The ability to perform coronary artery bypass grafting (CABG) without the use of CPB holds many potential hemostatic advantages. Lack of exposure to extracorporeal circulation minimizes the systemic inflammatory response, hemostatic defects, and thromboembolic risks that result from conventional CABG employing CPB. Additional benefits include the potential for lowered costs due to decreased perioperative bleeding, reduced need for transfusion, rapid patient recovery, and early extubation.[33,34]

Blood Conservation Strategies by Perioperative Time Interval

Preoperative	Pre-CPB	CPB	Postoperative
Erythropoietin/Iron	Whole blood harvest	HBC ± low heparin dose	Transfusion algorithms
Autologous pre-deposit	ANH	Leukoreduction	Tolerate anemia
D/C platelet inhibitors	Anti-fibrinolytics	Avoid cardiotomy	Anti-fibrinolytics
"Platelet Anesthesia"	PRP	High hep/low protamine	Reinfusion shed blood

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Cardiopulmonary Bypass/Extracorporeal Membrane Oxygenation/Left Heart Bypass: Indications, Techniques, and Complications

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KEYWORDS
• Cardiopulmonary bypass
• Extracorporeal membrane oxygenation • Left heart bypass
• Complications • Coronary artery bypass grafting
• Valve surgery

Cardiopulmonary bypass (CPB) has revolutionized the ability to provide cardiorespiratory support and has advanced the field of cardiac surgery. This invention has given surgeons the ability to perform many procedures that were not possible previously. The concept and development of CPB has been pioneered by numerous legendary surgeons. Alexis Carrel and Charles Lindbergh developed a device that successfully perfused organs, including hearts, keeping them alive for several days.[1] John Gibbon[2] deserves credit for devising the concept of a heart-lung machine after caring for a young woman with a massive embolus in 1930. Over the next 20 years, Gibbon developed the heart-lung machine during his time at the Massachusetts General Hospital, the University of Pennsylvania, and Thomas Jefferson University. In the early 1950s, Lillehei and colleagues[3,4] at the University of Minnesota developed a technique called controlled cross-circulation by using circulatory support from another person's native circulation, usually the patient's parent or relative. By 1955,

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Lillehei abandoned cross-circulation and began using CPB; this approach was rapidly adopted by many surgical groups.

The safe use of CPB requires an understanding of the device by all members of the operative team. Specifically, the cardiac surgeon, the anesthesiologist, and the perfusionist all must be experienced and knowledgeable in their understanding of the physiology of CPB, its risks and limitations, and the potential injuries that may result from its misuse. Protocols for the use of CPB are developed collaboratively, and any deviation from a protocol should be based on the needs of the individual patient and agreed to by all team members. If the surgeon is to realize the full advantage of CPB, he or she must have knowledge of the perfusion circuit in use at their institution. This includes priming solutions, speed and ability to vary perfusate temperature, maximum and minimum flow rates, and available cannula sizes.

Before each procedure, the surgeon must develop a plan for conducting the operation, especially the use of CPB. The surgeon should review with the other team members the planned incisions, methods of cannulating the heart and great vessels, the systemic and myocardial temperatures desired, the possible need for low flow or circulatory arrest, and any anticipated pathologic or anatomic variations that may require alterations in the plan.

The surgeon should consider all potential complications during the planning of the operation—possible anatomic variants and catastrophic events. Examples of anatomic variants might include mitral regurgitation with a heavily calcified posterior mitral annulus requiring a longer and more complex operation with additional steps to protect the myocardium, a persistent left superior vena cava (SVC) accompanying an atrial septal defect, or a tetralogy of Fallot with a variant coronary artery crossing the right ventricular outflow tract. Potential catastrophic events should be reviewed frequently, since they occur suddenly, and all members of the surgical team must be prepared to deal with them rapidly and precisely. Catastrophic events during reoperative surgery include unexpected right ventriculotomy or aortotomy, or ventricular fibrillation before the sternum is open.

INDICATIONS FOR CPB

The most common indication to use CPB is to provide cardiac and respiratory support during operations on the heart or great vessels. Coronary artery bypass grafting (CABG) still remains the most frequent use for CPB.[5] Roughly 20% of CABG procedures in the United States are performed without the use of CPB (off-pump CABG) and use the patient's own heart and lungs to maintain perfusion to the body.[5] Other common procedures where CPB is used in adult and/or acquired diseases include valve operations and operations on the ascending aorta and aortic arch. In these cases, it is not uncommon to use CPB to cool the patient and allow the bypass circuit to be temporarily ceased. This allows for a bloodless field to perform critical parts of the operation while protecting the brain. CPB has revolutionized the approach to repair of congenital heart defects. Rarely, CPB is also used to provide hemodynamic support during major venous reconstruction. An additional benefit of the bypass in this instance is in cases of major venous injury or bleeding, shed blood can be collected and recirculated to maintain intravascular volume and perfusion. Occasionally, CPB is used in complex airway and pulmonary operations and reconstructions. CPB has also been used for isolated hyperthermic limb perfusion to deliver chemotherapy at supranormal temperatures to treat malignancy confined to one limb.[6] The primary goals and purposes of CPB are listed in Box 1.

Box 1
Purposes and goals for CPB

1) Maintain perfusion to brain and other vital organs
2) Provide a bloodless field (heart, great vessels, or other) to allow the surgeon to visualize and perform the operation
3) Maintain thermoregulation for protection of organs (cooling and warming)
4) Provide cardiac assistance/protection
5) Provide pulmonary assistance/protection

COMPONENTS OF CPB CIRCUIT

The components of the CPB circuit include venous cannula(e) typically in the right atrium or vena cavae, a venous reservoir, a membrane oxygenator, a heat exchanger, a pump, a microfilter in the arterial line, and an arterial cannula(s) (Fig. 1). Cannulae can be placed in the right side of the heart, into the right atrium, or into the SVC and inferior vena cava (IVC) and secured in place with 3-0 or 4-0 polypropylene (Prolene) pursestring sutures. These can be placed directly by opening the pericardium or percutaneously through the internal jugular vein and femoral vein. These latter approaches are used during minimally invasive cardiac operations. They remove lines from the operative field and allow for smaller incisions. Venous drainage can be obtained with gravity, whereby the venous reservoir is placed 40 to 70 cm below the level of the heart, or with vacuum suction. Venous cannula size is determined by the patient size, size of the right atrium and/or vena cava, and amount of flow desired.

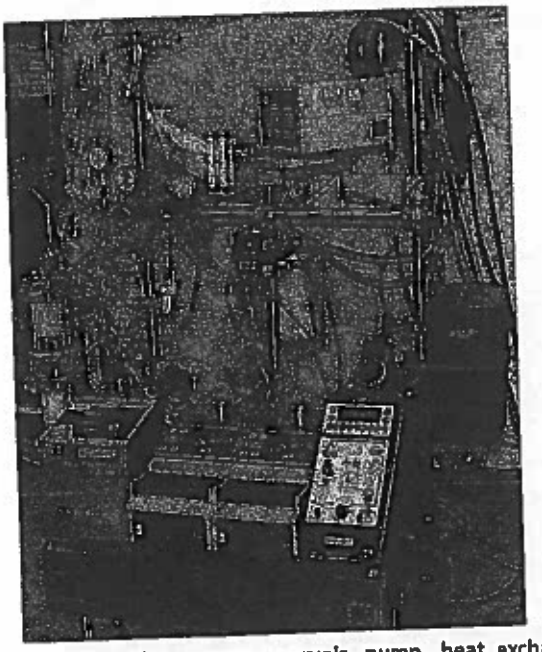

Fig. 1. CPB circuit, including the venous reservoir, pump, heat exchanger, membrane oxygenator, and arterial filter.

Venous reservoirs provide a low pressure chamber that serves as a storage chamber for venous and shed blood. The reservoir can hold an additional 2 to 3 L of blood volume to allow for uninterrupted arterial blood flow if venous return is occluded. Rigid canister reservoirs facilitate removal of venous air and are easier to prime, whereas soft plastic bags maintain a closed system and lower the risk of embolization.[7,8]

Blood in the circuit then goes through a membrane oxygenator which distributes a thin layer of blood over a large surface area with high differential gas pressures across a thin microporous (0.3–0.8 μm pores) hollow-fiber membrane layer to facilitate oxygenation. Since carbon dioxide is highly diffusible in the plasma, it is removed easily through the membrane oxygenator. Partial pressure of oxygen in arterial blood (PaO_2) is controlled by the fraction of inspired oxygen delivered to the oxygenator, whereas partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is controlled by the sweep speed of gas flow. Traditional bubble oxygenators were cheap, but they had a high risk for gas embolization and are no longer manufactured.

A heat exchanger is commonly used and allows for active cooling and rewarming of blood going into the patient. The temperature differential between the patient and blood is limited to a difference of 10°C to prevent bubble emboli. Moreover, blood should not be warmed over 42°C to minimize protein denaturation and emboli.[7,8] A separate heat exchanger is used for cardioplegia and is often kept at temperatures of 4°C to 15°C.

The most recognized component of the CPB circuit is the pump (Fig. 2). Two options for pumps include roller pumps and centrifugal pumps. Roller pumps are independent of afterload, requiring low prime volumes, and they are cheap; however, they have a potential for air embolism, and they can cause significant positive and negative pressure, resulting in tubing rupture. Centrifugal pumps are afterload sensitive, adapt to venous return, and are superior for left heart bypass (LHB) and for long-term bypass, at the expense of large priming volumes, higher cost, and potential for passive backward flow.

The risk of embolism has been greatly decreased by the introduction of filters. Numerous sources of gaseous microemboli smaller than 500 μm are present, including loose pursestrings around venous cannulae, stopcocks in the circuit used for injection of medications, priming solutions, oxygenators, and rapid warming of

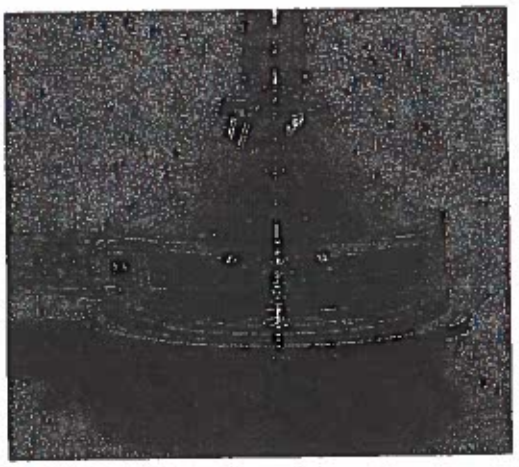

Fig. 2. Centrifugal pump used in CPB, ECMO, and LHB.

cold blood. Blood itself is the primary source for particulate emboli, including thrombin, fibrin, platelet clots, hemolyzed blood cells, and fat particles as well as shed muscle, bone, and marrow that gets aspirated into the cardiotomy reservoir.

Methods to minimize emboli to the arterial system include the use of membrane oxygenators, centrifugal pumps, and filters in the cardiotomy venous reservoir and in the arterial line. In our practice, we use two sequential arterial filters to decrease the number of microemboli in the arterial system. The temperature differential between the blood in the circuit and the body is maintained at less than 10°C to minimize emboli formation.

TECHNIQUES/CONDUCT OF CPB

Although the surgeon takes primary responsibility for the patient during the hospital course, a team of experts is required to administer anesthesia, maintain perfusion, and relay changes in the patient status during the operation. The surgeon will determine the plan of the operation, including methods of cannulation, cardioplegia, and cooling. The anesthesiologist is responsible for induction of anesthesia, endotracheal intubation, and the placement or insertion of most monitoring devices. In patients who are hemodynamically unstable, direct arterial pressure measurement should be established and a pulmonary artery catheter inserted before the induction of anesthesia. Often, the anesthesiologist provides assistance with transesophageal echocardiography (TEE) during the operation. The perfusionist helps to select the optimal cannula size, provides circulatory support and cardiac protection, and maintains anticoagulation during the operation. Further, the perfusionist is responsible for maintaining a written perfusion record and performing a series of safety checks. The surgeon, anesthesiologist, and perfusionist must have free and open communication.

Patient Positioning

Once all monitoring lines have been placed, the patient is positioned and pressure points are padded to prevent pressure necrosis. All monitoring cables and lines are secured to prevent displacement or disconnection during the operation. The traditional approach is through a median sternotomy. In this case, a padded roll is placed beneath the patient's shoulders and arms placed at the sides to avoid brachial plexus injury. Minimally invasive approaches to the mitral and tricuspid valve are often performed through a right mini-thoracotomy. In this setting, a small bump is placed under the right chest and arms are secured at the patient's sides.

Sterile preparation of the skin and draping is performed to ensure access to all aspects of the operative field. This typically includes the chest, abdomen, and both groins, as well as both lower extremities if saphenous vein is needed for CABG. In cases where the saphenous vein may be of poor quality and additional conduit for CABG is required, the nondominant arm is prepped in the field to harvest the radial artery.

The pump and cell-saving equipment are brought into position and the pump lines are passed to the field. The pump lines are located such that the operative field and surgeons are unhampered; with the pump lines in full view of the perfusionist, allowing immediate access to the lines should an event occur. The lines should be secured in a standard manner so that even excessive force cannot displace them. Inexperienced members of the team are instructed not to touch or compress the lines.

Incisions

The selection of the incision site for exposure and cannulation of the heart is based on considerations of safety, exposure, and cosmesis. Anatomic and pathologic

variations, such as a large ascending aortic aneurysm pressing against the sternum or severe pectus excavatum in which the entire heart is displaced to the left chest, may require careful planning to avoid catastrophe. Obviously, variations in the incision to achieve cosmesis must not compromise safety or adequate exposure.

The pericardium is opened in the midline from its reflection on the aorta down to the diaphragm. The pericardium is released from the diaphragm with a transverse incision, with care being taken to avoid entering the pleural space or injuring the phrenic nerve. At this point, consideration is given to the specific exposure that will be required for the operation. Heavy silk sutures are placed in the cut edges of the pericardium and tied to the presternal fascia on the ipsilateral side of the incision to elevate and stabilize the appropriate cardiovascular structures.

Cannulation

Once the pericardium is opened, the aortic cannulation site is chosen. Commonly the distal ascending aorta, just proximal to the innominate artery, is used. There are many methods to cannulate and secure the arterial cannula. The authors' preference is to use two opposing diamond pursestring sutures with pledgeted 3-0 polypropylene approximately 30% larger than the size of the arterial cannula. The sutures are kept on opposing tourniquets. Venous cannulation sutures are placed using nonpledgeted 3-0 polypropylene pursestring. One or two venous cannulae are used depending on the operation. In settings where the right atrium or left atrium will be opened, 2 venous cannulae are placed into the SVC and IVC. Other operations typically can be performed with 1 large venous cannula placed through the right atrial appendage directed toward the IVC.

After ensuring systemic heparinization (200–300 units/kg, confirmed by activated clotting time [ACT] >400 sec), the aorta is cannulated by creating an aortotomy with a #15 blade and inserting the cannula. It is important to ensure that the aortotomy is large enough to admit the cannula without difficulty to avoid injuring the aorta. In addition, care must be taken to avoid cutting the cannulation sutures. After the cannula is secured to the aorta with the tourniquets, it is attached to the arterial line and deaired. The arterial line is tested to ensure that flow into the arterial system is unobstructed and line pressure on the arterial cannula is not high.

Venous cannulation is performed by creating an atriotomy with scissors or a #11 blade. The atriotomy must be made large enough to admit the cannula easily. Deairing of the venous cannula and line is only necessary if using gravity drainage and an airlock needs to be avoided.

Additional cannulae are placed depending on the plan of the operation, including cannulas for cardioplegia and venting of the heart. Typically, a small cannula for cardioplegia is placed into the ascending aorta with 4-0 pledgeted polypropylene and a retrograde cardioplegia cannula placed through the right atrium into the coronary sinus secured with 4-0 polypropylene. These will be used to administer cardioplegia to arrest the heart and protect the myocardium. The left ventricle can be vented by using a cannula placed into the right superior pulmonary vein and advanced through the left atrium and mitral valve into the left ventricle. This will allow for a bloodless field when operating on the left ventricle or aorta.

Venous return can be achieved by a passive or assisted approach. Passive venous return is more traditional, and is dependent on gravity, the height of the operating table above the venous reservoir, and large-bore tubing. Assisted venous return is achieved with the aid of vacuum being applied to the venous line or reservoir and does not require gravity drainage. Assisted venous return provides some advantages over the traditional venous drainage, such as permitting smaller venous cannula, tubing,

incisions, and lowering the priming volume. It can increase the risk for gaseous microemboli if the vacuum is too great and the reservoir volume is too low to allow proper dissociation. Because of these concerns, the maximum amount of vacuum is limited to less than 80 mm Hg and maintains a venous reservoir volume that permits at least 10 second reaction time or no less than 1000 mL.

Blood Strategy During CPB

The pump is typically primed with 1.5 to 2 L of crystalloid. It is important to prime the pump before use in a patient to eliminate microemboli through the filter. The addition of this volume results in significant hemodilution. The usual hematocrit when on CPB is 20 to 25 mg/dL. The degree of hemodilution may be calculated before bypass is initiated, and if the expected priming volume would cause an unacceptable anemia, packed red blood cells may be added to the extracorporeal circuit.

Hemodilution provides an advantageous effect for perfusion by decreasing viscosity and by augmenting blood flow. Blood flow reflects the interaction of many influences; hemodilution aids in negating those inherent effects by diminishing blood's viscosity and resistance to flow and promotes increased microcirculatory flow and tissue perfusion. However, hemodilution can be deleterious by reducing oncotic pressure, resulting in tissue edema and decreasing oxygen delivery during bypass. Hypothermia also influences blood rheology and vascular geometry. A decrease in temperature provokes direct vasoconstriction and increases viscosity, creating sludging and stasis at the capillary level, and a reduced blood flow. These effects are counteracted by hemodilution.

The acceptable degree of hemodilution is highly contested. It is common to see hematocrit of 18% to 21% during CPB. Hematocrit less than 15% can also be tolerated in cases of circulatory arrest and in patients who will not accept blood transfusion. The authors use a blood conservation strategy that has established transfusion indicators during CPB, depicted in **Box 2**. A general rule of thumb is that the hematocrit in percent should not exceed the desired level of hypothermia in °C.

Initiating CPB

CPB is begun at the instruction of the surgeon. Visual inspection of the field, monitors, and bypass lines as the perfusionist initiates CPB will provide an immediate assessment of the conversion. The perfusionist initiates CPB by releasing the arterial line clamp and slowly transfusing the patient with the volume. The arterial blood flow of the extracorporeal circuit should be free-flowing and exhibit a reasonable

Box 2
Strategy for blood transfusion during CPB

1. During moderate hypothermic CPB, a hematocrit less than 18% is the trigger threshold for blood transfusion unless the patient exhibits a history of cerebrovascular accident and disease, carotid stenosis, or diabetes mellitus, in which case a hematocrit of 21% becomes the trigger.
2. The patient's clinical condition also determines the need for blood transfusion: age, severity of illness, cardiac function, end-organ ischemia, massive or active blood loss, mixed venous oxygen saturation (SVO_2), and so on. In this environment, a hematocrit of 21% to 24% becomes the authors' trigger.
3. Routine use of the cell saver except for patients with infection and malignancy
4. Low-prime and mini-extracorporeal bypass circuits

extracorporeal line pressure. A sudden spike in the extracorporeal line pressure may indicate an occluded arterial line, a malpositioned aortic cannula, or an aortic dissection. Should this occur, CPB should be terminated immediately and the cause identified and corrected.

As soon as it is obvious that arterial flow is unobstructed, the venous clamp is released, diverting the patient's venous blood into the CPB circuit. The right heart should be decompressed, and the central venous pressure should be less than 5 mm Hg. A high central venous pressure and poor venous drainage at the initiation of CPB may indicate a malpositioned venous cannula, a kinked venous line, an "air-lock," venous cannulas that are too large or too small, an inappropriate height between the operating table and the venous reservoir, an inappropriate amount of vacuum, or a vacuum leak.

During this transition period of 1 to 2 minutes, the perfusionist gradually increases the rate of arterial flow, the ventricles receive less blood, and the pulsatile arterial waveform diminishes and becomes "flat-lined." Once total bypass is achieved, a continued pulsatile arterial waveform signifies the left ventricle is receiving unwanted blood from aortic insufficiency, excessive bronchial venous return, or incomplete drainage of the systemic venous return.

Because of acute vasoactive substance release on initiating CPB, an acute, transient state of systemic arterial hypotension is common and can be treated with vasopressor agents if needed. Acceptable mean arterial pressure when on CPB ranges from 50 to 90 mm Hg. In the presence of cerebrovascular or renovascular disease, a perfusion pressure of 70 to 90 mm Hg is preferred. The adequacy of a mean arterial pressure in a patient is confirmed by a normal systemic vascular resistance index and mixed venous blood gas.

In patients with severe aortic regurgitation, the surgeon should be ready to cross-clamp the ascending aorta if ventricular fibrillation occurs. A distended, fibrillating left ventricle is subject to additional ischemia and injury to the myocardium. Once on full CPB support, the patient can be cooled to the desired temperature. The primary advantage of systemic hypothermia during CPB is the reduced metabolic rate and oxygen consumption of approximately 5% to 7% per °C.[9,10] In addition, hypothermia sustains intracellular reservoirs of high-energy phosphates (essential for cellular integrity) and preserves high intracellular pH and electrochemical neutrality (a constant OH^-/H^+ ratio). As a result of these associated interactions, hypothermic patients can survive periods of circulatory arrest of up to 1 hour without suffering from the effects of anoxia.[9,10]

In addition to core cooling with cold blood through the circuit, hypothermia may be augmented by surface cooling using cooling blankets and ice packs applied directly to the patient. Because tissues and organs have varying amounts of perfusion, systemic cooling is not a uniform process. To minimize this, the flows on the circuit are maintained at high rates (2.2 to 2.5 L/min/m^2), and the rate of the cooling is limited to less than 1°C per minute until the desired temperature is reached. Bladder and nasopharyngeal temperatures are monitored to ensure uniform temperatures.

In most cases, the beating heart will be arrested to cease motion and allow a bloodless field on the heart. This is achieved by administering cardioplegia antegrade through the coronary arteries or retrograde through the coronary sinus. Since there are no valves in the coronary sinus, cardioplegia is able to run retrograde into the coronary arteries and out the ostium.

In certain cases, a state of circulatory arrest may be desired where the blood flow to the patient is drained and the circuit is stopped to allow for a bloodless field. This state of "no blood flow" to the patient is achieved with extreme systemic cooling at 16°C to

22°C. Safe periods of circulatory arrest can be achieved based on the patient's core temperature (**Table 1**). Beyond these times there are risks for cerebral and other end-organ injury. The negative effects of circulatory arrest include additional time required to cool and rewarm the patient and systemic coagulopathy that often requires blood component replacement.

Systemic rewarming is instituted by gradually increasing the perfusate temperature. Rewarming is slower than cooling because of the maximum 10°C permissible temperature gradient between perfusate and nasopharyngeal temperatures, the maximum allowable blood temperature of 42°C, and the reduced thermal exchange as the temperature gradient between the patient and perfusate narrows. During this part of the procedure, warming blankets are set to 40°C, the perfusion flow rates are increased to 2.5 to 3.0 L/min/m^2, and, pressure permitting, pharmacologic vasodilation is used. When the bladder temperature reaches 32°C, the patient begins to vasodilate spontaneously and the pharmacologic vasodilator may be terminated.

Weaning Off of CPB

The heart is dealred before the cross-clamp is removed. The patient is placed in a 30° head-down (Trendelenberg) position, and the heart is filled with blood by manually restricting venous return to the pump. The right heart begins to fill, and the anesthesiologist ventilates the lungs. The heart is gently massaged. Vents in the left ventricle or in the aortic root cardioplegia cannula are used to remove air from within the heart. Once all air appears to have been evacuated, pump flow is reduced to half flow, arterial pressure is reduced to 50 mm Hg, and the aortic cross-clamp is removed while suction is maintained on the antegrade cardioplegic cannula. TEE is often used to determine if there is residual air within the heart. Maneuvers to remove any residual air include filling the heart, giving Valsalva breaths, and rocking the table from side to side when the aortic root vent is on. When echocardiography confirms that the left heart is free of air, the operating table is restored to a level position and the aortic cardioplegic/vent cannula and the retrograde cardioplegic cannula are removed.

Temporary pacing wires are sutured to the right atrium and ventricle if needed. Rewarming is continued until the patient's temperature reaches 36°C. Termination of CPB is performed gradually, with constant communication between surgeon, perfusionist, and anesthesiologist. The ventilator is turned on. The perfusionist progressively occludes the venous return line, translocating blood volume from the venous reservoir into the patient's vascular system. The patient is now on "partial" CPB, with blood flowing through the heart and pulmonary circulation. When the blood volume in the heart reaches an adequate level, the aortic valve begins to open with each heart beat, and a measurable cardiac output will be observed. The translocation of volume is continued until the arterial systolic pressure reaches 100 mm Hg. Simultaneously, the flow through the circuit is reduced. The surgeon checks for surgical

Table 1
Definition of levels of hypothermia and approximate safe circulatory arrest times

Hypothermia Level	Patient Temperature (°C)	Circulatory Arrest Times (min)
Mild	37–32	5–10
Moderate	32–28	10–15
Deep	28–18	15–60
Profound	<18	60–90

bleeding and assesses heart function, as well as checking heart and valve function by TEE. On the surgeon's approval, the perfusionist then terminates CPB by completely occluding the venous and arterial lines. Thereafter, the perfusionist transfuses volume to the patient to maintain a systolic blood pressure of 100 mm Hg unless the heart becomes distended.

If the heart does not function effectively when CPB is terminated, bypass is reinstituted to prevent overdistention or hypoxia. If heart functions appropriately with hemodynamic stability, decannulation can begin. The venous cannulae are removed but the tourniquets are still present should the need arise for rapid return to bypass. The heparin is reversed with protamine. When half of the protamine is administered, the aortic cannula should be removed to prevent arterial embolism from the cannula. Additional volume should be given to the patient as needed to fill the heart adequately though the aortic cannula before removing it. The protamine is then completed and arterial and venous cannulation sites are tied and secured. Shed blood should not be returned to the extracorporeal circuit once protamine is introduced into the patient's circulation. Thereafter, final hemostasis and surgical closure of the wound are performed.

COMPLICATIONS

Complications associated with CPB can be divided into those related to malfunction of the circuit, those related to problems with cannulation, and those related to the physiology of CPB on the body.

Complications Related to Cannulation

Cannulation of the heart must be done carefully because this can result in major catastrophes. The risk for ascending aortic dissection is less than 1% with direct cannulation; however, when it does occur, it may require circulatory arrest and complete replacement of the ascending aorta. More common is bleeding from the aortic cannulation site as a result of misplaced sutures, too small a pursestring, bites of the aorta that are full thickness (and too deep), or poor quality tissue. Many of these errors can be avoided with careful planning of the location of cannulation and meticulous suture placement. Repair of a distal aortic injury can often be performed by covering the site with an autologous pericardial patch. At this point of the operation, the patient is typically off bypass and the aortic cannula has been removed. The assistant will need to control the bleeding with direct pressure on the aortic cannulation site. The surgeon can harvest a 2 to 3 cm circular piece of autologous pericardium. Using 5-0 polypropylene the surgeon secures the pericardium to the aorta around the cannulation site, making certain to get good bites of the aortic adventitia and media. The suture is run circumferentially and tied down. This will control the bleeding in most cases. Rarely, femoral cannulation is required to go back on pump and the patient may need to be cooled and circulation arrested to fix the cannulation injury as with an aortic dissection.

Venous cannulation injuries can occur as well and are typically related to quality of the atrial tissue and location of the pursestring suture. When cannulating the right atrial appendage and the IVC, the surgeon should ensure there is enough atrial tissue to allow closure of the atriotomy without tension. A tear in the atrioventricular groove or down the IVC can be very challenging to repair but can often be repaired primary or with a large bovine pericardial patch.

Peripheral arterial and venous cannulation can also lead to complications. Femoral arterial cannulation should only be performed with some knowledge of the femoral,

iliac, and aortic anatomy to avoid retrograde aortic dissection, malperfusion of the body during bypass, and aortic or iliac injury. In cases of severe peripheral vascular disease, calcification of the vessels, or the presence of an aortic or iliac aneurysm, alternative cannulation sites should be considered with a preoperative CT scan. Femoral venous cannulation can also lead to venous injury in the retroperitoneum or abdomen leading to hemorrhage and poor flows when on bypass. Cannulation of the axillary artery should be performed by sewing a Dacron graft in an end to side fashion. In this setting, the surgeon must ensure there is no obstruction or disease in the axillary or innominate arteries by CT angiogram.

Complications Related to the Effects of CPB on the Body

Although CPB has advanced heart surgery to allow us to perform complex reconstruction on the heart, it is clearly not a physiologic state with nonpulsatile flow, manipulation of core temperature, alterations in venous pressure, and increased interstitial fluid. In addition to a host of inflammatory cytokines that are released during bypass, CPB also causes dysfunction of clotting factors and platelet activation and lysis which ultimately lead to coagulopathy and bleeding. Meticulous hemostasis is the first key to minimize bleeding. Longer procedure times are associated with higher risk for bleeding and more coagulopathy. Additional topical hemostatic agents can be used to minimize nonsurgical bleeding. Blood component administration is the most common method of treating coagulopathy following CPB. Antifibrinolytic agents including aminocaproic acid are commonly used during and after CPB in long or complex cases to prevent fibrinolysis.

In addition to effects on coagulation, there are multiple effects of CPB that can lead to organ damage. It can be difficult to determine the source of postoperative cardiac injury and attribute it to CPB or to cardiac arrest/cross-clamping. Ischemic reperfusion causes myocardial edema. Lung injury has been attributed to ischemic reperfusion injury as well as changes in pulmonary capillary permeability. Renal dysfunction is thought to be because of alterations in blood flow when on CPB as well as tissue edema. Neurologic dysfunction has been the focus of many studies and is thought to be a result of nonpulsatile cerebral blood flow, microemboli to the brain, and loss of cerebral autoregulation. Neurologic sequelae include frank strokes as well as mild cognitive dysfunction often termed "pump head." Careful planning of arterial cannulation, maintenance of adequate perfusion pressure when on CPB, and avoidance of microemboli with the use of arterial filters can minimize the risk for neurologic injury.

Complications Related to Pump Malfunction

Pump malfunctions are rare events but can have devastating consequences. Massive air embolism can occur with break in the integrity of the circuit, on depletion of the venous reservoir, during opening of the left atrium or ventricle without a cross-clamp (as can occur during insertion of a left ventricular vent), or from an inadvertent bolus of air into the arterial line. Systemic air embolism is treated by stopping the CPB and placing the patient in steep Trendelenberg. The circuit is reprimed to remove the air. The surgeon then cannulates the SVC and runs flow retrograde through the cerebral circulation for 1 to 2 minutes to allow air to exit through the aorta. Once the pump is primed and visible air in the arterial system is removed, the pump is restarted antegrade and the patient is cooled to 20°C to increase the solubility of the air embolism.

Air lock in the venous line can occur with gravity drainage and can result in loss of venous drainage and depletion of the venous reservoir. This is treated by closing the

source of venous entry, walking the air through the venous line into the reservoir, and adding fluid to the reservoir.

Pump failure can occur as a result of electrical or mechanical causes. This is prevented by frequent servicing of the equipment and ensuring a functioning backup battery. If the pump stops during CPB, if possible wean the patient off bypass. If this is not possible, then a manual hand crank can be used to continue perfusion through the pump.

EXTRACORPOREAL MEMBRANE OXYGENATION

The indications for extracorporeal membrane oxygenation (ECMO) are listed in Box 3. The ECMO circuit differs from the traditional CPB circuit in a number of ways. The ECMO circuit is a single closed system and is unable to tolerate air in the venous line. There is no separate circuit to administer cardioplegia as with the CPB circuit. ECMO is more compact than CPB, allowing for easier transportation of the patient (Fig. 3). Typical ECMO circuits have heparin bonded tubing allowing for lower levels of anticoagulation (ACT 180-220s).

Cannulation for ECMO can be performed with a variety of techniques. Venoarterial (VA) ECMO is performed for both circulatory and pulmonary support. VA ECMO is often performed for cardiogenic failure post cardiac surgery. In this scenario, the aorta is cannulated directly as aforementioned. If the aortic cannula is still present from CPB, it can be used as the arterial inflow for VA ECMO. In settings where the chest is not open, arterial cannulation is usually performed through the femoral artery. Venous cannulation is performed in the right atrium if the chest is open or through the femoral vein and/or internal jugular when the chest is not open. Femoral, arterial, or venous cannulation can be performed percutaneously or via a cutdown. When performed via cutdown, 5-0 pursestring suture is used to secure the cannulas. Once the cannulas are confirmed to be in good location providing good flows on ECMO, the cannulas and tubing are secured with heavy silk sutures to the skin to ensure they are not inadvertently moved during routine care of the patient.

Venovenous ECMO is used for isolated pulmonary support in cases of reversible pulmonary failure. Most often, cannulation is performed through the femoral and internal jugular veins. Inflow is from the femoral vein and outflow through a cannula in the right atrium positioned through the internal jugular vein.

Box 3
Indications for ECMO support

1. Cardiac support for reversible conditions
2. Postcardiotomy shock
3. Post myocardial infarction (MI)
4. High-risk coronary artery and intracardiac interventions (cath lab)
5. Respiratory support (reversible conditions)
   a. Acute lung injury (trauma)
   b. Post lung transplant
6. Hypothermia resuscitation

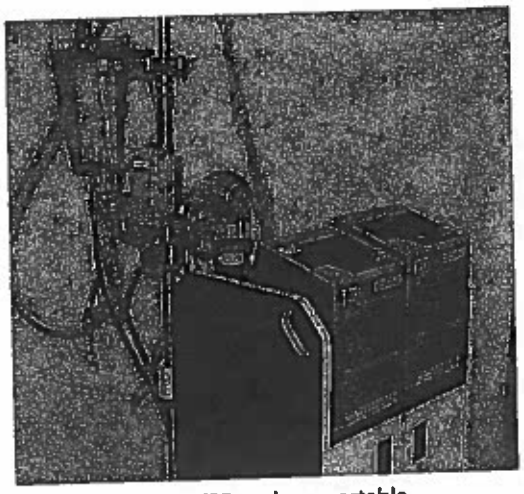

Fig. 3. ECMO circuits are smaller than CPB and are portable.

Complications

In addition to the aforementioned concerns with air embolism and microemboli, complications specifically related to ECMO are primarily because of the extended period of time in which a patient is anticoagulated while on cardiopulmonary support. This results in significant coagulopathy, especially when ECMO support is required for longer than 48 to 72 hours. Despite maintaining lower ACTs while on ECMO, the pump and circuit result in consumption of clotting factors and platelets. It is not unusual for patients on ECMO to receive several times their blood volume in blood component replacement while on support. The resultant transfusions can lead to reactions to the blood products and secondary injury to the lungs.

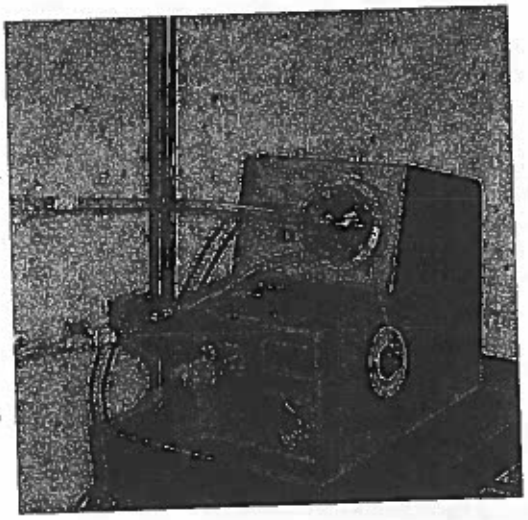

Fig. 4. LHB machine.

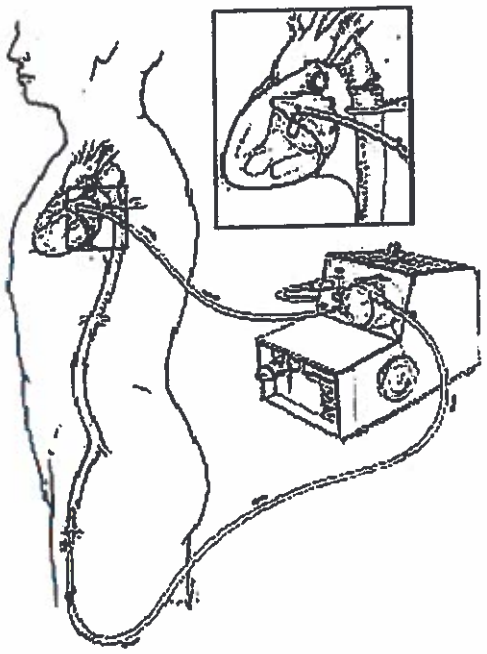

Fig. 5. Location cannulation strategy for LHB during descending and thoracoabdominal aortic surgery. *From* Szwerc M, Benckart D, Lin J, et al. Recent clinical experience with left heart bypass using a centrifugal pump for repair of traumatic aortic transection. Ann Surg 1999; 230:486; with permission.

LHB

LHB is partial heart bypass designed to provide partial blood flow to limited sections of the body during surgery (**Fig. 4**). LHB is primarily used to provide support and perfusion of the visceral vessels and lower extremities during reconstruction of the descending aorta, allowing the perfusionist to divert a portion of the patient's saturated blood from the patient's circulation after it has passed through the lungs and returns it to the arterial system by way of the distal aorta or femoral artery (**Fig. 5**). This parallel circuit technique permits the perfusionist to vary the preload of the left ventricle, controlling the volume of blood being ejected into the aorta, and it provides blood flow to the lower intercostals, lumbar, renal, and visceral arteries. The use of LHB has been shown to decrease the incidence of paraplegia and renal failure, and it limits intestinal ischemia during operations on the descending thoracic and thoracoabdominal aorta.[11–13]

Access to the thoracic and thoracoabdominal aorta is obtained through a left thoracotomy and a thoracoabdominal incision, respectively. Following exposure of the aorta, heparin is administered (100 units/kg) and ACTs are maintained at 200 sec. The femoral artery is cannulated with a 15F Bio-Medicus arterial cannula percutaneously or through femoral artery cutdown through a 5-0 polypropylene pursestring. If cannulating directly into the distal aorta, a 12F Bio-Medicus arterial cannula is used through a 4-0 polypropylene pursestring. The cannula is then attached to the outflow side of the circuit, with great care being taken to ensure the system is devoid of air bubbles. The left atrium is cannulated through the left inferior pulmonary vein with a 14F Bio-Medicus venous cannula and secured with a 5-0 polypropylene pursestring.

The inferior pulmonary ligament should be divided entirely and the inferior pulmonary vein should be isolated circumferentially. As noted on the arterial side, the cannula is secured to the circuit ensuring no air bubbles in the line.

A blood flow rate of 20 to 40 mL/kg, or a cardiac index of 1.3 m^2 (2.0–2.5 L/min) is generally acceptable for perfusing the viscera and lower extremity. Following the initiation of bypass and aortic cross-clamping, there are two parallel circulations. Circulation to the great vessels and heart is dependent upon the patient's native cardiac function and preload in the left ventricle, whereas the lower circulation is dependent on the bypass circuit. The regulation of blood flow and pressure is controlled by the rate in which the blood is removed by the bypass circuit. As the pump flow of the bypass circuit increases, the blood flow into the ascending aorta is decreased along with the upper extremity blood pressure; whereas the distal blood flow and pressure increases. By altering the flow through the circuit, the radial artery pulsatile pressure is maintained around 100/60 mm Hg, whereas the femoral artery mean pressure is maintained to roughly equal the radial diastolic pressure.

The LHB circuit is a simple circuit consisting of a centrifugal pump, tubing, and cannulae. The use of a centrifugal pump offers the advantage of providing a negative pressure on the inflow blood, allowing the pump to be close to and at table level, thus reducing the tubing length. This arrangement traps air bubbles that may entrain into the circuit, and it minimizes blood element trauma. In addition, two cell savers are used to process and return the patient's shed blood.

Complications

LHB does possess some unique hazards in addition to the aforementioned risks for CPB. Although meticulous care must be taken to avoid air embolism in other modes of CPB, this cannot be overstated using LHB. Excess flow through the circuit or relative hypovolemia will result in proximal aortic hypotension and suboptimal perfusion of the brain and upper extremities. Excessive rpm of the centrifugal pump may cause vortexing, which can generate microemboli that can be passed distally into the patient. Finally, femoral cannulation can result in limb ischemia by the arterial cannula obstructing flow in the distal femoral artery.

SUMMARY

CPB, ECMO, and LHB have revolutionized our ability to operate on the heart, great vessels, and aorta in addition to providing means of short-term support for reversible causes of cardiac and/or respiratory failure. The success of these approaches is dependent upon excellent communication between the surgeon, perfusionist, and anesthesiologist as well as constant vigilance and troubleshooting by the caregivers.

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REVIEW ARTICLE

MEDICAL PROGRESS

Heart Failure

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THE CLINICAL SYNDROME OF HEART FAILURE IS THE FINAL PATHWAY for myriad diseases that affect the heart. Since the mid-1990s, when the last review of heart failure appeared in the Journal,[1] discoveries from basic research and findings from key clinical trials have resulted in considerable change in the scope of therapies available and the continuing advancement of our understanding of the pathophysiological mechanisms of heart failure. In this article, we highlight these new developments.

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A COSTLY AND DEADLY DISORDER

Nearly 5 million Americans have heart failure today, with an incidence approaching 10 per 1000 population among persons older than 65 years of age. Heart failure is the reason for at least 20 percent of all hospital admissions among persons older than 65. Over the past decade, the rate of hospitalizations for heart failure has increased by 159 percent.[2] In 1997, an estimated $5,501 was spent for every hospital-discharge diagnosis of heart failure, and another $1,742 per month was required to care for each patient after discharge. Accordingly, substantial efforts have been made to identify and treat the factors that predict recurrent hospitalization. End points of large randomized trials now include the effect of the studied intervention on the rate of hospital admissions. For example, angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta-blockers, spironolactone, biventricular pacing, coronary bypass surgery, and the use of multidisciplinary teams to treat heart failure have all been shown to reduce the rate of hospitalizations substantially, as well as to reduce mortality or improve functional status.[3-5] Considerable debate has focused on the mechanisms that reduce the rate of admissions and on the type of physician who should care for patients with heart failure. In the United States, more than two thirds of patients with heart failure are cared for exclusively by primary care practitioners.

Multiple clinical trials completed during the past 15 years have unequivocally shown a substantial reduction in mortality for patients with systolic heart failure. Simultaneously, however, large epidemiologic surveys, such as the ongoing Framingham Study, have not documented any meaningful change in overall death rates. (Death seems to have been delayed, however, and occurs a longer time after major cardiac events such as a myocardial infarction.) Symptomatic heart failure continues to confer a worse prognosis than the majority of cancers in this country, with one-year mortality of approximately 45 percent.[6,7]

Why have the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure? It is important to recognize that heart failure is a clinical syndrome arising from diverse causes. Not all patients with the condition have poorly contracting ventricles and a low ejection fraction. Many have uncorrected valvular disease, such as aortic stenosis or mitral regurgitation, or abnormal filling, resulting in diastolic heart failure. A large majority of patients with heart failure are elderly, and 75

percent of patients have a history of hypertension. Many patients have at least one serious coexisting condition, in addition to advanced age. Such patients have not usually been subjects in investigational trials. Moreover, until recently, the majority of patients entered into trials of investigational drugs were middle-aged white men with heart failure due to ischemic cardiomyopathy. Fewer women and members of racial minorities have taken part in trials, and very few trials have included persons older than 75 years of age. Thus, despite the acknowledged successes of the therapies outlined below, there is much to be done in the prevention and management of heart failure in the large subgroups of patients who are not well represented in trials. Certainly, successful treatments have not been systematically applied to the majority of patients with heart failure, and for the reasons stated above, those that have been applied may not be efficacious.

Although heart failure is a major public health problem, there are no national screening efforts to detect the disease at its earlier stages, as there are for breast and prostate cancer or even osteoporosis. Heart failure is largely preventable, primarily through the control of blood pressure and other vascular risk factors. Yet, until recently, the factors that render a patient at high risk for heart failure had not been clearly defined or publicized. The guidelines for the evaluation and management of chronic heart failure that were published recently by the American College of Cardiology and the American Heart Association have corrected this deficit.[8] The writing committee developed a new approach to the classification of heart failure that emphasizes its evolution and progression and defined four stages of heart failure. Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. Patients with stage B heart failure have a structural abnormality of the heart but have never had symptoms of heart failure. Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Patients with stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment.

This staged classification underscores the fact that established risk factors and structural abnormalities are necessary for the development of heart failure, recognizes its progressive nature, and superimposes treatment strategies on the fundamentals of preventive efforts. The classification is a departure from the traditional New York Heart Association (NYHA) classification, which has primarily been used as shorthand to describe functional limitations.[9] Heart failure may progress from stage A to stage D in a given patient but cannot follow the path in reverse. In contrast, a patient with NYHA class IV symptoms might have quick improvement to class III with diuretic therapy alone. This staged heart-failure classification promotes a way of thinking about heart failure that is similar to our way of thinking about cancer — that is, the identification and screening of patients who are at risk, patients with in situ disease, and patients with established or widespread disease. The ensuing discussion about the treatment of heart failure is keyed toward this new staging classification.

THE SYNDROME OF HEART FAILURE

The traditional view that heart failure is a constellation of signs and symptoms caused by inadequate performance of the heart focuses on only one aspect of the pathophysiology involved in the syndrome. Currently, a complex blend of structural, functional, and biologic alterations are evoked to account for the progressive nature of heart failure and to explain the efficacy or failure of therapies used in clinical trials.[10] For example, the rationale for the use of beta-blockers in a patient with a poorly contracting heart is based on a conceptual framework broader than that which suggests the treatment of congestion with diuretics or digoxin. The rationale for using beta-blockers is predicated on an understanding of the role of the sympathetic nervous system in promoting the release of renin and other vasoactive substances that trigger vasoconstriction, tachycardia, and changes in myocytes that lead to disadvantageous ventricular dilatation.

Indeed, recent reviews have combined several models that had been used previously to understand heart failure in order to illustrate more fully the cascade of mechanisms, as well as the opportunities for intervention.[11] Thus, the hemodynamic model of heart failure emphasized the effect of an altered load on the failing ventricle and ushered in the era of vasodilators and inotropic agents. The neurohumoral model recognized the importance of activation of the renin–angiotensin–aldosterone axis and the sympathetic nervous system in the progression of cardiac dysfunction. More recently, efforts to antagonize the effects of circulating norepinephrine and angiotensin II have shifted with the

recognition that these and other vasoactive substances are also synthesized within the myocardium and therefore act in an autocrine and paracrine manner, in addition to their actions in the circulation. For example, brain natriuretic peptide is produced by the ventricular myocardium in response to stretch; its vasodilatory and natriuretic effects counteract the opposing actions of angiotensin II and aldosterone. Other studies have scrutinized myocytes from failing hearts in an attempt to detect abnormal signaling, gene expression, or contractile protein structure. Table 1 details many of the factors that contribute to the heart-failure syndrome as it is currently understood. Because no single pathophysiological model can account for the host of clinical expressions of heart failure, current therapy often targets more than one organ system, as outlined in Figure 1. Additional pathophysiological concepts that have become clinically meaningful areas for investigation or treatment are described below.

Table 1. Pathophysiological Mechanisms Important in the Syndrome of Heart Failure.

Cardiac abnormalities
Structural abnormalities
Myocardium or myocyte
Abnormal excitation–contraction coupling
β-Adrenergic desensitization
Hypertrophy
Necrosis
Fibrosis
Apoptosis
Left ventricular chamber
Remodeling
Dilatation
Increased sphericity
Aneurysmal dilatation or wall thinning
Coronary arteries
Obstruction
Inflammation
Functional abnormalities
Mitral regurgitation
Intermittent ischemia or hibernating myocardium
Induced atrial and ventricular arrhythmias
Altered ventricular interaction
Biologically active tissue and circulating substances
Renin–angiotensin–aldosterone system
Sympathetic nervous system (norepinephrine)
Vasodilators (bradykinin, nitric oxide, and prostaglandins)
Natriuretic peptides
Cytokines (endothelin, tumor necrosis factor, and interleukins)
Vasopressin
Matrix metalloproteinases
Other factors
Genetic background, including effects of sex
Age
Environmental factors, including use of alcohol, tobacco, and toxic drugs
Coexisting conditions
Diabetes mellitus
Hypertension
Renal disease
Coronary artery disease
Anemia
Obesity
Sleep apnea
Depression

REMODELING

Increased levels of circulating neurohormones are only part of the response seen after an initial insult to the myocardium. Left ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Remodeling occurs in several clinical conditions, including myocardial infarction, cardiomyopathy, hypertension, and valvular heart disease; its hallmarks include hypertrophy, loss of myocytes, and increased interstitial fibrosis.[12,13]

For example, after a myocardial infarction, the acute loss of myocardial cells results in abnormal loading conditions that involve not only the border zone of the infarction, but also remote myocardium. These abnormal loading conditions induce dilatation and change the shape of the ventricle, rendering it more spherical, as well as causing hypertrophy. Remodeling continues for months after the initial insult, and the eventual change in the shape of the ventricle becomes deleterious to the overall function of the heart as a pump (Fig. 2A).[14] In cardiomyopathy, the process of progressive ventricular dilatation or hypertrophy occurs without the initial apparent myocardial injury observed after myocardial infarction (Fig. 2B).

Several trials involving patients who were studied after a myocardial infarction or who had dilated cardiomyopathy found a benefit from ACE inhibitors, beta-adrenergic antagonists, or cardiac resynchronization.[15-18] Such beneficial effects were associated with so-called reverse remodeling, in which the therapy promoted a return to a more normal ventricular size and shape.[15-18] The reverse-remodeling process is a mechanism through which a variety of treatments palliate the heart-failure syndrome.

MITRAL REGURGITATION

Another potential deleterious outcome of remodeling is the development of mitral regurgitation. As

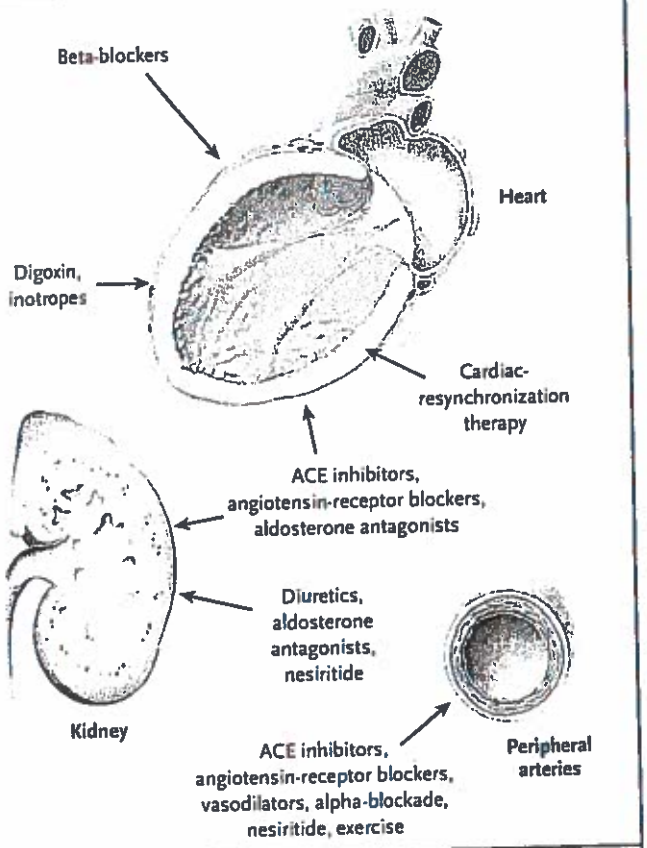

Figure 1. Primary Targets of Treatment in Heart Failure.

Treatment options for patients with heart failure affect the pathophysiological mechanisms that are stimulated in heart failure. Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers decrease afterload by interfering with the renin–angiotensin–aldosterone system, resulting in peripheral vasodilatation. They also affect left ventricular hypertrophy, remodeling, and renal blood flow. Aldosterone production by the adrenal glands is increased in heart failure. It stimulates renal sodium retention and potassium excretion and promotes ventricular and vascular hypertrophy. Aldosterone antagonists counteract the many effects of aldosterone. Diuretics decrease preload by stimulating natriuresis in the kidneys. Digoxin affects the Na^+/K^+–ATPase pump in the myocardial cell, increasing contractility. Inotropes such as dobutamine and milrinone increase myocardial contractility. Beta-blockers inhibit the sympathetic nervous system and adrenergic receptors. They slow the heart rate, decrease blood pressure, and have a direct beneficial effect on the myocardium, enhancing reverse remodeling. Selected agents that also block the alpha-adrenergic receptors can cause vasodilatation. Vasodilator therapy such as combination therapy with hydralazine and isosorbide dinitrate decreases afterload by counteracting peripheral vasoconstriction. Cardiac resynchronization therapy with biventricular pacing improves left ventricular function and favors reverse remodeling. Nesiritide (brain natriuretic peptide) decreases preload by stimulating diuresis and decreases afterload by vasodilatation. Exercise improves peripheral blood flow by eventually counteracting peripheral vasoconstriction. It also improves skeletal-muscle physiology.

the left ventricle dilates and the heart assumes a more globular shape, the geometric relation between the papillary muscles and the mitral leaflets changes, causing restricted opening and increased tethering of the leaflets and distortion of the mitral apparatus. Dilatation of the annulus occurs as a result of increasing left ventricular or atrial size or as a result of regional abnormalities caused by myocardial infarction.[19-21] The presence of mitral regurgitation results in an increasing volume overload on the overburdened left ventricle that further contributes to remodeling, the progression of disease, and symptoms. Correction of mitral regurgitation has been an appropriate focus of therapy.

ARRHYTHMIAS AND BUNDLE-BRANCH BLOCK

The myocardial conduction system is vulnerable to the same pathophysiological processes that occur in the myocytes and interstitium, with altered conduction properties observed in response to ischemia, inflammation, fibrosis, and aging. Supraventricular arrhythmias, particularly atrial fibrillation, are often the precipitating events that herald the onset of either systolic or diastolic heart failure.[22] Elevated ventricular end-diastolic pressure in a patient with hypertension or abnormal myocardial function leads to atrial stretch, which in turn incites electrical instability. Recognition of the presence of atrial fibrillation in a patient is critical, since several studies have now demonstrated the effectiveness of oral anticoagulant therapy for the prevention of stroke.[23]

Abnormal myocardial conduction can also lead to delays in ventricular conduction and bundle-branch block. Left bundle-branch block is a significant predictor of sudden death and a common finding in patients with myocardial failure.[24-26] Its presence also affects the mechanical events of the cardiac cycle by causing abnormal ventricular activation and contraction, ventricular dyssynchrony, delayed opening and closure of the mitral and aortic valves, and abnormal diastolic function. Hemodynamic sequelae include a reduced ejection fraction, decreased cardiac output and arterial pressure, paradoxical septal motion, increased left ventricular volume, and mitral regurgitation.[27-30] Ventricular arrhythmias are thought to be secondary to a dispersion of normal conduction through nonhomogeneous myocardial tissue, which promotes repetitive ventricular arrhythmias.

The rate of sudden cardiac death among persons with heart failure is six to nine times that seen in the

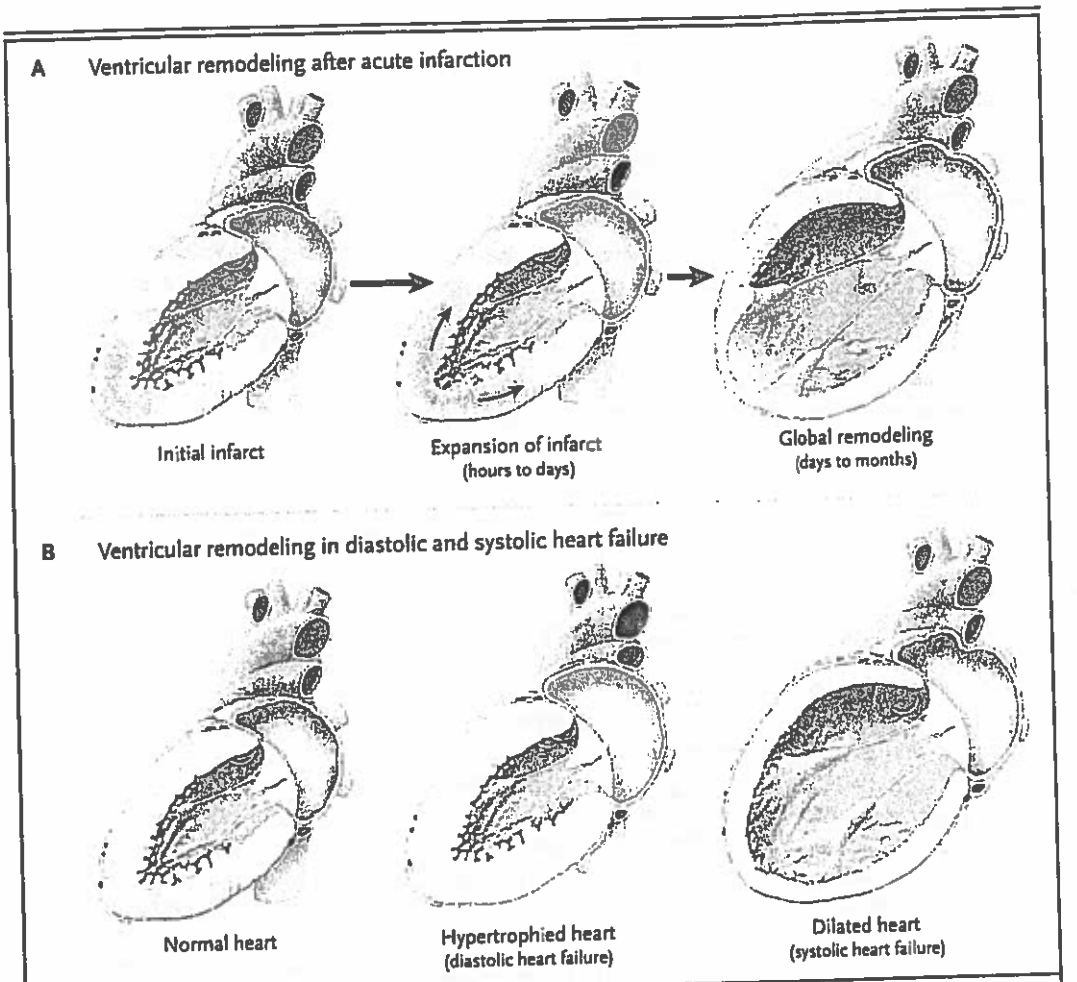

Figure 2. Ventricular Remodeling after Infarction (Panel A) and in Diastolic and Systolic Heart Failure (Panel B).
At the time of an acute myocardial infarction — in this case, an apical infarction — there is no clinically significant change in overall ventricular geometry (Panel A). Within hours to days, the area of myocardium affected by the infarction begins to expand and become thinner. Within days to months, global remodeling can occur, resulting in overall ventricular dilatation, decreased systolic function, mitral-valve dysfunction, and the formation of an aneurysm. The classic ventricular remodeling that occurs with hypertensive heart disease (middle of Panel B) results in a normal-sized left ventricular cavity with thickened ventricular walls (concentric left ventricular hypertrophy) and preserved systolic function. There may be some thickening of the mitral-valve apparatus. In contrast, the classic remodeling that occurs with dilated cardiomyopathy (right side of Panel B) results in a globular shape of the heart, a thinning of the left ventricular walls, an overall decrease in systolic function, and distortion of the mitral-valve apparatus, leading to mitral regurgitation.

general population.[31] Major innovations in medical and device-based therapy for the primary and secondary prevention of lethal ventricular arrhythmias have occurred during the past decade but are beyond the scope of this article. Increasing use of implantable cardioverter–defibrillators has unequivocally reduced mortality in a subgroup of patients with heart failure.

DIASTOLIC HEART FAILURE

It is estimated that 20 to 50 percent of patients with heart failure have preserved systolic function or a normal left ventricular ejection fraction. Although such hearts contract normally, relaxation (diastole) is abnormal. Cardiac output, especially during exercise, is limited by the abnormal filling characteristics of the ventricles. For a given ventricular volume,

ventricular pressures are elevated, leading to pulmonary congestion, dyspnea, and edema identical to those seen in patients with a dilated, poorly contracting heart.[32-35] Characteristics of patients with systolic heart failure and those with diastolic heart failure are compared in Table 2. Patients with diastolic heart failure are typically elderly, often female, and usually obese and frequently have hypertension and diabetes. Mortality among these patients may be as high as that among patients with systolic heart failure, and the rates of hospitalization in the two groups are equal.[36] The diagnosis of diastolic heart failure is usually made by a clinician who recognizes the typical signs and symptoms of heart failure and who is not deterred by the finding of normal systolic function (i.e., a normal ejection fraction) on echocardiography. Echocardiography may be useful in the detection of diastolic filling abnormalities.

Unfortunately, unlike heart failure due to systolic dysfunction, diastolic heart failure has been studied in few clinical trials, so there is little evidence to guide the care of patients with this condition. Physiological principles used in the treatment of such patients include the control of blood pressure, heart rate, myocardial ischemia, and blood volume.

Table 2. Characteristics of Patients with Diastolic Heart Failure and Patients with Systolic Heart Failure.*

Characteristic	Diastolic Heart Failure	Systolic Heart Failure
Age	Frequently elderly	All ages, typically 50–70 yr
Sex	Frequently female	More often male
Left ventricular ejection fraction	Preserved or normal, approximately 40% or higher	Depressed, approximately 40% or lower
Left ventricular cavity size	Usually normal, often with concentric left ventricular hypertrophy	Usually dilated
Left ventricular hypertrophy on electrocardiography	Usually present	Sometimes present
Chest radiography	Congestion with or without cardiomegaly	Congestion and cardiomegaly
Gallop rhythm present	Fourth heart sound	Third heart sound
Coexisting conditions		
Hypertension	+++	++
Diabetes mellitus	+++	++
Previous myocardial infarction	+	+++
Obesity	+++	+
Chronic lung disease	++	0
Sleep apnea	++	++
Long-term dialysis	++	0
Atrial fibrillation	+ (usually paroxysmal)	+ (usually persistent)

* A single plus sign denotes "occasionally associated with," two plus signs "often associated with," three plus signs "usually associated with," and a zero "not associated with."

MANAGEMENT OF HEART FAILURE

CLINICAL ASSESSMENT

Breathlessness, fatigue, and even edema may be due to a host of noncardiac conditions and do not necessarily indicate the presence of heart failure. Nevertheless, the clinician must have a high index of suspicion that the source of a patient's problems may be cardiac and must become adept at assessing patients for fluid overload and cardiac abnormalities. Measurement of serum brain natriuretic peptide may aid in the diagnosis of heart failure.[37] Serial measurements of weight at office visits, combined with instructions for daily weighing at home, help to alert the clinician and the patient to the possibility of fluid retention. The patient should be evaluated regularly in an appropriate position (45-degree elevation), with notation of the jugular venous pressure. Hepatojugular reflux, presence of a gallop rhythm, and peripheral edema are key findings on physical examination that may indicate a need for additional diuretic therapy and may be prognostically important.[38]

TREATMENT OF PATIENTS WITH STAGE A HEART FAILURE

Control of risk factors in stage A (e.g., hypertension, coronary artery disease, and diabetes mellitus) has a favorable effect on the incidence of later cardiovascular events (Fig. 3). Results from trials have shown that the effective treatment of hypertension decreases the occurrence of left ventricular hypertrophy and cardiovascular mortality, as well as reducing the incidence of heart failure by 30 to 50 percent.[39,40] Guidelines have recommended that the target for diastolic blood pressure in patients considered to be at high risk, particularly those with diabetes, be below 80 mm Hg, with the goal of further reducing morbidity and mortality.[41] Patients with diabetes have a high incidence of heart disease, with multiple

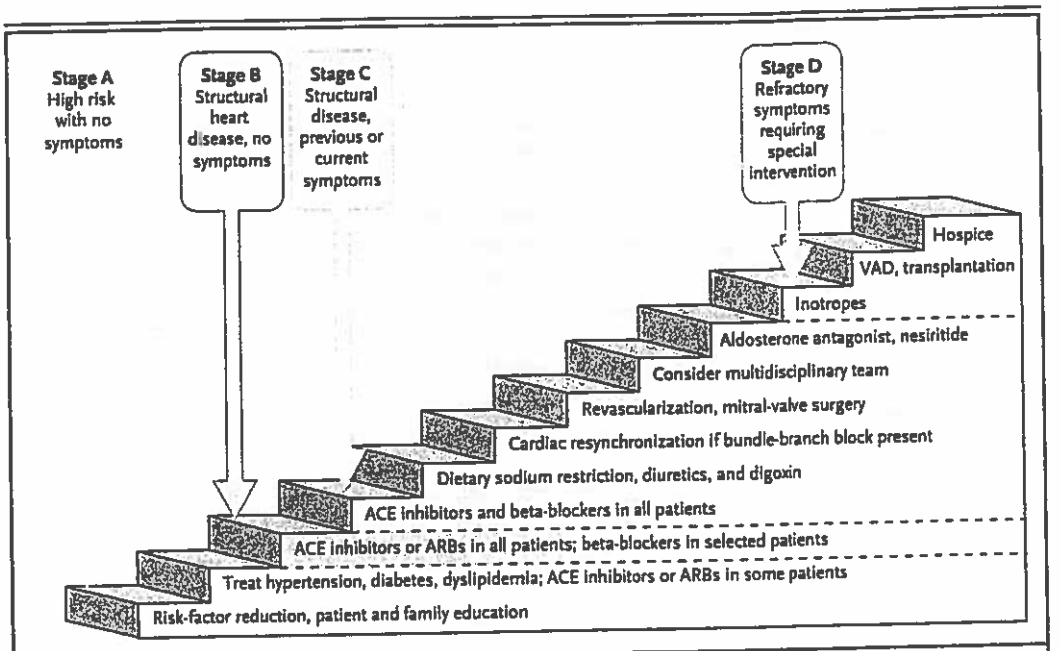

Figure 3. Stages of Heart Failure and Treatment Options for Systolic Heart Failure.

Patients with stage A heart failure are at high risk for heart failure but do not have structural heart disease or symptoms of heart failure. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy. Patients with stage B heart failure have structural heart disease but have no symptoms of heart failure. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction, or valvular heart disease, all of whom would be considered to have New York Heart Association (NYHA) class I symptoms. Patients with stage C heart failure have known structural heart disease and current or previous symptoms of heart failure. Their symptoms may be classified as NYHA class I, II, III, or IV. Patients with stage D heart failure have refractory symptoms of heart failure at rest despite maximal medical therapy, are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA class IV symptoms. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and VAD ventricular assist device.

adaptive and maladaptive biochemical and functional cardiac abnormalities.[42] ACE-inhibitor treatment of asymptomatic high-risk patients with diabetes or vascular disease and no history of heart failure has yielded significant reductions in the rates of death, myocardial infarction, and stroke.[43-45] The use of the angiotensin-receptor blocker losartan has been shown to delay the first hospitalization for heart failure in patients with diabetes mellitus and nephropathy.[46] In short, the goal of treatment in stage A is to prevent remodeling.

TREATMENT OF STAGE B, C, OR D HEART FAILURE WITH OR WITHOUT SYMPTOMS

The goals of therapy for patients with heart failure and a low ejection fraction are to improve survival, slow the progression of disease, alleviate symptoms, and minimize risk factors. Modifications of lifestyle can be helpful in controlling the symptoms of heart failure. For example, basic habits of moderate sodium restriction, weight monitoring, and adherence to medication schedules may aid in avoiding fluid retention or alerting the patient to its presence. Moderation of alcohol intake is advised; avoidance of nonsteroidal antiinflammatory drugs (NSAIDs) is also important.[47] NSAIDs have been associated with an increase in the incidence of new heart failure, decompensated chronic heart failure, and hospitalizations for heart failure. For selected patients, a regularly scheduled exercise program may have beneficial effects on symptoms.[48,49] ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, thereby minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium and

causes natriuresis in the kidney. The beneficial effects of ACE inhibitors in heart failure and after a myocardial infarction include improvements in survival, the rate of hospitalization, symptoms, cardiac performance, neurohormonal levels, and reverse remodeling.[50-52]

ACE inhibitors have not been unequivocally shown to reduce the incidence of sudden death. They are recommended for many patients with stage A heart failure and all patients with stage B, stage C, or stage D heart failure. But unresolved issues persist. First, underuse of ACE inhibitors by physicians for fear of potential side effects has been a concern. Yet side effects are fairly predictable and reversible and can usually be successfully managed. Second, the optimal dose of an ACE inhibitor is uncertain. Most randomized trials have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors.[53-56] Finally, it is uncertain whether there are any meaningful differences among the many ACE inhibitors available today. Table 3 details some common clinical problems with recommended approaches.

Beta-blockers have long been used for the treatment of hypertension, angina, and arrhythmias and for prophylaxis in patients who have had a myocardial infarction. This class of medication has had a

Table 3. Common Clinical Problems in Patients with Heart Failure and Recommended Solutions.*

Clinical Problem	Recommended Solutions
The patient has classic symptoms of heart failure with a normal left ventricular ejection fraction.	Consider diastolic heart failure, valvular heart disease, hypertensive heart disease, and ischemia.
The patient has hypotension: when is the systolic blood pressure too low?	Asymptomatic patients with dilated cardiomyopathy often tolerate a systolic blood pressure of 90 mm Hg. If the patient has no lightheadedness or undue fatigue, peripheral perfusion is adequate, and blood urea nitrogen and creatinine are unchanged, continue the same doses of medications. In symptomatic patients, decrease the dose of diuretic. If symptoms persist, adjustment of the timing of concomitant medications may be helpful. Decreasing the dose of the ACE inhibitor, beta-blocker, ARB, or vasodilator is indicated.
The patient has hyperkalemia.	Ensure that the patient is taking no exogenous potassium supplement or potassium-containing salt substitute. Avoid hypovolemia. Consider decreasing the dose of a potassium-sparing diuretic. Concomitant use of an ACE inhibitor or ARB and spironolactone may increase the risk of hyperkalemia. Avoid high doses of ACE inhibitors and ARBs in patients receiving spironolactone. Avoid use of spironolactone in patients with renal failure, and use low doses of ACE inhibitors and ARBs.
The patient has increasing azotemia while taking ACE inhibitors.	Decrease the dose of diuretic. Consider renal-artery stenosis if azotemia persists.
The patient has a cough while taking ACE inhibitors.	Rule out worsening congestive heart failure. Change to ARB if severe cough persists.
Should the dose of the ACE inhibitor be increased or should beta-blocker therapy be initiated in a symptomatic patient?	Start beta-blocker therapy if there are no contraindications.
Should an ARB be added to ACE-inhibitor therapy or should a beta-blocker be added in a symptomatic patient?	Start beta-blocker therapy if there are no contraindications.
The patient has worsening symptoms of congestive heart failure after starting beta-blocker therapy.	Increase the dose of diuretic and slow the titration of the beta-blocker.
The patient has worsening bronchospasm after starting beta-blocker therapy.	Decrease the dose of the beta-blocker. Consider a beta-selective agent. Discontinue treatment with the drug if the problem persists.
Persistent paroxysmal nocturnal dyspnea or orthopnea or daytime fatigue despite absence of fluid retention on physical examination.	Evaluate the patient for central or obstructive sleep apnea.
The patient requires repeated hospitalizations.	A multidisciplinary approach should be initiated, with a visiting nurse in the home. Referral for heart failure is indicated.

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

remarkable effect on chronic heart failure. The primary action of beta-blockers is to counteract the harmful effects of the sympathetic nervous system that are activated during heart failure. The beneficial effects of these drugs have been demonstrated in trials involving patients with heart failure from various causes and of all stages. These effects include improvements in survival, morbidity, ejection fraction, remodeling, quality of life, the rate of hospitalization, and the incidence of sudden death.[3,57] Beta-blockers should be used in all patients in stable condition without substantial fluid retention and without recent exacerbations of heart failure requiring inotropic therapy. There are a few populations of patients in whom beta-blockers should not be used or should be used only with extreme caution. Such patients include those with reactive airway disease, those with diabetes in association with frequent episodes of hypoglycemia, and those with bradyarrhythmias or heart block who do not have a pacemaker.

Although the short-term effects of beta-blockers may result in a temporary exacerbation of symptoms, their long-term effects are uniformly beneficial. Placebo-controlled trials involving long-term treatment have shown improved systolic function after three months of treatment and reverse remodeling after four months.[18,58,59] In the United States, two beta-blockers are specifically approved for the treatment of heart failure: carvedilol and long-acting metoprolol. Currently, neither drug has proved to be consistently superior; both have shown significant clinical efficacy. Carvedilol is a nonselective β-adrenergic antagonist with alpha-blocking effects; metoprolol is a selective β_1-adrenergic antagonist with no alpha-blocking effects. A large trial comparing these drugs is nearing completion. However, the most frequently prescribed beta-blocker in the United States is atenolol; there have been no studies to date on the use of atenolol in patients with heart failure. Drugs that antagonize the sympathetic nervous system through alternative pathways, such as clonidine or moxonidine, have been less clinically useful in patients with heart failure.

Available angiotensin-receptor antagonists block the effects of angiotensin II at the angiotensin II subtype 1 receptor. The recently published guidelines recommend that these drugs should not be used as first-line therapy for heart failure of any stage but should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.[8] Several trials involving patients with heart failure have shown that angiotensin-receptor antagonists have efficacy similar to that of ACE inhibitors but are not superior.[60-62] On the other hand, in a randomized trial of patients with symptomatic left ventricular systolic dysfunction, the addition of valsartan to ACE-inhibitor treatment reduced the rate of the combined end point of death or cardiovascular events and improved clinical signs and symptoms of heart failure.[63] However, patients who were receiving beta-blockers, an ACE inhibitor, and the angiotensin-receptor blocker valsartan had more adverse events and increased mortality. More recently, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial was completed in patients with stage B heart failure — specifically, asymptomatic patients with hypertension and left ventricular hypertrophy on electrocardiography. Treatment with the angiotensin-receptor blocker losartan yielded improvements in cardiovascular morbidity and survival, as well as a decrease in the incidence of new-onset diabetes, as compared with treatment with the beta-blocker atenolol.[64] Thus, accumulating data lend support to the contention that angiotensin-receptor antagonists are a reasonable alternative to ACE inhibitors.

ADDITIONAL THERAPY FOR SYMPTOMATIC PATIENTS WITH STAGE C OR STAGE D HEART FAILURE

There is evidence to support the use of spironolactone, an aldosterone antagonist, in patients with advanced symptoms of heart failure — specifically, NYHA class III or IV symptoms.[65] In patients with advanced heart failure, circulating levels of aldosterone become elevated in response to stimulation by angiotensin II, and there is a decrease in the hepatic clearance of aldosterone due to hepatic congestion. Aldosterone stimulates the retention of salt, myocardial hypertrophy, and potassium excretion; spironolactone counteracts these responses.[66] The beneficial effects of spironolactone in heart failure may also include a decrease in collagen synthesis that promotes organ fibrosis.

Since heart failure is a salt-avid syndrome resulting in intravascular volume overload, diuretics are a mainstay for controlling symptoms of congestion. Thiazide or loop diuretics are often prescribed, and combination therapy may be used to promote effective diuresis in advanced cases.[67,68]

It is only within the past five years that a large, randomized, placebo-controlled study of digoxin for symptomatic patients with a low ejection frac-

tion has been completed. There was no difference in mortality between patients receiving digoxin and patients receiving placebo, but there were decreases in the digoxin group in the rates of worsening heart failure and hospitalization.[69] Recent data suggest that the maintenance of a low serum digoxin concentration (<0.09 ng per milliliter) is as effective in reducing the rate of cardiovascular events as the maintenance of a higher concentration and is associated with a lower rate of toxic effects.[70] Elderly patients and those with renal insufficiency are more prone to toxic effects. There is a commonly observed and clinically important interaction between digoxin and amiodarone: digoxin levels can become markedly elevated after the introduction of amiodarone.

There are some patients who cannot tolerate either ACE inhibitors or angiotensin-receptor blockers, usually because of hyperkalemia or renal insufficiency. In such patients who remain symptomatic despite diuretic and beta-blocker therapy, treatment with the vasodilator combination of hydralazine and isosorbide dinitrate may be an option.[71]

NONPHARMACOLOGIC THERAPY

Cardiac resynchronization therapy is an innovative, pacemaker-based approach to the treatment of patients with heart failure who have a wide QRS complex on 12-lead electrocardiography. The purpose of resynchronization is to provide electromechanical coordination and improved ventricular synchrony in symptomatic patients who have severe systolic dysfunction and clinically significant intraventricular conduction defects, particularly left bundle-branch block.

A percutaneous, three-lead, biventricular pacemaker system is used; one lead is placed in the right atrium, one is placed in the right ventricle, and a third is passed through the right atrium, through the coronary sinus, and into a cardiac vein on the lateral wall of the left ventricle. This left ventricular lead constitutes the key difference between resynchronization therapy and standard dual-chamber pacing. Beneficial effects include reverse remodeling, resulting in decreased heart size and ventricular volumes, improved ejection fraction, and decreased mitral regurgitation. Clinical improvements in exercise tolerance, quality of life, and the rate of hospitalization have been documented.[72-78] To date, however, resynchronization therapy has not been shown to enhance survival.

REVASCULARIZATION AND SURGICAL THERAPY

Patients with heart failure of any stage who are at risk for coronary artery disease should be screened for myocardial ischemia. Revascularization, through either a catheter-based or a surgical approach, often improves ischemic symptoms, improves cardiac performance, and reduces the risk of sudden death.[79,80] Patients with stage C or stage D heart failure, who have heretofore been considered unacceptable candidates for surgery, may in fact derive substantial benefit from bypass surgery and additional techniques designed to reduce myocardial wall stress. Procedures to eliminate or exclude areas of infarction, repair mitral regurgitation, or support the failing myocardium are undergoing clinical trials.[81-83] Similarly, the role of mechanical devices that serve to support patients who are awaiting heart transplantation or are definitive therapy for end-stage (stage D) heart failure continues to evolve, and such devices offer great hope to many patients who are not eligible for cardiac transplantation.[84]

THE FUTURE

Many common clinical problems encountered in patients with heart failure remain unresolved. The role of anticoagulant therapy in patients with systolic dysfunction and sinus rhythm is unclear; neither the type of therapy needed nor the appropriate duration of treatment is known. There may be an important adverse interaction between aspirin and ACE inhibitors that will be clarified in upcoming trials.[85] The optimal care for patients with heart failure and preserved systolic function (diastolic heart failure) awaits further research. The value of revascularization in patients with symptoms of heart failure but without angina will be explored in an important trial that is slated to begin soon.[86] How will we identify patients with familial cardiomyopathy at an earlier stage?[87-89] How do we identify patients with the greatest risk of sudden death? What is the best way to prevent sudden death in a cost-effective manner? Who will be best served by mechanical cardiac-support devices? Can we afford optimal care for the growing number of patients with heart failure? These questions and many others will undoubtedly be answered in the years to come. Perhaps our most intensive investigations, however, should be reserved for efforts that have been shown to prevent this cardiac plague — the control of hypertension and vascular risk factors.

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Diastolic Dysfunction, Cardiovascular Aging, and the Anesthesiologist

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KEYWORDS
• Diastolic dysfunction • Cardiovascular aging
• Echocardiography • Tissue doppler imaging • Perioperative

A 74-year-old woman presented to the preoperative assessment clinic (PAC) before elective, right shoulder arthroplasty. Her past medical history was significant for hypertension, osteoarthritis, and mild chronic obstructive pulmonary disease. She denied any cardiovascular symptoms with the exception of increasing exertional shortness of breath while walking her dog up the hill to her house. She attributed this change in exercise tolerance to getting older and out of shape. The patient quit smoking 25 years ago and regularly takes her antihypertensive regimen of hydrochlorothiazide and lisinopril. In the PAC her vital signs were as follows: blood pressure 158/64 mmHg, pulse 78 beats/min, and room air oxygen saturation 100%. Auscultation of her chest revealed clear lung sounds and a regular cardiac rate and rhythm with a midgrade (3–4/6) systolic ejection murmur radiating to her carotid arteries. A 12-lead electrocardiogram showed normal sinus rhythm and nonspecific S-T wave changes. A transthoracic echocardiogram was obtained which revealed a normal ejection fraction of 65%, impaired left ventricular relaxation, moderate concentric left ventricular hypertrophy, moderate left atrial enlargement, and severe aortic valve stenosis (aortic valve atresia [AVA] = 0.9 cm^2; peak gradient 60 mmHg) with mild aortic regurgitation. The patient was referred to cardiology and subsequently underwent a coronary and right heart catheterization, which showed nonobstructive coronary disease, a peak left ventricular pressure gradient of 75 mmHg, and an end-diastolic pressure of 22 mmHg.

The patient was scheduled for aortic valve replacement surgery with cardiopulmonary bypass (CPB). Intraoperative anesthetic and surgical care of the patient were

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uneventful; she was managed with an isoflurane- and fentanyl-based anesthetic, and muscle relaxation was achieved with cisatracurium. A 23-mm stentless, bioprosthetic aortic valve was inserted and the patient was weaned from CPB without inotropes. Following closure of her sternum, transient episodes of hypotension (80/60 mmHg) occurred with concomitant echocardiographic evidence of left ventricular (LV) underfilling that responded to volume loading with colloid. The patient was hemodynamically stable on transfer to the intensive care unit (ICU), sedated with dexmedetomidine, and on a low dose infusion of phenylephrine. During the first 6 hours in the ICU, the patient's cardiac index dipped below 2.0 which corresponded to her low cardiac filling pressure (left ventricular end diastolic pressure [LVEDP] < 18 mmHg) and labile blood pressure. Because of the minimal chest tube drainage and hemodynamic lability, a bedside transesophageal echocardiogram (TEE) was performed which was negative for evidence of cardiac tamponade, but it did confirm a relative hypovolemia. The patient responded well to volume resuscitation and her hemodynamics stabilized at an LVEDP 24 mmHg. She was subsequently weaned from the ventilator on the morning of postoperative day (POD) 1 and remained hemodynamically stable and cognitively intact before transfer to a floor bed on POD 2.

On POD 3 her family remarked that she was not herself and somewhat disoriented. Her oxygen requirements had increased over the preceding 24 hours, and her physical examination and chest radiograph were consistent with pulmonary edema. An electrocardiogram revealed atrial fibrillation. Her blood pressure was 95/60 mmHg. The patient was transferred to the ICU for closer observation, and for reintubation after low oxygen saturation did not respond to face shield oxygen or Bi-level Positive Airway Pressure (BiPAP). Her cardiac rhythm was medically converted with amiodarone, and she was carefully diuresed with furosemide before extubation a day later. She progressed slowly and was discharged to a rehabilitation facility on POD 8 before returning to her home.

The above case represents a common scenario. Changes in the epidemiology of patients undergoing cardiac and major noncardiac surgery,[1–3] coupled with the growing number of older persons with HF,[4,5] may make future perioperative care more difficult.[6] Although our patient reached hospital discharge with no long-term sequelae, her postoperative course was prolonged and complicated. She exemplifies the limited physiologic reserve that characterizes many persons in her cohort. The question of how to recognize and manage this situation arises and is best addressed through an examination of the physiology of the early spectrum of cardiovascular disease, specifically that of aging and diastolic dysfunction. The valvular lesion that was discovered should not distract the reader from the physiologic derangements that were exposed after aortic valve repair; this patient's hemodynamic lability, poor tolerance of volume shifts, cardiac arrhythmia, and eventual reintubation and ICU recidivism occurred despite normal systolic indices and a well-functioning aortic valve prosthesis. In addition, this patient could revisit the same set of perioperative issues when she returns for her shoulder arthroplasty.

This review focuses on the physiology and management of the patient with diastolic dysfunction from the standpoint of the cardiac anesthesiologist, echocardiographer, and general anesthesiologist. Diastolic dysfunction, the precursor of diastolic HF, has been called the great masquerader.[7] Because its clinical presentation may erroneously be ascribed to chronic obstructive pulmonary disease or to normal aging, diastolic heart disease may remain undiagnosed or ignored. Other than exercise intolerance,[8,9] symptoms associated with isolated diastolic HF in the elderly include weakness, anorexia, fatigue, and mental confusion. One clue in identifying this disorder is the diastolic dysfunction phenotype; that is, the 65-year-old,

postmenopausal, hypertensive female patient.[10] Indeed, diastolic dysfunction represents a part of the physiologic spectrum that progresses from normal aging to advanced cardiovascular disease. Although the perioperative risk for the healthy, elderly patient with isolated diastolic dysfunction is not yet known,[11,12] extrapolations from cardiac surgery and cardiology data suggest that it is associated with increased morbidity and mortality.[13–17] Therefore, the perioperative physician is obliged to understand age-related changes in the heart and vasculature that affect diastolic function and to become knowledgeable on the diagnostic and prognostic echocardiographic measures of diastolic function so that perioperative management can be modified in a way that may improve outcomes in the elderly.

PHYSIOLOGIC CHANGES OF AGING AND DIASTOLIC DYSFUNCTION

Several changes in cardiac structure and function occur with aging that contribute to diastolic dysfunction. On the structural level, there is a decrease in myocyte number, an increase in myocyte size, and an increase in the amount of connective tissue matrix.[18,19] Myocyte number decreases because of cell necrosis and apoptosis. As myocytes are lost they are replaced with fibroblasts, and the remaining myocytes hypertrophy. As the fibroblasts produce collagen, interstitial fibrosis occurs and the heart becomes stiffer and less compliant. The stiffer and less compliant ventricle affects diastolic relaxation as well as systolic contraction. Chronically elevated afterload from stiff vasculature leads to left ventricular hypertrophy (LVH) and prolongation in systolic contraction time. Prolonged systolic contraction, in turn, impinges on early diastole.[20–23]

The two main consequences of age-related arterial stiffening are decreased aortic distensibility and increased pulse wave velocity.[24,25] The aorta is responsible for cushioning the pulse energy generated by the heart and converting it into stored energy through the elastic recoil of the vessel. The loss of distensibility during systole results in a higher systolic pressure (**Fig. 1**), and less stored energy to augment forward flow during diastole. This loss is manifested by a lower diastolic pressure (Fig. 2). The resultant increased pulse pressure is an established risk factor for cardiovascular events.[26–29]

The pulse wave velocity is the speed at which the pressure wave, generated by the contracting heart, travels to the periphery and is responsible for a palpable pulse. As vessels become stiffer, the pulse wave becomes faster. The pressure wave is reflected from the periphery, mainly at arterial branch sites, similar to sound waves reflected as echoes. In the younger adult with compliant vessels, the reflected wave returns to the heart during diastole, which augments aortic diastolic pressure and coronary perfusion. However, as the pulse wave velocity increases with stiffened vessels, the reflected wave returns during late systole, which augments systolic pressure, increasing afterload and the pulse pressure width. This increase is analogous to a mistimed intra-aortic balloon pump (IABP). Inflation of an IABP before aortic valve closure leads to an increase in left ventricular end-diastolic volume (LVEDV), LVEDP, LV wall stress (afterload), and oxygen demand. Thus, the large vessel stiffening of advanced age can lead to greater myocardial stroke work, wall tension, and oxygen consumption in the older heart compared with the younger heart. In addition, these arterial changes contribute to altered diastolic function; afterload directly affects LV relaxation, and is a stimulus for hypertrophy of the myocardium.[30,31]

Although most elderly patients presenting for surgery will have normal ejection fractions (EFs) by echocardiogram, up to a one-third of these patients will have abnormal diastolic function.[14] An understanding of the phases of diastole and associated

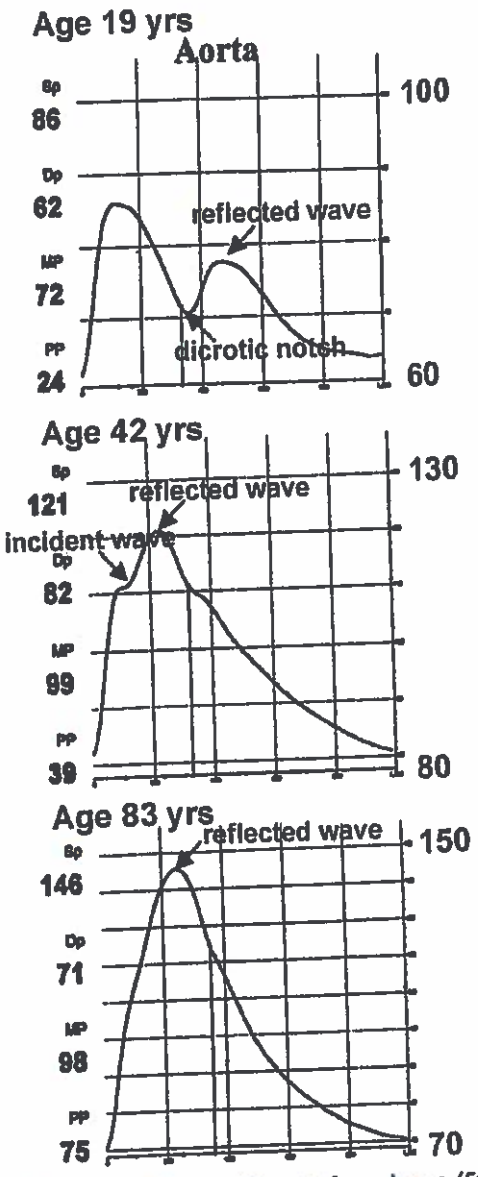

Fig.1. Age-related arterial stiffness and pressure waveform shapes. (*From* Dudley M, Groban L. Cardiovascular changes in the elderly and their anesthetic implications. Curr Rev Clin Anesth 2009;22:266; with permission.)

physiologic determinants is important to understand how age-related changes in cardiac structure and function influence diastology (**Box 1**). At the mechanical level (**Fig. 3**), diastole begins with aortic valve closure when the pressure within the left ventricle begins to decrease, and is called the isovolumic relaxation phase. The LV pressure will continue to decrease even after the opening of the mitral valve. In fact, LV pressure falls below left atrial pressure as a result of elastic recoil, creating a suction effect. Rapid filling of the left ventricle occurs during this phase. Normally, LV

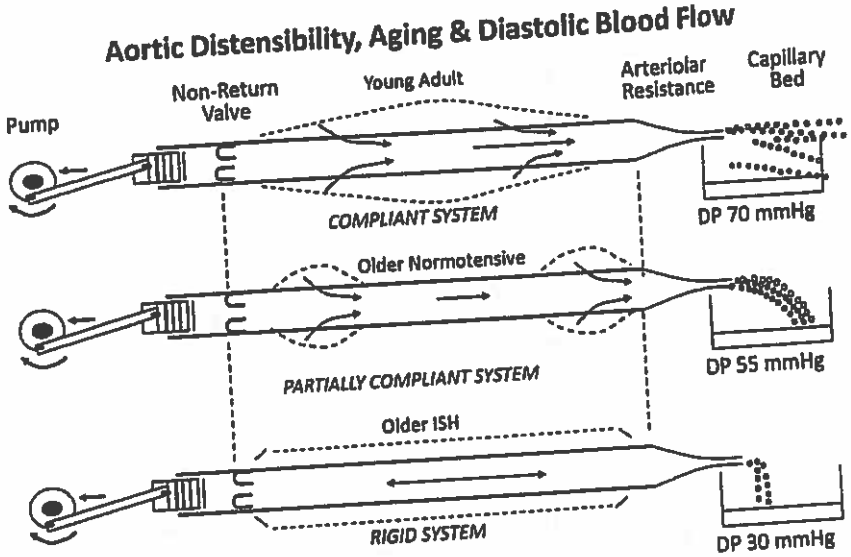

Fig. 2. Blood pressure as a result of ejection of blood (eg, stroke volume) into a series of tubes the diameter of which vary with pulsating pressure. In the young adult, the aorta cushions the cardiac pulsation by converting pressure energy into elastic energy through distension. Once the heart ceases ejection and the pressure falls, the walls of the aorta recoil and the elastic energy is reconverted into pressure energy. This conversion reduces the magnitude of pressure change and allows for a steady flow beyond the arterioles, which accounts for the diastolic component of BP. With aging and hypertension, the aorta and other major conduit vessels become rigid, leading to a loss of cushioning of the ejected energy. Accordingly, this loss of stored energy manifests in extremes in pressure; increased pulse pressure and low diastolic pressure. (*Adapted from* Baird RN, Abbott WM. Pulsatile blood-flow in arterial grafts. Lancet 1976;ii:948; with permission.)

relaxation ends in the first third of rapid filling so that most left ventricular filling is dependent on such properties as left ventricular compliance, ventricular interaction (eg, synchronicity), and pericardial restraint. Finally, atrial systole contributes to the rest of LV volume. In the young heart, approximately 80% of LV filling is complete by the end of the passive filling phase, with the remainder occurring during active atrial transport. In contrast, with advanced age, impairments in early diastolic relaxation and ventricular compliance alter filling dynamics such that atrial transport becomes the

Box 1
Principle effects of aging on the cardiovascular system

- Increased arterial stiffness
- Increased myocardial stiffness
- Impaired β-adrenergic responsiveness
- Impaired endothelial function
- Reduced sinus node function
- Decreased baroreceptor responsiveness
- Net effect: marked reduction in cardiovascular reserve

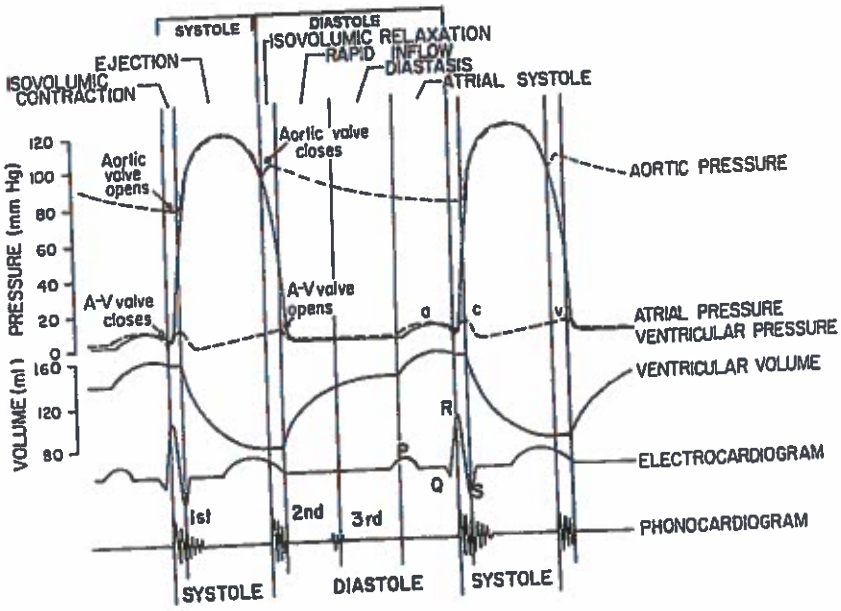

Fig. 3. Cardiac cycle with phases of diastole.

more important contributor to diastolic volume. This so-called atrial kick is essential to maintain an adequate preload, particularly if the preceding three phases of diastole are adversely influenced by age-related changes in cardiac structure and function.

The diagnosis of diastolic dysfunction can be made from cardiac catheterization and Doppler LV diastolic filling patterns. Catheterization data show increases in ventricular diastolic pressure (>16 mmHg) with preserved systolic function and normal ventricular volumes. Most Doppler LV diastolic filling patterns can be categorized into 1 of 4 distinct categories (**Fig. 4**). The normal pattern is seen in healthy young and middle-aged persons. In sinus rhythm, there are two peaks in the Doppler diastolic filling profile that occur in response to the pressure gradient between the left atrium (LA) and left ventricle; early in diastole following mitral valve opening when LV pressure falls below LA pressure, and late in diastole when atrial contraction increases LA pressure above LV pressure. The LV filling pattern in healthy young subjects is characterized by predominant rapid filling early in diastole with modest additional filling during atrial contraction. The filling pattern can be quantified by measuring the peak early diastolic flow velocity (E) and the peak flow velocity during atrial contraction (A), and expressing this as E/A ratio (**Fig. 5**). Normally, the E/A ratio in young subjects is greater than one.

The first pattern of altered LV filling is called "delayed relaxation" (see **Fig. 4**). In this pattern there is reduced peak rate and amount of early filling, and the relative importance of atrial filling is enhanced, resulting in a reversed E/A ratio of less than 1 (eg, E<A). This decreased rate of early filling is a result of a decreased early diastolic LA to LV pressure gradient, caused by a slowed rate of LV relaxation. Although a delayed relaxation pattern can be seen in patients with LV hypertrophy, atrial hypertension, and coronary artery disease, it is normally seen in healthy older persons who are free of cardiovascular disease.

The other two patterns (see **Fig. 4**) of altered LV filling are always abnormal, including in the elderly. The first has been called pseudonormalization, as the E/A ratio

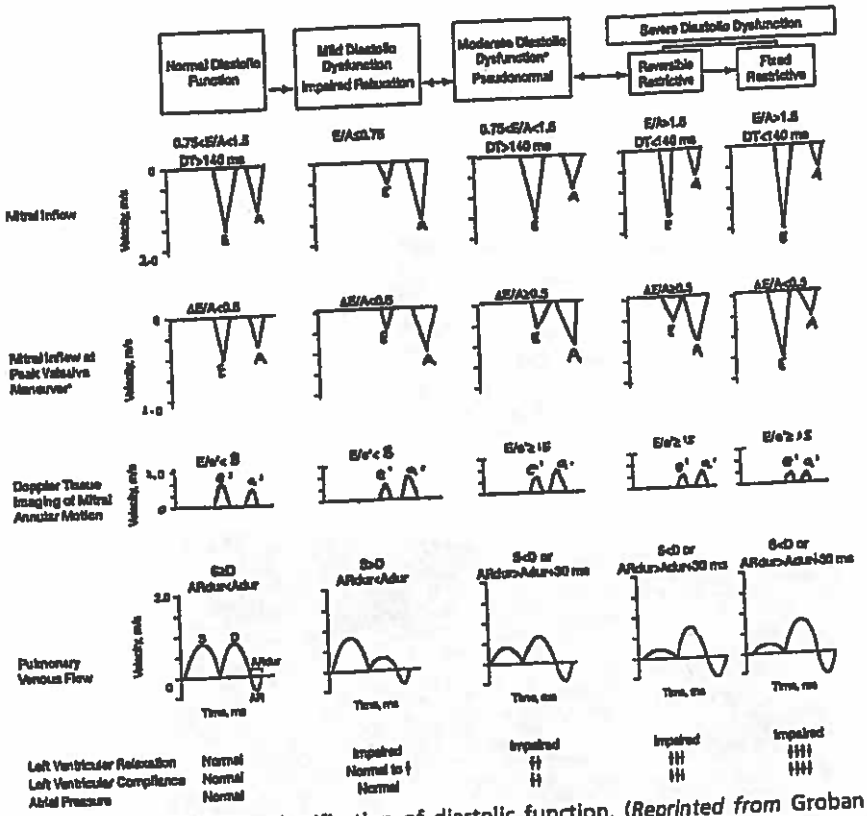

Fig. 4. Doppler criteria for classification of diastolic function. (*Reprinted from* Groban L, Dolinski SY. Transesophageal echocardiographic evaluation of diastolic function. Chest 2005;128:3658; with permission.)

is greater than one (as seen in young normals). This pattern results from an increase in LA pressure that compensates for the slowed rate of LV relaxation and restores early diastolic LV pressure gradient to the baseline level seen in younger persons. The left atrium pushes to fill the LV, whereas in the young patient, the left ventricle fills by creating a suction effect. Elevated left atrial pressure results in left atrial enlargement as a result of pressure and volume overload. It has been suggested that left atrial enlargement is associated with age;[32,33] however, there is evidence that increased left atrial size is not a normal result of aging,[34,35] and is more likely a compensatory response to impaired LV relaxation. Left atrial volume increases with progressively worsening diastolic function,[36–38] and is a risk factor for complications including atrial fibrillation and embolic stroke. To differentiate normal from pseudo-normal, the patient's preload can be reduced using nitroglycerin or with the introduction of a Valsalva maneuver, potentially uncovering an E <A pattern and impaired relaxation. Another way to circumvent the preload dependency of transmitral Doppler is the use of myocardial (or annular) velocities by tissue Doppler (TDI) as discussed later.

In the final altered LV filling pattern, called "restrictive," early filling is increased abnormally, even more than that seen in young normals. Moreover, as a result of diminished atrial filling, because of reduced atrial contractility, the E/A ratio is often greater than two. This pattern is seen in patients with severe diastolic dysfunction, pulmonary congestion, and end-stage dilated cardiomyopathy. Similar to

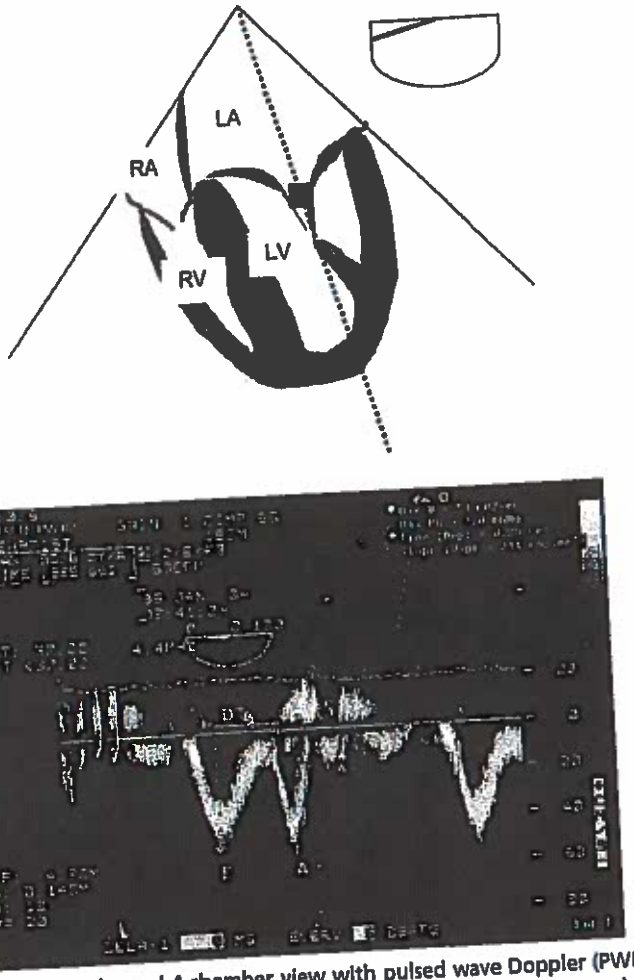

Fig. 5. (*Top*) the midesophageal 4-chamber view with pulsed wave Doppler (PWD) imaging sample volume at the level of the tips of the open mitral valve leaflets. (*Bottom*) transmitral blood flow velocity profile obtained with PWD imaging at the midesophageal 4-chamber view. (*Reprinted from* Groban L, Dolinski SY. Transesophageal echocardiographic evaluation of diastolic function. Chest 2005;128:3656; with permission.)

pseudonormalization, reversible and irreversible restrictive disease can be distinguished from each other by Valsalva maneuver. In reversible, restrictive disease the mitral inflow pattern becomes abnormal with the A > E whereas in irreversible, restrictive disease the E wave remains greater than the A wave owing to the stiff ventricle and high filling pressures. Each abnormal filling pattern results from a variable combination of delayed early relaxation, increased LA pressure, and increased LV chamber stiffness. Indeed, these patterns represent a continuum from normal to severe diastolic dysfunction, with progressively increasing LV chamber stiffness.

It is important to distinguish the difference between diastolic dysfunction and diastolic HF (**Box 2**). Diastolic dysfunction is a physiologic or preclinical state in which abnormal relaxation or increased LV stiffness is compensated for by increasing LA pressure so that LV preload remains adequate. These patients may be considered

Box 2
Risk factors for diastolic heart failure

- Age >70 years, hypertensive woman
- Systolic hypertension, increased pulse pressure (>60 mmHg)
- Diabetes, chronic renal insufficiency
- Echo: normal EF, delayed relaxation, left atrial enlargement (LAE) > 50 mm, LVH
- ECG: previous myocardial ischemia (MI), LVH, atrial fibrillation (AF)
- Recent weight gain (fluid overload)
- Exercise intolerance
- B-type natriuretic peptide (BNP) > 120 (BNP of 200 pg/mL may not be clinically significant in older, postmenopausal women)

American College of Cardiology/American Heart Association (ACC/AHA) stage A or stage B because they are asymptomatic.[39] Progression to diastolic HF, ACC/AHA stage C or D, is characterized by signs and symptoms of HF with normal EF (>50%), the absence of valvular disease, and echocardiographic evidence of diastolic dysfunction. Diastolic HF is a true heart failure syndrome, as neurohormonal activation is triggered in a similar manner to that which occurs in systolic HF.[40,41]

The pathophysiology of diastolic HF is characterized by a low cardiac output state resulting from a stiff, thickened ventricle with a small cavity. Relaxation is slow in early diastole and offers greater resistance to filling in late diastole, so that diastolic pressures are elevated. Elevated left atrial pressure is transmitted backward through the valveless pulmonary veins to the pulmonary capillary bed. Under normal resting conditions, the patient may be asymptomatic. However, periods of activity or stress which increase heart rate, stroke volume, end-diastolic volume or blood pressure (BP) result in pulmonary overload, manifesting as shortness of breath, fatigue, and, most commonly, exertional dyspnea.[8] Accordingly, because patients with diastolic dysfunction are often asymptomatic at rest, it is important to inquire about exercise tolerance.[9] Indeed, the presentation of HF in older patients may be insidious or sudden with the onset of severe shortness of breath usually attributable to pulmonary edema. However, patients may complain only of fatigue or lack of energy, which may be attributable to physical deconditioning. Even though signs/symptoms and clinical examination can provide useful information, such as AF, displaced apex, and jugular venous distension, accurately diagnosing older patients with suspected HF can be difficult. Although it is beyond the scope of this review, investigations for an older patient with suspected HF should include a combination of simple blood tests such as serum electrolytes, 12-lead electrocardiogram, chest radiology, BNP, and echocardiography.

THE CARDIAC SURGERY PATIENT WITH DIASTOLIC DYSFUNCTION

It is well established that complications following cardiac surgery are encountered in patients of advanced age. Other risk stratification characteristics that are typically encountered include prolonged CPB time, female sex, and diminished systolic function;[42,43] however, there may exist a group of patients who are still at elevated risk for a more complicated hospital course who do not necessarily display these characteristics. Specifically, the echocardiographic identification of diastolic dysfunction and

the presence of elevated diastolic filling pressures can yield meaningful information that can help identify these patients and guide perioperative management.

As discussed previously, the LV inflow Doppler is the most commonly used measurement in the echocardiographic examination of diastolic function because transmitral flow patterns and associated deceleration times represent increasing degrees of LV diastolic impairment. Because these measurements, along with the pulmonary venous waveform patterns, change rapidly with preload variations, heart rate (HR) and rhythm disturbances,[44–46] tissue Doppler imaging is considered to be a more sensitive tool in the assessment of diastolic function (Fig. 6). Tissue Doppler imaging (TDI) is a modality that measures myocardial velocity, in contrast to traditional Doppler, which measures blood flow velocity and may not represent actual myocardial properties.[47] Mitral annular motion has been shown in experimental animal work and in humans to relate well with invasive indices of relaxation.[48–51] The measurements e′, representing the early diastolic active relaxation phase, and a′, the late diastolic atrial

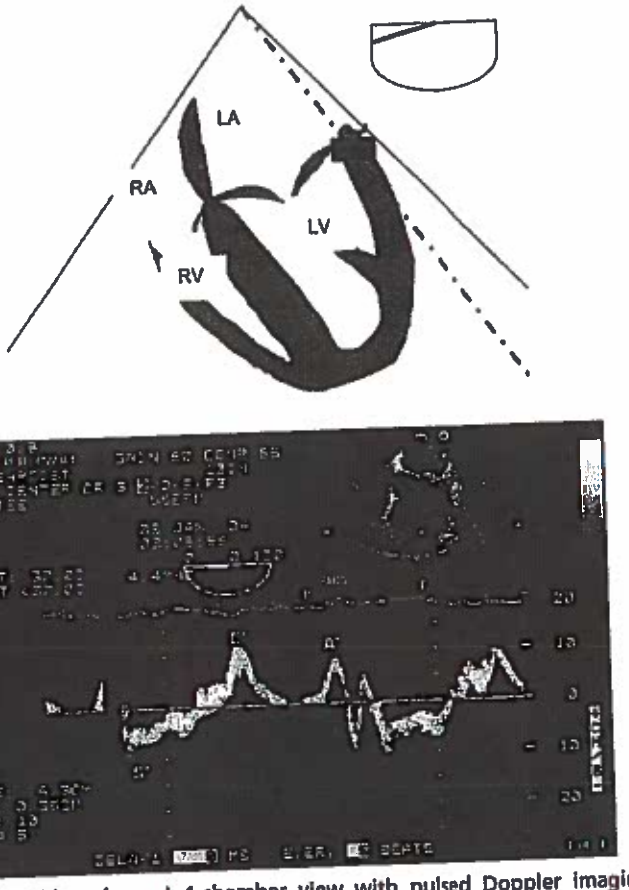

Fig. 6. (*Top*) the midesophageal 4-chamber view with pulsed Doppler imaging sample volume located at the lateral mitral annular wall for TDI assessment of diastolic function. (*Bottom*) lateral mitral annular tissue Doppler waveforms for the assessment of left ventricular diastolic function. (*Reprinted from* Groban L, Dolinski SY. Transesophageal echocardiographic evaluation of diastolic function. Chest 2005;128:3660; with permission.)

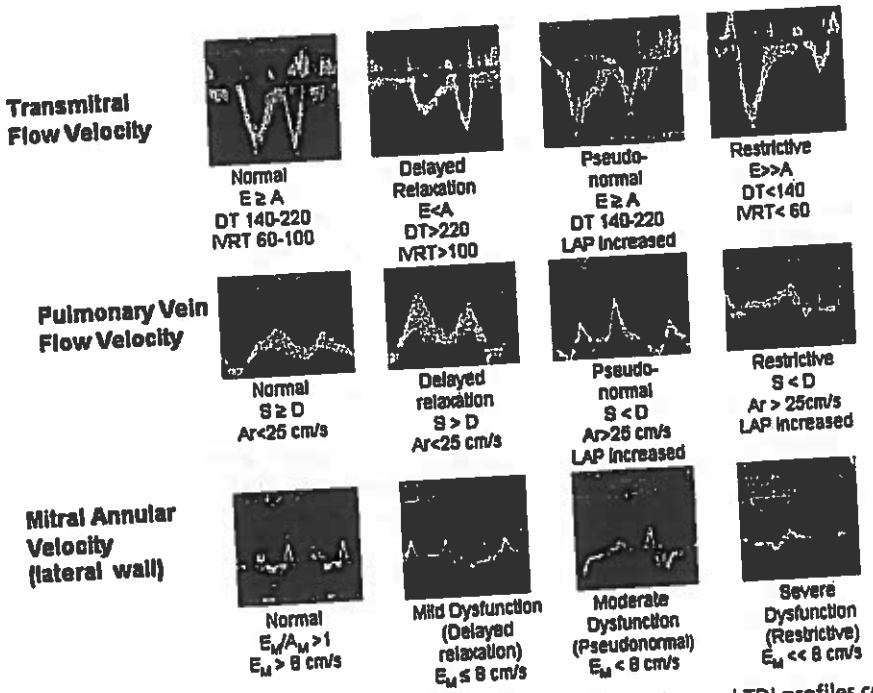

Fig. 7. Transmitral Doppler imaging, pulmonary view Doppler imaging, and TDI profiles corresponding to normal, delayed relaxation, pseudonormal, and restrictive filling patterns. (*Reprinted from* Groban L, Dolinski SY. Transesophageal echocardiographic evaluation of diastolic function. Chest 2005;128:3659; with permission.)

contraction phase, can be used to identify and quantify diastolic dysfunction (Figs. 6 and 7).

In the normal heart, e′ may be influenced by alterations in preload;[52] however, in the presence of diastolic dysfunction, e′ decreases and becomes preload independent.[53] This allows for the severity of diastolic dysfunction to be quantified by a decreasing e′ value. Age influences the e′ and a′ values; an e′ < 10 cm/s in those less than 50 years of age, and e′ < 8 in those older than 50 years should be considered abnormal.[52] The e′ to a′ ratio verifies abnormal diastolic function (e′/a′ > 1 is considered normal), as an e′/a′ ratio of less than 1 during Valsalva confirms the presence of diastolic dysfunction.[54] Age also influences the e′/a′ ratio, and after the age of 50 e′/a′ < 1 is frequently encountered and should be correlated with other echocardiographic measurements.

A robust quantification of elevated left ventricular filling pressures in diastolic dysfunction is the ratio of transmitral E wave velocity to mitral annular velocity (E/e′).[55–58] This ratio normalizes early transmitral left ventricular filling to mitral annular motion and is used to estimate mean left atrial pressure (with values >15 representing elevated filling pressures, and <8 reflecting normal filling pressures).[17,50,55] Moreover, accuracy of this measurement has been shown to be relatively independent of LV systolic function, rhythm abnormalities (such as tachycardia and AF), LV hypertrophy, and functional mitral regurgitation.[17,50,59–62]

Although e′ relates to global indices of LV relaxation, it must be realized that it is a regional index, as errors can occur in patients with regional wall motion abnormalities at the Doppler sampling site. A limitation to E/e′, a′, and e′ is that myocardial motion at the lateral annulus is higher than the septal annulus, as the septum is

tethered to the right ventricle and other structures in the middle of the heart.[55,63] For this reason, and because of its accessibility with transesophageal echocardiography, the lateral mitral annular velocity may be easier to use in the intraoperative transesophageal setting. Although relatively independent of EF, the reliability of E/e′ in predicting pulmonary capillary wedge pressure in decompensated advanced systolic HF has been called into question.[64] The previously mentioned age-related changes and influence of preload in the normal heart when using TDI measures must also be kept in mind. Despite these limitations, TDI is a powerful tool for identifying whether mitral valve inflow velocity patterns represent pseudonormalization and elevated filling pressures.

Doppler echocardiography of diastolic function has proved useful as a diagnostic tool in predicting outcome in patients undergoing cardiac surgery. A recent prospective report of 191 coronary artery bypass graft (CABG) patients found greatly increased mortality (12% vs 0%) following cardiac surgery in patients with significant diastolic dysfunction; risk scores based on systolic function and patient characteristics were less accurate in predicting complications in this patient group than were markers of diastolic dysfunction.[65] Bernard and colleagues[66] identified diastolic dysfunction as an independent predictor of difficult separation from CPB. Liu and colleagues[13] identified that pseudonormal or restrictive transmitral flow patterns were predictive of cardiac events following CABG, whereas left ventricular ejection fraction and the presence of left main coronary artery disease were not independent predictors of poor outcome.

The importance of diastolic dysfunction in cardiac surgery patients is supported by the mechanism of progression of myocardial dysfunction in ischemic heart disease. Diastolic dysfunction has been identified as the earliest potential marker of myocardial ischemia,[67–69] and thereby may represent an early range of the spectrum of myocardial dysfunction that occurs before gross systolic impairment, nonetheless representing a diseased myocardium. An incremental relationship between severity of diastolic dysfunction and outcomes has been demonstrated by Whalley and colleagues,[70] in which nonsurgical congestive HF patients with restrictive diastolic filling patterns had more complications than those with pseudonormal filling patterns or abnormal relaxation. Furthermore, nonsurgical patients with preserved and depressed EF admitted for acute myocardial ischemia (AMI) could be stratified for risk using E/e′ to identify patients with diastolic dysfunction with elevated filling pressures.[17] In that study group, AMI patients were shown to have a higher incidence of HF and poor outcomes with restrictive and pseudonormal LV filling patterns. Elevated filling pressures in that study group were identified by an E/e′ > 15 mmHg, consistent with several previous reports.[17,50,55]

This evidence suggests that elevated LV diastolic filling pressures may be the factor most important in poor outcomes, rather than simply the existence of delayed relaxation.[71] Elevated filling pressures have also been found to be a predictor of mortality in cardiac surgery patients independent of systolic function.[16] In that group, those patients identified as having LV filling pressures more than 22 mmHg were found to have twice the mortality of patients with filling pressures less than 14 mmHg.

There is some indication that elevated LV filling pressures may predict a prolonged and more complicated ICU or hospital stay following cardiac surgery. In a retrospective study of 205 cardiac surgery patients, a 12% increase in hospital length of stay was observed in those patients who had tissue Doppler–based evidence of elevated filling pressures as defined by E/e′ > 17.[72] EF and patient comorbidities were equal between groups. Also, in a study of ICU readmissions following cardiac surgery, ICU recidivism has been shown to be more likely in those with diastolic dysfunction.

This analysis examined 41 ICU readmissions and their likelihood of requiring reintubation. With similar EF, age, baseline BP, HR, and renal function, those who required reintubation were observed to have worse diastolic function, increased E/e', and increased left atrial size on the preoperative echocardiogram.[17]

Diastolic dysfunction and elevated filling pressures should alert the clinician that the cardiac surgery patient may be more challenging than appreciated, even if systolic function is normal. The increased sensitivity of the cardiovascular system to acute changes in loading conditions, and thus the need for strict management of volume status, is of critical importance. The speed with which intravenous fluids are administered may be more significant, with patients of poor diastolic function less able to tolerate rapid volume shifts. Myocardial protection strategies are, as always, of paramount importance, but may need to be reexamined on a patient-by-patient basis in the presence of diastolic dysfunction to ensure an optimal strategy. Myocardial calcium regulation is abnormal in diastolic dysfunction, and may affect the choice to use an inotrope, or to administer specific agents. Lusitropic agents such as milrinone may be of particular benefit in weaning off cardiopulmonary bypass. Although there is no directed strategy for acutely improving diastolic function, these are a few strategies that have been used in the management of these patients.

The newer, TDI-based diastolic variables e', a', and E/e' are simple to incorporate into the echocardiographic examination, and can give valuable information with respect to postoperative complications following cardiac surgery. These measures are easy to obtain, and can identify patients without traditional predictors of complications following cardiac surgery who still may be at high risk.

PERIOPERATIVE IMPLICATIONS AND ANESTHETIC MANAGEMENT OF DIASTOLIC DYSFUNCTION FOR THE GENERAL SURGICAL PATIENT

Given the cardiovascular changes that occur with diastolic dysfunction and in the elderly (**Table 1**), the perioperative management of these patients can be challenging. A thorough preoperative assessment is needed to risk-stratify these patients. Particularly in the elderly, it is important to inquire about functional capacity as individuals unable to climb a flight of stairs (four metabolic equivalents [METs]), walk indoors around the house, or do light house work (one MET), are at an increased risk for complications. The functional capacity evaluation may further alert the anesthesiologist to signs of clinically significant diastolic dysfunction. Because an HF history, independent of coronary artery disease is associated with increased morbidity and mortality after noncardiac surgery,[73] risk factors for HF should be sought in the preoperative evaluation. Although not specific to the elderly, the reader should refer to the latest ACC/AHA published guidelines for a complete discussion of perioperative care and evaluation of cardiac patients undergoing noncardiac surgery.[74] In brief, patients with asymptomatic heart disease can safely undergo elective noncardiac surgery without first requiring angioplasty or coronary bypass grafting to lower the risk for surgery. Noninvasive and invasive preoperative cardiac testing should not necessarily be performed unless results will affect patient management. Patients with severe or symptomatic cardiovascular disease or active cardiac conditions should undergo evaluation by a cardiologist and treatment before noncardiac surgery. Statins should not be discontinued before surgery. If a cardiac intervention is required before elective noncardiac surgery, then the patient should have angioplasty with the use of a bare-metal stent followed by 4 to 6 weeks of antiplatelet therapy plus aspirin.

During anesthesia, the cardiovascular changes discussed in the preceding sections predispose the elderly patient to greater hemodynamic instability and

Table 1
Age-related cardiovascular changes and implications

Age-Related Change	Mechanism	Consequences	Anesthetic Implications
Myocardial hypertrophy	Apoptotic cells are not replaced and there is compensatory hypertrophy of existing cells; reflected waves during late systole create strain on myocardium leading to hypertrophy	Increased ventricular stiffness, prolonged contraction and delayed relaxation	Failure to maintain preload leads to an exaggerated decrease in CO; excessive volume more easily increases filling pressures to congestive failure levels; dependence on sinus rhythm and low-normal HR
Myocardial stiffening	Increased interstitial fibrosis, amyloid deposition	Ventricular filling dependent on atrial pressure	—
Reduced LV relaxation	Impaired calcium homeostasis; reduced β receptor responsiveness, early reflected wave	Diastolic dysfunction	—
Reduced β receptor responsiveness	Diminished coupling of β receptor to intracellular adenylate cyclase activity, decreased density of β receptors	Increased circulating catecholamines; limited increase in HR and contractility in response to endogenous and exogenous catecholamines; impaired baroreflex control of BP	Hypotension from anesthetic blunting of sympathetic tone, altered reactivity to vasoactive drugs; increased dependence on Frank-Starling mechanism to maintain CO; labile BP, more hypotension
Conduction system abnormalities	Apoptosis, fibrosis, fatty infiltration, and calcification of pacemaker and His-bundle cells	Conduction block, sick sinus syndrome, AF, decreased contribution of atrial contraction to diastolic volume	Severe bradycardia with potent opioids, decreased CO from decrease in end-diastolic volume
Stiff arteries	Loss of elastin, increased collagen, glycosylation cross linking of collagen	Systolic hypertension Arrival of reflected pressure wave during end-ejection leads to myocardial hypertrophy and impaired diastolic relaxation	Labile BP; diastolic dysfunction, sensitive to volume status
Stiff veins	Loss of elastin, increased collagen, glycosylation cross linking of collagen	Decreased buffering of changes in blood volume impairs ability to maintain atrial pressure	Changes in blood volume cause exaggerated changes in cardiac filling

greater sensitivity to volume status.[6,19,22,75] Several mechanisms can explain the hemodynamic instability. First, the elderly have a higher resting sympathetic tone and have altered β receptor sensitivity. Removal of the baseline sympathetic tone with the induction of general or neuraxial anesthesia often results in hypotension. Second, older patients have a greater sensitivity to volume status. They often arrive on the day of surgery with a depleted intravascular volume because of more frequent use of diuretics, a decreased thirst response to hypovolemia, and age-related changes in renal function. As they are intensely dependent on preload to fill the left ventricle, the reduction in preload induced by anesthesia may result in profound hypotension. Third, the direct effects of intravenous and volatile anesthetics impair cardiac inotropy and lusitropy, and produce arterial and venous vasodilatation.

Anesthetic management of the elderly patient must be planned on a case-by-case basis. Instead of a specific type of anesthetic for the older patient, the authors offer suggestions on a set of principles that address the problems often encountered with the elderly patient. Monitoring volume status is critical to management of the older patient. For patients with known HF, coronary artery disease, or moderate diastolic dysfunction (eg, delayed relaxation with indications of elevated filling pressures), the decision to place an intra-arterial cannula for invasive BP measurement and frequent blood sampling is based on the same considerations applied to the younger patient. Certainly, age-related alterations and coexisting disease may persuade the experienced anesthesiologist to institute such monitoring. However, because no clear evidence exists to specifically recommend this practice before or after induction of anesthesia, the timing of direct arterial pressure monitoring is best based on experience and local practice. For major surgery or vascular surgery, it is imperative that normovolemia be maintained. In such cases, consider use of central venous catheter, pulmonary artery catheter, or transesophageal echocardiography for intraoperative monitoring. Because evidence regarding the efficacy of central venous pressure, pulmonary artery pressure, or transesophageal echocardiographic monitoring as a means to evaluate intravascular volume in the elderly has not been specifically addressed in the perioperative setting, it is not possible to recommend any of these for routine monitoring at this time. Moreover, given the inability of several noninvasive devices, such as the esophageal Doppler or arterial pulse contour, to measure pressures in the central circulation, their usefulness in patients for whom there is concern about the development of pulmonary edema, remains limited.[76] Indeed, future studies are warranted to determine their potential benefit in the elderly surgical patient when combined with an intraoperative goal-directed fluid strategy.

Induction of anesthesia should be accomplished in a smooth and controlled manner. The elderly require a reduced dose of any given induction agent to produce unconsciousness. The induction dose of most agents is decreased by 30% to 50% in the elderly. In addition, induction may be prolonged because of a slow circulation time. Therefore, consider titrating induction agents and waiting for an effect before administering additional doses. It is also important to prevent hypoxemia and hypercarbia, as these patients are prone to pulmonary hypertension. Adequate mask ventilation should be initiated as early as possible. Control of the patient's BP is also essential. It is reasonable to maintain the systolic BP within 10% of the baseline. At the same time, diastolic BP must be maintained, as a low diastolic BP can lead to myocardial ischemia. An attempt should be made to keep the pulse pressure less than the diastolic BP; an increased pulse pressure indicates increased aortic impedance which, as described earlier, will increase wall stress, alter ventricular contraction time, and impair early diastolic filling.

Simultaneous infusions of low dose nitroglycerin and titrated phenylephrine can help to alleviate these physiologic alterations. Administered alone, however, these agents may worsen cardiac function in the elderly. For example, phenylephrine stiffens the vasculature and increases the return of the reflective wave (manifested by an increase in the pulse pressure), potentially impinging on systole and increasing myocardial work. Nitroglycerin alone decreases vascular tone and preload; ultimately reducing cardiac output. However, in contrast to phenylephrine, nitroglycerin decreases the amplitude of the reflected wave and, when used under normovolemic conditions, it reduces the pulse pressure.[77] Thus, the benefits of using combination low dose infusions of phenylephrine and nitroglycerine in the elderly are: (1) the preservation of vascular distensibility; (2) avoidance of reductions in preload and coronary perfusion pressure; and (3) maintenance of stroke volume with minimal cardiac work. In addition, HR should be maintained in the low to normal range (60–70 bpm). At this rate, there is adequate time in diastole to fill the noncompliant ventricle. In general, these principles can be remembered by using the Rule of 70s. For patients age > 70 years, maintain diastolic blood pressure (DBP) > 70, pulse pressure < 70, and HR = 70.

In the early postoperative period, patients with known diastolic heart disease should be watched over closely. As illustrated by this case scenario, elderly patients with diastolic dysfunction can acutely decompensate after initially appearing stable. Hypoxemia or AF are among the most common complications these patients may encounter in the postoperative anesthesia care unit as a consequence of volume overload. Importantly, when vascular sympathetic tone is restored on emergence from general anesthesia or resolution of neuraxial blockade, the noncompliant heart may not be able to tolerate the increased shift in central blood volume thus resulting in pulmonary edema or AF. Indeed, maintaining the low dose infusion of nitroglycerin (eg, 25 μg/min), as discussed previously, may mitigate this from occurring because of its advantageous actions on the pulmonary vasculature. Nonetheless, the assessment of the postoperative patient with suspected HF should include an electrocardiogram for signs of ischemia, LV hypertrophy, AF, and left bundle branch block. If the ECG is abnormal, a further objective assessment of the patient is required. In most cases, this would involve an echocardiogram. Echocardiography is the ideal investigation as information can be obtained about cardiac valves as well as ventricular function. Particularly in older patients, obstructive valvular disease can be detected and other factors influencing the LV preload, including diastolic dysfunction. If echocardiography is not readily available, a chest radiograph may be obtained to provide information about the presence or absence of cardiomegaly and the presence of pulmonary fluid. Also, before treatment commences, additional blood tests such as arterial blood gas, serum electrolytes, and complete blood count (CBC) should be performed in the older patient with confirmed HF. Although treatment options include a carefully chosen dose of intravenous diuretic therapy, a β blocker or calcium channel blocker for HR control, and a venodilator such as nitroglycerin (if tolerated), treatment is best when delivered as part of a multidisciplinary team.

SUMMARY

As the number of persons aged 65 years and older continues to increase, the anesthesiologist will more frequently encounter this demographic. Cardiovascular changes that occur in this patient population present difficult anesthetic challenges and place these patients at high risk of perioperative morbidity and mortality. The anesthesiologist should be knowledgeable about these age-related cardiovascular changes, the pathophysiology underlying them, and the appropriate perioperative management.

Whether presenting for cardiac or general surgery, the anesthesiologist must identify patients with altered physiology as a result of aging or diastolic dysfunction and be prepared to modify the care plan accordingly. With a directed preoperative assessment that focuses on certain aspects of the cardiovascular system, and the assistance of powerful echocardiographic tools such as tissue Doppler, this can be achieved.

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Approach to the Treatment of Aortic Dissection

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KEYWORDS
• Acute dissection • Chronic dissection
• Diagnosis • Surgical treatment • Medical treatment
• Endovascular treatment

Acute aortic dissection is the most common catastrophic event that involves the aorta, presenting to the emergency room much more often than a ruptured abdominal aortic aneurysm.[1] Timely intervention, whether medical, surgical, or endovascular, is essential to yield the best short-term and long-term results for patients with acute dissection, who are often only a few hours away from death. Unfortunately, the ability of acute aortic dissections to masquerade as a myriad of other pathologic processes can make the diagnosis difficult to pinpoint at times. An aortic dissection essentially represents a pathologic state in which a tear occurs in the intima of the aortic wall, allowing blood to split the aorta in two, like an onion peeling apart. Dissections swirl down the aorta for a variable length, shearing off side branches along the way. Most commonly, the entry tear is short (0.5–3 cm in length or less) and located at the proximal extent of the dissection, with the false lumen extending distally as a consequence of blood shearing off the inner layers in an antegrade fashion. Retrograde dissection can also occur, but it is much less common. **Fig. 1** demonstrates a typical dissection in the ascending aorta on transesophageal echocardiography (TEE). **Fig. 2** demonstrates a typical dissection in the descending aorta on TEE. Side branch involvement occurs in 30%, due to either compression of the branch by the distended false lumen, or by shearing off the side branch as the dissection travels beyond. The most common vessels involved clinically are the renal and iliac arteries, followed by the mesenteric, cerebral, coronary, and spinal arteries.[2–5] Although fenestrations between the true and false lumen are most frequent at branch points, fenestrations can occur anywhere along the aorta, allowing blood to travel between the two lumens in locations beyond the primary tear.

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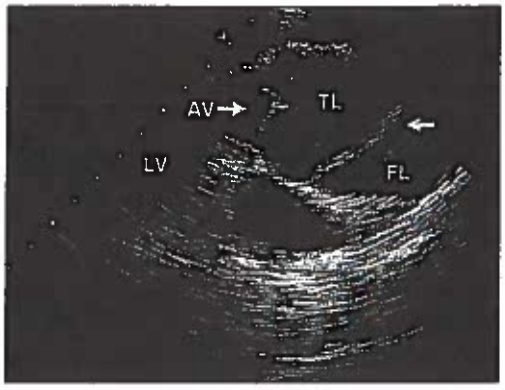

Fig. 1. Transesophageal echocardiogram demonstrating a dissection flap (*unlabeled arrow*) in the ascending aorta. The arrow labeled AV is the aortic valve, LV is left ventricle, TL is true lumen, and FL is false lumen.

NATURAL HISTORY AND CLASSIFICATION OF ACUTE DISSECTION

Acute aortic dissections are lethal if not diagnosed early and treated with aggressive medical or surgical therapy. In a classic natural history study, Hirst and associates demonstrated 30% mortality by 24 hours, 50% mortality by 48 hours, and 90% mortality at 1 year in 505 patients with acute aortic dissection (Fig. 3).[6] This study is the source for the commonly referenced "one percent per hour" mortality rate for the first 48 hours following acute dissection. The clinical manifestations of aortic dissection are protean, and some reports suggest that 25% to 50% of aortic dissections are misdiagnosed.[7,8] As for other catastrophic disease processes, a "high-index of suspicion" is important, but it is important to remember that less than 1% of patients with chest or back pain on presentation to the emergency room have an aortic dissection.[9,10]

Numerous classification systems have been proposed, but the 2 that have stood the test of time are the DeBakey classification (3 types: I, II, and III) and the Stanford classification (2 types: A and B).[11,12] The Stanford classification is the most important for determining the need for surgical intervention. Fig. 4 demonstrates the classification systems.[13] The Stanford system is a functional classification that separates dissections into type A (involving the ascending aorta) (Fig. 5) and type B (not involving

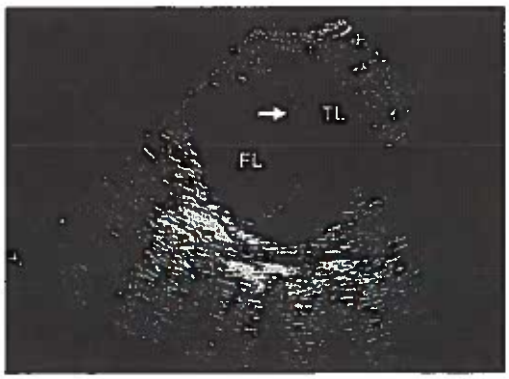

Fig. 2. Transesophageal echocardiogram demonstrating a dissection flap (*arrow*) in the descending aorta. The false lumen (FL) is typically larger and often compresses the true lumen (TL) potentially impacting distal aortic flow.

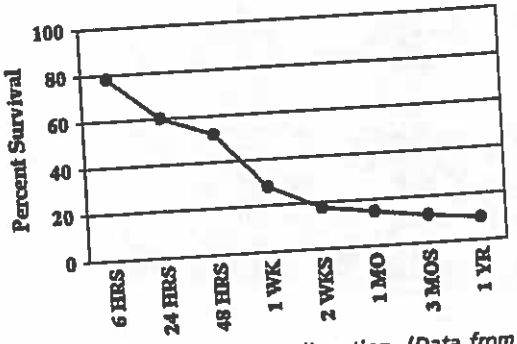

Fig. 3. Mortality rate of untreated acute aortic dissection. (*Data from* Hirst AD, Johns VJ, Kime SW. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine 1958;37:217–79.)

the ascending aorta) (Figs. 6 and 7) regardless of the location of the primary tear or the distal extent of the dissection. The DeBakey classification subcategorizes the Stanford type A into either a DeBakey type I or II, depending on its distal extent. DeBakey type I dissections extend beyond the ascending aorta, generally into the descending and possibly abdominal aorta. DeBakey type II dissections do not extend beyond the ascending aorta, the surgical implications of which are that the entire length of the dissection can be replaced without having to deal with the arch (Fig. 8). DeBakey type III dissections are equivalent to Stanford type B dissections.

In autopsy series, type A dissections outnumber type B dissection almost 2:1, with isolated arch dissections accounting for only 1% to 2%.[1,8] By far, the most common cause of death in untreated type A dissection is intrapericardial rupture with tamponade (80%–90%) followed by extrapericardial rupture (5%–10%) and obstruction of an aortic tributary causing end-organ failure (5%–10%).[6] The most common causes of death in untreated type B dissection are rupture (60%), which is usually intrathoracic, and obstruction of an aortic tributary causing end-organ failure (40%).

WHEN AND WHY DO DISSECTIONS OCCUR?

Dissections can present at a young age in patients with Marfan syndrome or other connective tissue diseases (Ehlers-Danlos, Loeys-Dietz, Turner syndrome), but they

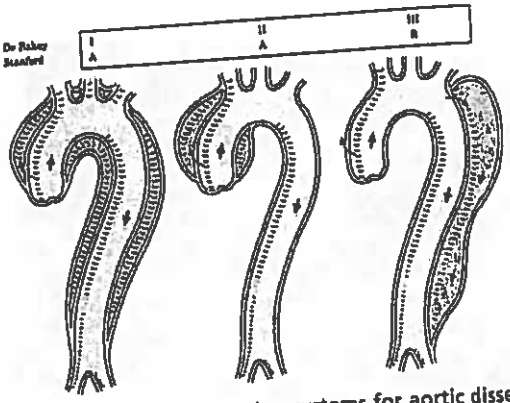

Fig. 4. The Debakey and Stanford classification systems for aortic dissection. (*From* Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection. Eur Heart J 2001;22:1642–81; with permission.)

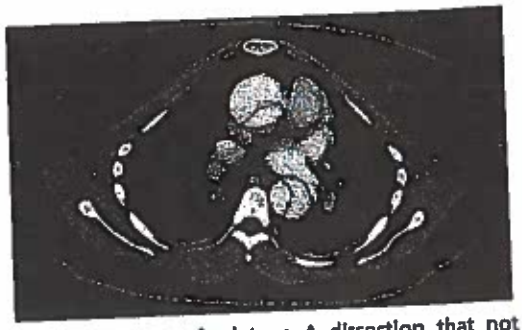

Fig. 5. CT scan demonstrating a Stanford type A dissection that not only involves the ascending aorta but also the descending aorta.

are most common in the 40- to 70-year-old age groups.[5,8] In patients greater than 40 years of age, hypertension is overwhelmingly the most common predisposing factor. In either age group, it is important to consider bicuspid aortic valve disease as a predisposing factor, because dissections are 5 to 10 times more common than in patients with trileaflet valves.[14] The "classic" patient with an acute aortic dissection is a hypertensive man in his 50s, but, unfortunately, this is also the "classic" patient with coronary artery disease. Therefore, although it is interesting to identify subgroups that are most commonly affected, it is not helpful in the diagnosis of an individual patient.

Bicuspid Aortic Disease

Bicuspid aortic valves are often associated with ascending aortic dilation and dissections.[15] At Washington University, the incidence of an ascending aortic aneurysm in patients with bicuspid valves undergoing aortic valve replacement is 22%.[16] The classic teaching that ascending aortic dilation in patients with valvular disease is the consequence of abnormal flow patterns in the root with stenosis or regurgitation does not explain the increased incidence of ascending aortic involvement in patients with bicuspid valves. The authors have identified increased expression of genes associated with cell death and apoptosis (interleukin-1-β, tumor necrosis factor-α) in ascending aortic aneurysms, but not genes associated with atherosclerosis and inflammation (apolipoprotein-E, interleukin-8), as are typically found in descending thoracic and abdominal aortic aneurysms.[17] These findings are consistent with our

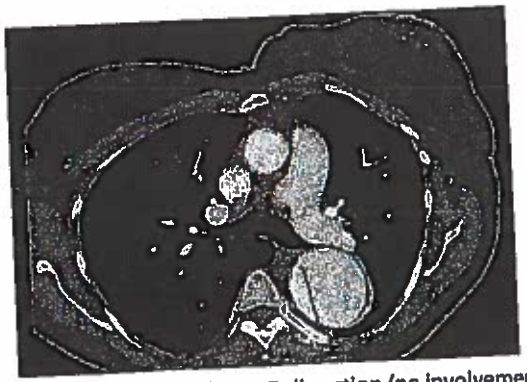

Fig. 6. CT scan demonstrating a Stanford type B dissection (no involvement of the ascending aorta).

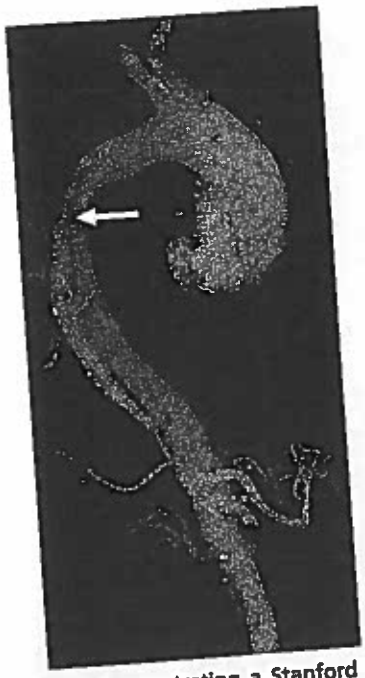

Fig. 7. Three-dimensional CT scan demonstrating a Stanford type B dissection (the *arrow* identifies the dissection flap).

biochemical and histologic analysis demonstrating elastin fragmentation and noninflammatory loss of smooth muscle cells in the ascending aorta of patients with bicuspid valves with a diminution in collagen content strikingly similar to that observed in Marfan syndrome (Fig. 9).[18] In contrast to aneurysms associated with Marfan syndrome, however, the genetic predilection to dilation seems mainly to affect the ascending aorta above the sinotubular junction, with relative sparing of the sinuses and arch in many cases. The Stanford group demonstrated recently that the proximal and distal extent of the aortopathy in bicuspid disease represents a spectrum of variable phenotypic expression.[19]

Hypertension and Aortic Wall Stress

In patients with degenerative or atherosclerotic aneurysms, hypertension is the most important factor for instigating a dissection. Elefteriades' group at Yale identified either physical exertion or emotional stress as the direct predecessor of acute pain in two thirds of acute dissections,[20] presumably due to acute blood pressure changes during the event. Ascending aortic tissue was harvested from 35 patients with aneurysms for biomechanical testing.[21] Force transducers were employed for biaxial testing and it was found that, with regard to their respective impact on the determination of aortic wall stress, a 26-mm Hg increase in systolic blood pressure was equivalent to a 1-cm increase in aortic diameter. For example, wall stress in a patient with a 4-cm aorta and a systolic blood pressure of 172 mm Hg is equivalent to a patient with a 6-cm aorta and a systolic blood pressure of 120 mmHg. In addition, the burst strength of intact ascending aortic rings, which identifies the point of stress failure (ie, rupture or dissection), was intimately related to age. Older patients had a greater opening angle, representing stiffer tissue with diminished wall strength (Fig. 10). Thus,

Fig. 8. Three-dimensional CT scan demonstrating a DeBakey type II dissection (the *arrow* identifies the dissection flap).

our biomechanical studies demonstrated that the risk of aortic rupture and dissection is directly related to patient age, aortic size, and blood pressure. Studies examining the cellular and molecular perturbations of ascending aortic disease have also demonstrated an important role for matrix metalloproteinases (specifically MMP-2 and

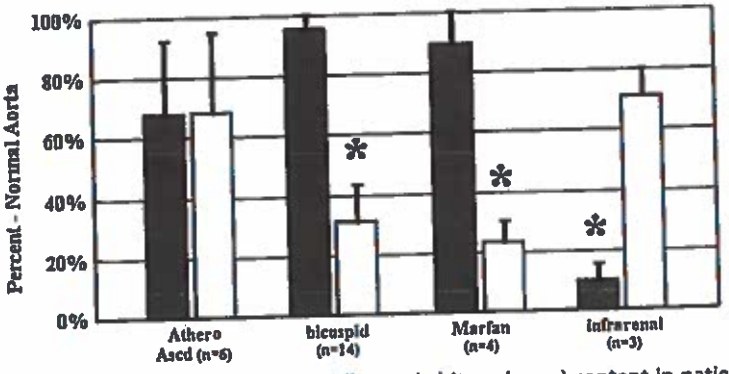

Fig. 9. Aortic elastin (black columns) and collagen (white columns) content in patients with aneurysmal disease of the ascending (atherosclerotic, bicuspid, or Marfan etiology) versus infrarenal aorta. *$P < .01$ versus normal thoracic (n = 8) or abdominal (n = 3) aorta. (*Data from* Curci JA, Thompson RW, Davis CG, et al. Heterogeneity of matrix changes in aneurysms of the thoracic and abdominal aorta. Circulation 2000;102(Suppl II):II-400.)

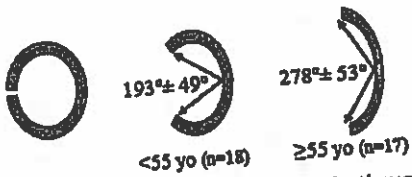

Fig. 10. Opening angle of intact rings of ascending aortic tissue. After severing rings of ascending aortic tissue, the rings either spring open (large opening angle), demonstrating increased stiffness and wall stress as in the older patients, or they remain intact (small opening angle), demonstrating decreased stiffness and wall stress as in the younger patients. (*Data from* Okamoto RJ, Xu H, Kouchoukos NT, et al. The influence of mechanical properties on wall stress and distensibility of the dilated ascending aorta. J Thorac Cardiovasc Surg 2003;126:842–50.)

MMP-9) and their tissue inhibitors (TIMP-1 and TIMP-2) in the pathophysiology of aneurysms and their progression to dissection.[22–27]

Can Aortic Dissections be Prevented?

Prophylactic oral β-blocker use in patients with Marfan syndrome has been reported to decrease hemodynamic stress and slow aortic growth due to their negative chronotropic and inotropic responses.[28] Prophylactic therapy seems most effective when aortic diameter is less than 40 mm, but although β-blockers may slow aortic growth, they do not prevent growth. Improved results have been suggested with the angiotensin converting enzyme enalapril, and more recently with the angiotension II receptor antagonist losartan in a mouse model of connective tissue disease.[29,30] The use of prophylactic agents in other high-risk groups, specifically patients with bicuspid valves, remains speculative, but as outlined in the discussion of how to manage patients with chronic dissections, it may be appropriate to initiate low-dose β-blocker therapy in patients with bicuspid valves and small aortic aneurysms, as long as there are no contraindications, especially if the patient is borderline hypertension.[31] As outlined in the 36th Bethesda Conference consensus report, exercise limitation is also warranted for patients with known ascending aortic aneurysms between 4.0 cm and 4.5 cm (only noncontact moderate-intensity sports) and for those greater than 4.5 cm (only low-intensity sports, such as bowling or golf).[32,33]

CLINICAL PRESENTATION AND DIAGNOSIS OF ACUTE DISSECTION

Patients with aortic dissection can present with a myriad of symptoms, and although "typical" symptoms are often present, it is not uncommon for patients to arrive in the emergency room following substantial improvement in their presenting complaints. Type A dissection typically presents with sharp, tearing anterior chest pain, often radiating to the neck or through to the back and abdomen, if the descending thoracic or abdominal aorta are involved. Although diaphoresis is common, shortness of breath and other respiratory complaints are less common than with acute coronary syndromes, unless contained rupture with tamponade is present.

Type B dissection typically presents with sharp, tearing pain between the shoulder blades that shoots down to the abdomen. Pain generally abates once blood pressure control is achieved unless there is end-organ compromise. With either type A or B dissection, compromise of the spinal artery or, much more often, one of the iliac arteries, can produce leg pain, parasthesias, or even paralysis. In such circumstances, unlike when treating paralysis or parasthesias that present

following thoracoabdominal aneurysm repair,[34] the goal is to lower, rather than raise, systemic blood pressure to diminish pressure within the false lumen, which, with expansion, is generally responsible for obstructing true lumen flow.

It is important to specifically question the patient, rather than to blindly accept the history on the chart or the account of the patient's relatives or friends. Patients can often pinpoint the exact time at which the dissection occurred, which may have been several days before their presentation to the emergency room, yielding more of a subacute than acute presentation. It is not uncommon for a patient with a chronic type B dissection and aneurysmal dilation in the thoracoabdominal region to present to the emergency room with intrascapular, low back, or flank pain that has been present for 3 months following an initial inciting event for which they did not seek medical attention. Although aortic dissection has often been referred to as the "great imitator" in that the presentation can mimic many disease processes depending on the specific aortic tributaries it impacts along its course, with a careful history, its presentation can often be differentiated from a typical myocardial infarction or other catastrophic intrathoracic event. The power to differentiate, for example, an acute type A dissection from an acute coronary syndrome in a patient with a chronic dissection on a computed tomography (CT) scan (a clinical scenario that presents itself at least a couple of times every year in a busy aortic center), depends heavily on the history taken by an experienced aortic surgeon, more so than the physical examination. Nowadays, most trauma centers have rapid CT imaging capabilities, so in a patient with acute, tearing chest pain, following an electrocardiogram that does not show classic signs of acute myocardial infarction, a CT scan of the chest should be performed. Although patients with aortic dissection can present with coronary involvement producing myocardial ischemia and classic ST changes, such a presentation is uncommon.

Patients presenting with an acute coronary syndrome far outnumber those presenting with a type A dissection and myocardial ischemia. Most often, electrocardiographic changes are absent or nonspecific (diffuse ST depression due to pericardial irritation) in patients with an acute dissection.[35] Patients who present with an acute dissection that has sheared off or is obstructing one of the coronary orifices are most often in extremis, and although efforts to save the patient should not be abandoned, prognosis is poor.[36] A patient in extremis with tombstone ST changes is many orders of magnitude more common with myocardial infarction than dissection, and for a patient with a clinical picture and electrocardiogram changes most consistent with an acute coronary syndrome, transfer to the catheterization laboratory should not be delayed to perform a CT scan unless there are other circumstances that question the diagnosis.

Physical Examination

The most important aspects of the patient's evaluation for diagnostic purposes are the history and CT scan. The physical examination becomes important when determining the need (and ultimate approach) for surgical intervention. Important details of the physical examination include:

- *Systemic blood pressure.* Most patients with acute dissection present with severe hypertension, often greater than 200 mmHg systolic. A systemic blood pressure lower than normal (less than 100 mmHg systolic) in a patient with cold and clammy skin should prompt suspicion of a contained rupture with tamponade.

- *Differential blood pressures or pulses in the arms.* Involvement of the innominate artery or subclavian artery is important to identify to avoid maladaptive blood pressure manipulation due to inaccurate monitoring, dissuade use of the axillary artery as a cannulation source, and monitor appropriate flow following surgical reconstruction.
- *Central neurologic changes* (somnolence, coma, hemispheric neglect, or weakness) imply cerebral malperfusion, but not necessarily irreversible stroke. Carotid bruits or an absent carotid pulse, although rare, suggest dissection into the head vessels.
- *Jugular venous distention* suggests contained rupture with tamponade.
- *Cardiac murmurs.* Systolic murmurs are present in patients with underlying aortic stenosis (ie, with a bicuspid valve), and if associated with a transvalvular gradient should prompt valve replacement at the time of ascending aortic repair. Diastolic murmurs are loud along the left sternal border when acute aortic regurgitation is severe, which may alter the intraoperative perfusion and venting strategies. However, in contrast to the prevalent beliefs of the late 1980s, if the aortic valve leaks, it does not necessarily need to be replaced. It is now known that a competent valve is most often the result of a careful reconstruction of the sinotubular junction during ascending aortic repair, without the need to intervene on the valve.
- *Abnormal abdominal findings* (tenderness, distention, absent bowel sounds, flank pain) suggest visceral or renal malperfusion with impending ischemia.
- *Differential femoral pulses or loss of sensation or motor strength in the legs.* Differential femoral pulses in a patient without peripheral vascular disease (ask about chronic leg claudication) suggest iliac obstruction by the false lumen, which may alter the perfusion strategy during cardiopulmonary bypass. Neurologic changes can suggest spinal artery involvement but most often are secondary to iliac malperufsion and often reverse following adequate blood pressure control.

TEE Versus CT Scans

Some units have purported the benefits of TEE over CT scans for its specificity and sensitivity in diagnosing aortic dissection,[13] but at Washington University, although it takes more than 1 or 2 hours to set up for a TEE in the middle of the night, a CT scan can be performed and read by an attending radiologist (who may even be lying in his bed at home) in 20 minutes or less. If a dissection is suspected in the catheterization laboratory following a nondiagnostic coronary examination, a TEE is better than a makeshift low-contrast aortogram, but TEE is generally reserved as a secondary diagnostic tool in equivocal cases following CT imaging. In centers with more ready access to TEE, TEE may be used as a primary diagnostic tool, but it does have limitations depending on the experience of the examiner and his or her ability to visualize the entire ascending aorta and arch.

Transthoracic Echocardiography

Transthoracic echocardiography is most helpful in the acute setting to identify pericardial fluid or tamponade, quantify the degree of aortic regurgitation, and evaluate right and left ventricular function preoperatively. However, a well-performed examination can identify abnormalities in the aortic root and proximal ascending aorta, whereas the arch is difficult, if not impossible to visualize.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) should be reserved for the subacute or chronic evaluation of equivocal cases (ie, to identify the exact location of the initiation point of a dissection in the arch) or to image complex true versus false lumen anatomy in the arch or other branch vessels. In the last few years, MRI has become less important because three-dimensional CT scanning reconstruction techniques can generate beautiful images in patients who do not have a dye allergy or prohibitively elevated creatinine level. Branch vessel three-dimensional reconstructions are ideal when considering a percutaneous interventional approach to treat a peripheral complication (ie, superior mesenteric artery (SMA) stenting for intestinal ischemia or claudication). For acute diagnosis, MRI is not ideal due to prolonged imaging times, inaccessibility of the MRI scanner in most institutions, and its suboptimal environment for monitoring acutely ill patients.

Other (Less Helpful) Tests

Chest radiographs are essentially useless in the diagnosis of aortic dissection, because findings are either absent or so subtle that they cannot be identified on a portable emergency room examination. Furthermore, although mild cardiac enzyme elevation can occur, blood tests are generally unhelpful in the diagnosis. A couple of decades ago, aortography was considered the gold standard for diagnosis of dissection, but today, the only relevant application for aortography is during percutaneous intervention on an aortic tributary (branch vessel stenting) or the thoracic or abdominal aorta (distal fenestration or stent-grafting at the primary tear to improve distal flow).[4,37–41]

GENERAL MANAGEMENT OF ACUTE DISSECTION

With acute type A dissection, operative intervention is performed to prevent the expected sequelae of rupture with cardiac tamponade, acute aortic regurgitation as a consequence of loss of commissural suspension, or myocardial infarction secondary to coronary artery involvement. Operative mortality rates range from 10% to 25% compared with the 90% mortality rate at 3 months for nonoperative management (50% within the first 48 hours).[3,5,42–48] In contrast, acute type B dissections can most often be treated successfully with medical therapy alone as long as complications do not arise. The International Registry of Acute Aortic Dissections (IRAD) has been collecting data prospectively since 1996, and although mortality rates may be underestimated because several patients may have died before they could consent to participate in the study, it provides the best prospective, although unrandomized, contemporary comparison of medical and surgical therapy.[45] The IRAD investigators analyzed hospital mortality in 464 patients with type A (62%) and type B (38%) dissections from 12 centers. For type A dissections, mortality with medical therapy was more than double with surgical therapy (58% versus 26%). However, for type B dissections, mortality with medical therapy was only 11%, compared with 31% with surgical therapy. However, surgery in type B dissections was only performed if complications were present.[49]

With acute type A dissection, surgical intervention should be offered for all patients deemed survivable, including patients with signs of severe cerebrovascular accident (often mental status is impaired due to cerebral malperfusion that can completely reverse following aortic reconstruction),[50] patients in hemodynamic shock (most likely secondary to contained rupture with pericardial tamponade), and patients of all ages. For type B dissections, surgery is reserved for rupture, "impending rupture", malperfusion, persistent pain, and uncontrolled hypertension. Impending rupture is a difficult

diagnosis, but the presence of frank blood (not serous or serosanginous fluid) in the pleural space has been used as a criterion to intervene. A reactive, serous, left pleural effusion will develop within 2 to 3 days in almost all patients with dissection in the descending aorta, which should not be interpreted as impending rupture and most often resolves in a few weeks. In addition, persistent pain is most often due to fluctuations in blood pressure, and most patients who return to the hospital with recurrent pain but a CT scan that is unchanged can be managed medically with resolution of symptoms. Occasionally, a patient will return with early dilation of the proximal descending thoracic aorta to 5 cm or greater. These patients may be considered for early surgical intervention, although it is ideal to wait 8 to 12 weeks if possible to allow the aortic wall to thicken and the flap to stabilize to improve surgical risk from a technical standpoint.

SPECIFIC THERAPEUTIC APPROACH FOR TYPE A DISSECTION

The initial goal of therapy in acute aortic dissection is to get the patient out of the operating room and out of the hospital. Issues that need to be addressed during surgical repair of a type A dissection include perfusion strategy, cross-clamping versus circulatory arrest, extent of proximal resection, and extent of distal resection. The specific technical aspects of surgical repair are beyond the scope of this report, but have been described in previous reports from our unit and from others.[8,51–54] The goals of surgical therapy in acute type A dissection are as follows:

- *Obviate the usual causes of death*, which are local phenomena in nearly 90% of cases. The proximal and distal aortic cuffs are reconstructed with a strip of Teflon felt interior and exterior, and occasionally between the intimal and adventitial layers, before insertion of an interposition graft. Reconstruction at both ends eliminates the false lumen proximally and directs flow into the true lumen distally. Reconstruction diminishes direct flow into the false lumen, decreasing the risk of intrapericardial rupture through the previously partial thickness false lumen wall.
- *Reverse hemodynamic shock.* Patients with hemodynamic compromise generally have a contained rupture with pericardial tamponade. Not uncommonly, such patients will sustain a hemodynamic collapse following induction of anesthesia. At that point, the initial surgical move should be to perform immediate sternotomy and open the pericardium to relieve tamponade. This is more important than getting the patient on pump by way of the groin, which may take longer than opening the sternum and does not address the immediate cause of the collapse. Once tamponade has been relieved, shock will reverse and femoral access can be obtained.
- *Extent of proximal resection.* Historically, it was felt that if the aortic valve leaked, it had to be replaced, but this is rarely the case. Patients with Marfan syndrome require total root replacement, and patients with bicuspid aortopathy require aortic valve replacement; however, most patients with aortic dissections have normal trileaflet aortic valves that leak when they are pulled apart consequent to dilation at the sinotubular junction. Following proximal reconstruction, the aortic valve is usually competent, without the need to address the valve itself. At Washington University, although aortic valve replacement was common in the late 1980s (greater than 50% of cases), it is currently rare (less than 10% of cases).[5]
- *Extent of distal resection.* After resecting the region of the aorta containing the primary tear, distal reconstruction can either be performed in the ascending aorta, or to the lesser curve of the arch, a so-called "hemiarch" procedure

with a beveled, open distal aortic anastomosis under profound hypothermic circulatory arrest (Fig. 11). The authors do not perform total arch replacement for acute dissection. Total arch replacement increases surgical risk substantially more than any potential benefit in regard to late reoperation. Studies from our center have found that the extent of distal resection does not have an impact on late survival or late reoperation on the distal aorta, although the need for proximal reoperation on the ascending aorta may be lower following hemiarch repair.[3,31] Each surgeon should select an approach with which he or she is most comfortable.

- *Correct compromise of contiguous aortic branches.* As presentation, branch vessel involvement is common; however, redirection of flow in the ascending aorta exclusively into the true lumen at the distal anastomosis is usually adequate to reverse malperfusion without intervention on the branch vessels themselves. The most common site of malperfusion that needs to be addressed following ascending reconstruction is one or both legs. If only one leg is malperfused, a femoral-femoral bypass is sufficient, but if both legs are malperfused, an axillary-femoral bypass may be required. Malperfusion to the renals or viscerals generally requires an interventional radiology approach for branch vessel stenting. Rarely, when there is obstruction to flow at the aortic level, an aortic stent-graft may help restore distal flow, but these types of advanced, experimental procedures should be reserved for centers with extensive endovascular experience.
- *Resect the primary tear.* The authors generally resect the primary tear if practical, but do not perform complete arch replacement during acute dissection unless there is rupture of the arch itself, which is rare. Total arch replacement in this setting is technically hazardous, increases bleeding (which is often troublesome), and doubles circulatory arrest times and mortality rates in most series.[51,55–57] If the primary tear resides in the descending aorta, it is left alone at the time of acute repair. Recent series from centers with extensive endovascular experience have reported initial success in reconstructing the descending aorta with open stent-graft placement at the time of hemiarch repair,[58] but as noted above, these advanced procedures should be reserved for selected centers with defined protocols.

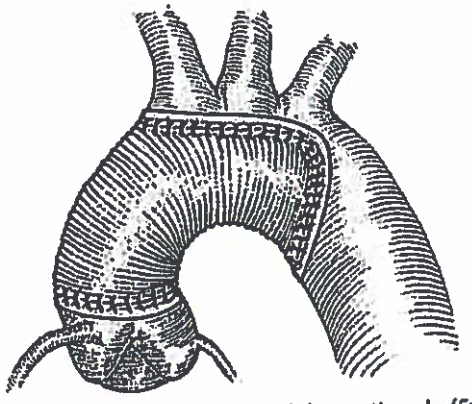

Fig. 11. Hemiarch replacement to the lesser curve of the aortic arch. (*From* Moon MR, Sundt TM: Aortic arch aneurysms. Coron Artery Dis 2002;13:85–92; with permission.)

- *Eliminate flow in the false lumen.* This is seldom accomplished. Studies have shown that the distal false lumen remains patent in most cases (up to 85%) after proximal thoracic aortic repair,[59] and in some cases (especially in chronic dissections), the false channel may be the only source of blood to major organs. At Washington University, the authors found that persistence of the false lumen was associated with a greater chance of aortic growth long-term, but not specifically with the need for late reoperation.[31] In the Mount Sinai series, extending the initial resection into the arch did not necessarily obliterate the false lumen;[48] 23% of patients who underwent partial or total arch replacement for an arch tear had a patent false lumen. Persistence of the false lumen depends more on the presence of distal fenestrations between the true and false lumens rather than complete resection of the primary tear.

Perfusion Strategy

Initial cannulation is generally by way of the femoral artery that has the strongest pulse.[60] After exposing the vessel, an 8-mm Dacron graft is sewn end-to-side to the common femoral artery. The authors prefer the side-graft to direct cannulation because it permits flow down the leg during the period of cardiopulmonary bypass, is immune to the problems associated with atherosclerotic disease of the iliacs or femorals, and at the end of the procedure can be stapled off without having to reconstruct the artery. Venous cannulation is performed following standard sternotomy. If circulatory arrest is planned, then the superior and inferior vena cavae are cannulated separately to allow for retrograde cerebral perfusion if desired. Retrograde cerebral perfusion allows additional cerebral cooling and back flushing of particulate matter during circulatory arrest. Details of retrograde cerebral perfusion can be found in several previous reports.[51,61–63] The axillary artery can also be used for cannulation (with a Dacron side-graft), but is not the initial choice in acute cases, simply because if it turns out to be dissected, manipulation can be troublesome. When cardiopulmonary bypass is initiated, TEE is used to document flow in the true lumen in the ascending aorta, and temperatures are measured above and below the diaphragm to ensure an even distribution of blood flow and cooling. If flow is not adequate, central aortic cannulation can be performed.[64]

Cross-clamping Versus Open Distal with Circulatory Arrest

The distal extent of the dissection repair can be performed either with a cross-clamp on the distal ascending aorta (anastomosis to the mid ascending aorta) or under profound hypothermic circulatory arrest (anastomosis to the mid ascending aorta or lesser curve of the arch). A complete description of the technical aspects of hypothermic circulatory arrest is beyond the scope of this article, but can be found in several excellent previous publications.[8,51–54,65] The potential benefits of using circulatory arrest are that it permits an open distal anastomosis (which may allow a more sound distal anastomosis), facilitates direct inspection of the arch to assess the extent of intimal disruption (if the tear extends into the arch), and avoids clamp injuries to the distal ascending aorta. However, recent studies have failed to demonstrate a difference in operative morbidity or mortality, long-term survival, or the incidence of late aortic growth and reoperation rate between circulatory arrest and cross-clamping,[31,42,66] and bleeding can often be troublesome following circulatory arrest due to extreme perturbations in the coagulation cascade. Our current thinking is that either approach is acceptable, as long as the entire tear is visible within the ascending aorta, and the final choice depends on the experience and preference of the aortic surgeon

performing the repair. With either approach, following reconstruction of the distal aorta, the authors generally anastomose a 28-mm Dacron graft with a 10-mm prefabricated side-graft end-to-end. This procedure allows us to reposition the arterial cannula into the side-graft and reconstitute antegrade flow during rewarming, which has been associated with earlier neurologic recovery from circulatory arrest.[46,62] For high-risk patients in whom only a small segment of the aorta had to be removed to resect the primary tear, a primary anastomosis between the two reconstructed ends of the aorta may be possible after freeing up the distal aortic attachments. Such an approach is associated with less bleeding and shorter operative times than standard ascending aortic replacement, but it leaves a significant amount of ascending aorta in situ that may dilate over time.

Operative Results

At Washington University, during a 22-year period ending in 2006, 201 patients underwent acute type A dissection repair by 25 different surgeons. Mean age was 61 years (range 18–88 years) and 64% were men.[5] Operative mortality was 16%, and independent factors predicting death included concomitant aortic valve replacement, preoperative malperfusion, and non-Marfan syndrome patients. Cerebrovascular accident occurred in 5%, but the incidence was not related to the specific surgical technique (circulatory arrest vs cross-clamp, ascending replacement only vs hemiarch, use of retrograde cerebral perfusion). Long-term survival was 75% at 1 year, 63% at 5 years, and 49% at 10 years. Factors associated with diminished long-term survival included advanced age and the presence of coronary artery disease.

Subacute Type A Dissection

With rare exceptions,[67,68] patients who present to the emergency room soon after they develop symptoms should undergo emergent surgical intervention. However, it is not uncommon for the diagnosis of type A dissection to be delayed as a consequence of its complex presentation, such that transfer to a tertiary center does not occur for 48 hours or more following the initial tear. Patients who have survived several days after the onset of symptoms have been fortunate to have passed through the initial, most deadly period of the disease. The timing of surgical intervention under these subacute conditions was recently addressed in two studies from Yale, examining 93 patients over a 20-year period with a delayed presentation or diagnosis.[69,70] In essence, their question was: "If a patient is transferred or presents in the middle of the night with a dissection that occurred more than 48 hours earlier, is it essential to perform emergency surgery at that time, or is it safe to schedule the operation for the following morning?" Their short answer was: "No, it is not necessary to perform nighttime surgery for subacute dissections." Morbidity and mortality rates were similar to those who underwent immediate surgical intervention, leading the Tale group to conclude that patients who present several days after an acute type A dissection can safely be treated with an initial period of medical management, followed by a semi-elective, rather than emergent operation. However, such delays are not recommended within the first 48 hours, as patients can become unstable rapidly during this period. Many centers are simply not experienced enough to perform acute dissection repair, and in such circumstances, the patient's best chance for survival is transfer to a tertiary care hospital. The risks of delayed intervention to allow tertiary transfer are likely far less than immediate surgical intervention by an inexperienced aortic surgeon or surgical team.

Radiologic Versus Surgical Definition of Type A Dissection

The differentiation of aortic dissections into type A and type B represents a surgical definition not a radiologic definition, which is essential to determine the most appropriate initial therapeutic approach for each patient. Occasionally, an attending radiologist, with all good intentions, will dictate that a "type A dissection is present" when the tear resides in the arch, proximal to the left subclavian artery (for example, in the lesser curve across from the left carotid orifice). From a practical therapeutic perspective, if the primary tear extends distally from the arch, these patients should be treated as though they had a type B rather than type A dissection, considering that, with good medical therapy, the dissection will not extend retrograde to involve the ascending aorta. The intent when repairing or replacing the ascending aorta in an acute type A dissection is to eliminate the most common cause of death, that is, intrapericardial rupture with tamponade. Rupture is much more common with type A than type B dissection, potentially due to elevated developed pressure (dP/dt) and flow in the ascending versus descending aorta. With this in mind, emergency surgery by way of sternotomy when the tear resides in the arch is unnecessary. Thus, it is essential for aortic surgeons in busy tertiary centers to have extensive experience reading aortic CT scans (including normal, aneurysmal, and acute and chronic dissections) to allow the surgeon to most appropriately triage the patient from a therapeutic perspective.

SPECIFIC THERAPEUTIC APPROACH FOR TYPE B DISSECTION

Uncomplicated type B dissections are treated medically in most centers, and excellent results can be expected when therapy is continued long-term. Acute operations are performed only when complications are present such as rupture or malperfusion.[71–74] In the classic Stanford-Duke series of patients with acute type B dissection, the 30-day mortality for patients with no compelling indication for emergency operation was 10% with medical therapy versus 19% with surgical therapy.[74] In some centers, there has been a push toward early operation (proximal descending aortic replacement or stent-graft placement over the primary tear) in younger patients in an attempt to prevent the adverse late sequelae of persistent dissection.[56,75–78] Although this type of aggressive surgical approach seems intuitively logical, excellent short-term and long-term results can be expected with aggressive medical therapy, with most patients needing neither an early nor late surgical intervention.[79,80] All new prophylactic-based therapies must be compared with appropriate medical therapy before their widespread use can be advocated.

Estrera and associates in Houston followed 159 patients with a type B dissection who underwent an initial medical management strategy with surgery reserved only for complications.[79] Medical therapy alone was successful in 86% of patients with a mortality rate of 7%. When a surgical or endovascular intervention was necessary (14% of patients), the mortality rate increased to 17%. Overall, 1-year survival was 83% and 5-year survival was 75%. Hsu and colleagues[80] from Taiwan similarly reported excellent results with medical management of type B dissections. Medical therapy alone was successful in 85% of patients, with a 5-year survival rate of 99%. Endovascular options have become popular for complicated dissections, but their use in uncomplicated dissections remains unsupported.

Medical Management

The goals of medical therapy are to first decrease aortic and left ventricular peak dP/dt, then reduce mean, peak, and diastolic recoil aortic pressure. Intravenous β-blockers (typically esmolol) should be initiated to decrease dP/dt, followed by an

afterload reducing agent (typically nitroprusside) if additional blood pressure control is needed. Often, decreasing blood pressure from the severely hypertensive levels that are generally present during the initial evaluation of a patient with an acute dissection can reverse malperfusion and stabilize the flap. Pain may wax and wane, possibly due to movement of the flap with blood pressure fluctuations, but severe pain should dissipate. During the initial hospitalization, a complex oral antihypertensive regimen may be necessary to achieve the desired level of blood pressure control, but following hospital discharge, it is often necessary to decrease drug dosages significantly. Blood pressure should be closely monitored (not only by the physician but also the patient) to ensure the most appropriate level of control long-term. Ideally, the patient should become familiar with their disease so that they can play an active role in monitoring changes in therapy.

Endovascular Therapy for Complicated Type B Dissections

Patients who develop ischemic complications due to distal aortic branch compromise should undergo angiographic investigation, potentially with CT or MRI angiography initially to create a three-dimensional roadmap of the aorta and its branches. Bare stenting of branch vessels or covered stent-grafting of the aorta itself can follow to increase distal flow, with or without fenestration of the dissection flap.[37,39–41] The dissection anatomy in these patients is often complex, and these procedures can be challenging. In 2003, the authors published early results for endovascular interventions in type B dissections with malperfusion,[37] and although our initial report was anecdotal in nature, 21 of 23 vascular territories were successfully reperfused with no hospital mortality and no late recurrent ischemia. Dake and associates from Stanford were the first to report their attempts to cover the primary tear with a covered stent-graft in 1999.[38] Using an archaic delivery system, they were able to completely thrombose the false lumen in 79% with a mortality rate of 16%. More recent studies have reported similar results, and studies to compare the endovascular approach to open surgery in complicated type B dissections are being developed.[71–73,76,77]

The goals of endovascular therapy are to reverse malperfusion with either a peripheral or central approach, re-expand the true lumen, exclude or close the primary tear, and obliterate the false lumen. Early experimental work from the Stanford laboratories demonstrated that intravascular stents could restore distal flow in acute type B dissection, but that obliteration of the false lumen required stents to be placed throughout the length of the dissection.[81] Stenting limited to the proximal dissection did not prevent the development of a chronic patent distal false lumen, probably due to branch vessel fenestrations distal to the stents. A study from Vienna evaluated the ability of a stent-graft implanted over the primary tear to thrombose the false lumen.[77] At the level of the stent-graft, they noted a 60% false lumen thrombosis rate immediately postoperatively that increased to 90% at 1 year. In contrast, just distal to the stent-graft, the thrombosis rates fell to 20% and 60% postoperatively and at 1 year, whereas at the celiac artery the rates were 0% and 22% postoperatively and at 1 year.

A meta-analysis of 37 studies was recently published examining the results of endovascular stent-grafting for acute type B dissections in 184 patients.[76] Using the IRAD database, 30-day survival with endovascular therapy compared favorably with medical therapy, both of which were significantly better than open surgical therapy. Also in 2006, the IRAD investigators reviewed 242 patients with acute dissection undergoing either medical (78%), open surgical (11%), or endovascular (11%) therapy with an overall hospital mortality rate of 12%.[82] Survival at 3 years was similar in all

groups: 78% ± 7% for medical therapy, 83% ± 19% for open surgical therapy, and 76% ± 25% for endovascular therapy.

The most common indication currently for surgical intervention on the aorta (rather than its branches) in type B dissections is patients who demonstrate early growth (greater than 5 cm diameter) or recurrent refractory pain in the early months following successful initial medical therapy. Subacute dilation is usually isolated to the proximal descending aorta, for which elective proximal descending replacement or placement of a stent-graft over the primary tear should be considered if there are adequate proximal and distal landing zones. The goal is not to remove all dissected aorta, but rather to address the area of maximal dilation. Generally, following replacement of the proximal third of the aorta, the residual dissection will grow in less than 20% of cases with adequate medical therapy.[31,83]

INTRAMURAL HEMATOMA AND PENETRATING ULCER

Intramural hematoma is a variant of aortic dissection in which there is blood present in the aortic wall, but no tear can be identified.[84–88] **Fig. 12** demonstrates an intramural hematoma in the ascending aorta on TEE. Proposed causes include spontaneous bleeding in the wall, but may also simply represent a small entry hole that cannot be identified.[87] Intramural hematomas in the ascending aorta can progress to overt dissection or spontaneous rupture, but the rupture risk is less than with classic dissection. Acceptable results have been reported from a large series employing medical management as first line therapy for patients with type A intramural hematoma;[88] however, this approach requires aggressive monitoring until stabilization (generally for several days), with a watchful eye for progression to overt dissection. In general, it is probably best to perform urgent (not necessarily emergent) surgery in otherwise healthy patients to avoid progression to dissection, which occurs in about one third of patients despite aggressive medical therapy. Penetrating atherosclerotic ulcers in the ascending aorta with surrounding wall hematoma also have a significant risk of rupture and should be considered for urgent surgery if comorbidities do not portend a poor surgical outcome.[84,89,90] Intramural hematomas in the descending aorta should be managed similarly to type B dissection and have been known to resolve over 3 to 6 months with appropriate medical therapy.[91]

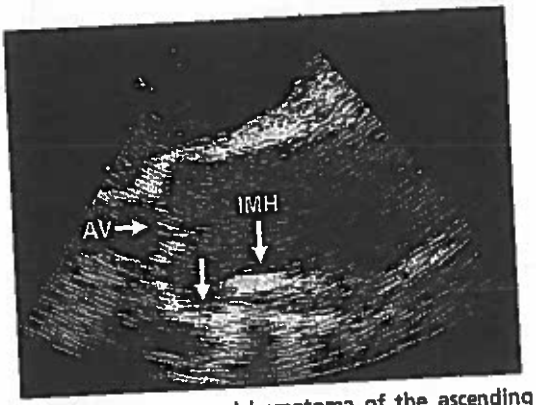

Fig. 12. TEE demonstrating an intramural hematoma of the ascending aorta. The arrow labeled AV is the aortic valve, the arrow labeled IMH is the intima of the intramural hematoma, and the unlabeled arrow is the normal aortic wall proximal to the intramural hematoma.

MANAGEMENT OF CHRONIC DISSECTION

In an attempt to identify important factors that could predict aneurysmal development in a residual dissected aorta, the authors followed 168 operative survivors following acute type A repair.[31] Late reoperation was performed in 15% of patients an average of 5 years postoperatively. Freedom from reoperation among operative survivors was 95% at 1 year, 90% at 5 years, 74% at 10 years, and 65% at 15 years. Risk factors that predicted the need for late reoperation included Marfan syndrome, a nonresected primary tear, absence of postoperative β-blocker therapy, and elevated systolic blood pressure late postoperatively. During long-term follow-up, the incidence of aortic growth between consecutive imaging studies was 18%, with a mean growth rate of 1.3 mm in the abdominal and 1.8 mm in the descending aorta. In several patients, aortic growth was not identified for many years postoperatively (6 years on average and up to 167 months in 1 patient), reinforcing our belief that follow-up for life is essential following successful treatment of an aortic dissection. Independent predictors of aortic growth included (1) increased aortic diameter, (2) patent false lumen, and (3) elevated systolic BP at late follow-up. The incidence of aortic growth increased from 14% to 15% for patients with late systolic BP less than 140 mmHg to 34% when systolic BP was greater than 140 mmHg.

DeBakey and associates were the first to suggest a relationship between poor blood pressure control and dilation in patients with aortic disease, noting that aneurysms subsequently developed in 46% of patients with uncontrolled hypertension, but only in 17% with controlled blood pressure long-term.[83] In our series from Washington University, ideal blood pressure control not only decreased the reoperation rate from 35% to 8%, but the incidence of aortic expansion also fell threefold.[31] **Fig. 13** illustrates the impact of poor blood pressure control on late reoperation, which approaches 50% to 70% at 15 years in those with less than ideal systolic pressures. **Fig. 14** demonstrates the impact of β-blocker therapy to diminish the need for late reoperation from 75% to 25% at 15 years.

To determine the appropriate time interval between which postoperative imaging studies should be obtained, the authors performed a two-way analysis of the impact of aortic diameter and time between scans on the chance of identifying aortic

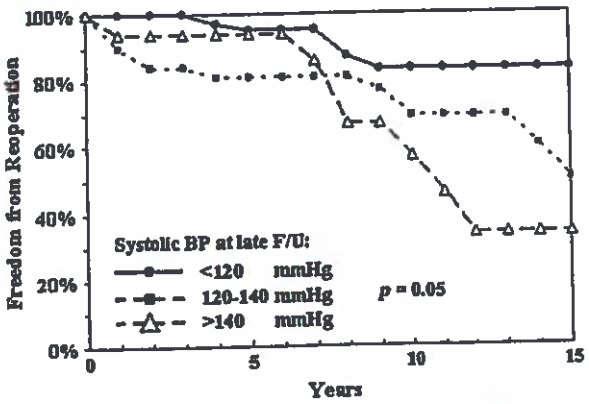

Fig. 13. Freedom from reoperation following repair of type A aortic dissection in relation to the degree of late postoperative systolic blood pressure control. (*From* Zierer A, Voeller RK, Hill KE, et al. Late aortic enlargement and reoperation after repair of acute type A aortic dissection. Ann Thorac Surg 2007;84:479–87; with permission.)

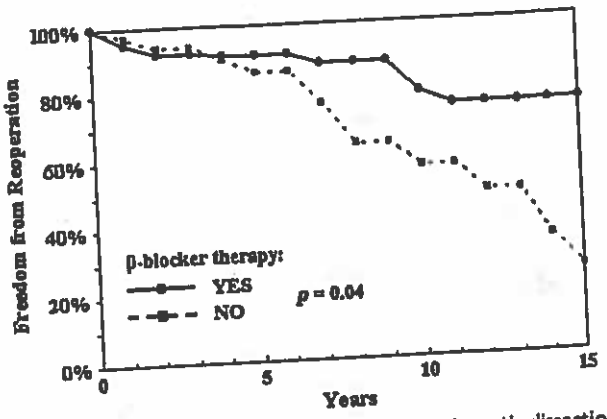

Fig. 14. Freedom from reoperation following repair of type A aortic dissection in relation to late postoperative β-blocker use. (*From* Zierer A, Voeller RK, Hill KE, et al. Late aortic enlargement and reoperation after repair of acute type A aortic dissection. Ann Thorac Surg 2007;84:479–87; with permission.)

growth.[31] **Table 1** demonstrates that when the aortic diameter is small (<35 mm), and the interval between scans is low, it is rare to identify growth. In contrast, when the aorta is large (>50 mm), growth is frequent at all intervals, reaching 83% for intervals greater than 1 year. At the Center for Diseases of the Thoracic Aorta at Washington University, the importance of long-term blood pressure control is reinforced to the patients, with a goal of maintaining systolic BP less than 120 to 140 mmHg, including β-blocker therapy, as long as there are no contraindications to their use. It is often difficult to maintain systolic BP below 120 mmHg, especially in elderly patients with diminished vascular compliance, but when possible, it is an appropriate goal for these patients because of the potential to otherwise need major reoperations as they age. Surveillance of patients with aortic dissection, whether treated medically or surgically, should include a CT scan or MRI before hospital discharge and later studies as follows:

- An initial outpatient scan at 3 to 4 months to identify those who experience rapid early growth (when the aortic wall is most vulnerable).
- If aortic size is stable, a 6-month interval follows.
- Further imaging intervals are based on aortic size; whereas small aneurysms can be followed at 12-month intervals (35–40 mm), large aneurysms (45–50 mm) should be followed at 6-month intervals.

Table 1
Impact of aortic size and the interval between consecutive imaging studies on the incidence of aortic growth (overall incidence 18%)

	Incidence (%)		
	<6 mo	6–12 mo	>12 mo
Small (<35 mm)	5	13	21
Moderate (35–49 mm)	12	27	31
Large (≥50 mm)	34	23	83

Data from Zierer A, Voeller RK, Hill KE, et al. Late aortic enlargement and reoperation after repair of acute type A aortic dissection. Ann Thorac Surg 2007;84:479–87.

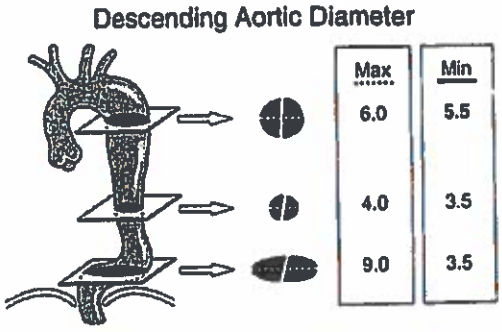

Fig. 15. Inexperienced radiologists often overestimate the size of the aorta due to measurements made on the oblique or as the aorta travels horizontal as demonstrated most obviously at the diaphragm in this schematic. (*From* Juvonen T, Ergin MA, Galla JD, et al. Prospective study of the natural history of thoracic aortic aneurysms. Ann Thorac Surg 1997;63:1533–45; with permission.)

- If aortic expansion is identified, the interval is decreased on subsequent scans until aortic size again becomes stable.
- If diameter measurements are in question, consider three-dimensional CT reconstructions or MRI. It is not uncommon for the aorta to become tortuous following dissection, causing inexperienced radiologists to document inflated aortic sizes (**Fig. 15**).[92]
- For patients with renal impairment, or for those who require frequent scans, noncontrast images are often satisfactory if the major question regards aortic size.

Our current indications for resection of a chronic residual dissection depend on the region of interest, but in general include: (1) aortic diameter greater than 6 to 6.5 cm (possibly 5.0 cm or 5.5 cm in younger patients with rapid growth); (2) enlargement of more than 7 to 10 mm in 1 year; (3) recurrent persistent pain attributable to the aneurysm that does not respond to medical management (it is important to remember that many patients present with pain during periods of acute hypertension that resolves with blood pressure control); and (4) localized saccular dilation, which might put the patient at a higher risk of rupture. Patients with Marfan syndrome are generally younger and are more prone to rapid dilation, so replacement should be considered when aortic diameter exceeds 5 to 5.5 cm or when expansion exceeds 3 to 5 mm per year in healthy individuals. These criteria need to be individualized by each aortic surgeon after evaluating his own institution-specific morbidity and mortality rates for these often complicated procedures.

SUMMARY

Acute aortic dissection is a fatal disease if not identified and treated appropriately. Even then, there are times when mortality cannot be prevented, despite our greatest efforts. For type A dissections, surgical therapy is essential to offer the patient a reasonable chance at long-term survival; however, it is important to remember that surgical treatment does not cure the generalized disease. For type B dissections, medical therapy is the mainstay of treatment and is associated with excellent survival when continued long-term. With either type A or type B dissections, close medical follow-up is essential after hospital discharge with a mandate for strict blood pressure

control, anti-impulse therapy with β-blockers (even if the patient is normotensive), and serial imaging surveillance for the life of the patient. The initial goal of therapy in acute aortic dissection is to get the patient out of the operating room and hospital, whereas the long-term goal is to decrease the risk of late aneurysmal dilation and reoperation.

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Inverventional Board Review

Cardiac Tamponade

Henry Meltser, MD, and Vijay G. Kalaria,* MD

Cardiac tamponade is a common cardiac emergency requiring prompt diagnosis and intervention. A thorough understanding of the spectrum of clinical and hemodynamic changes in patients with pericardial effusion is vital for interventional cardiologists. This review discusses pathophysiology of cardiac tamponade with emphasis on hemodynamic aberrations. Specific clinical situations that lead to atypical hemodynamic presentations of cardiac tamponade are emphasized with a review of various diagnostic and therapeutic procedures. *Catheter Cardiovasc Interv 2005;64: 245–255.* © 2005 Wiley-Liss, Inc.

Key words: cardiac tamponade; hemodynamic; pericardial effusion; pericardium

INTRODUCTION

Cardiac tamponade is a clinical syndrome characterized by hemodynamic abnormalities resulting from an increase in pericardial pressure due to accumulation of contents such as serous fluid, blood, pus, and rarely gas. Cardiac tamponade was first recognized in the 19th century as a cause of impaired cardiac function [1]. In 1935, Beck C.S. described a diagnostic triad for cardiac compression consisting of decreasing arterial pressure, increasing venous pressure, and a small quiet heart. Increasing intrapericardial pressure leads to restriction of cardiac filling, reduction of stroke volume and cardiac output. Clinical signs in a patient with cardiac tamponade include tachycardia, hypotension, pulsus paradoxus (> 12 mm Hg inspiratory fall in systolic blood pressure), raised jugular venous pressure, muffled heart sounds, decreased electrocardiographic voltage with pulsus alternans [2,3], and an enlarged cardiac silhouette on chest roentgenogram (Table I). The magnitude of clinical and hemodynamic abnormalities depends on the rate of accumulation and amount of pericardial contents, the distensibility of the pericardium, and the filling pressures and compliance of the cardiac chambers. Various etiologies for pericardial effusion and cardiac tamponade are listed in Table II.

EVOLUTION IN THE UNDERSTANDING OF CARDIAC TAMPONADE PATHOPHYSIOLOGY

The classic hemodynamic description of cardiac tamponade physiology was described by Reddy et al. [4]. They initially proposed that tamponade was an all-or-none phenomenon. In the classic model of cardiac tamponade, the pericardial space fills to a critical hemodynamic point, at which time hypotension and decline in cardiac output ensue. This schema divided tamponade physiology into three phases. In phase 1, pericardial pressure equilibrates with the right ventricular filling pressure, but the cardiac output does not change. During phase 2, the contents in the pericardial space continues to accumulate and the pericardial and right ventricular filling pressures rise simultaneously and equilibrate with left ventricular filling pressure, a point when there is depression of cardiac output but pulsus paradoxus is still absent. In phase 3, further accumulation of pericardial fluid results in a simultaneous elevation of the pericardial, right ventricular, and left ventricular filling pressures, with further decline in the cardiac output and appearance of pulsus paradoxus.

Over the last 20 years, the widespread use of echocardiography and new hemodynamic data have revised the all-or-none concept. Important echocardiographic observations were made in patients who underwent pericardio-

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TABLE I. Cardiac Tamponade Characteristics

Clinical signs of cardiac tamponade
Tachycardia
Hypotension
Elevated jugular venous pressure with a blunter Y-descent
Pulsus paradoxus
Distant heart sounds
Physical features/signs of the underlying etiology (e.g., connective tissue disorders)
Enlarged cardiac silhouette on chest X-ray
Hemodynamic changes in cardiac tamponade
Elevation of filling pressures in all four cardiac chambers
Diastolic equalization of pressures
Blunted Y-descent in RA pressure waveform
RV and LV peak systolic pressures out of phase
Peak aortic pressure varying more than 10–12 mm Hg
Decrease in cardiac output

TABLE II. Etiology of Pericardial Effusion and Cardiac Tamponade

Common
Idiopathic or viral pericarditis
Iatrogenic (invasive procedure-related, post-CABG)
Trauma
Neoplasm/malignancy
Uremia
Uncommon
Collagen vascular diseases (SLE, scleroderma)
Tuberculosis
Radiation induced
Postmyocardial infarction
Aortic dissection
Bacterial infection
Pneumopericardium

SLE, systemic lupus erythematosis.

centesis for small- or moderate-size pericardial effusions with no clinical findings of tamponade. After pericardial drainage, the pericardial pressure, ventricular filling pressures, and respiratory variations in systolic blood pressure were all reduced as compared with the prepericardial drainage values. Wayne et al. [5] noted that in patients with pericardial effusion but no clinical signs of tamponade, there was an exaggerated respiratory variation in the left ventricular systolic ejection time. Such findings indicate that even mild to moderate pericardial effusions affect cardiac hemodynamics in the absence of overt clinical findings of tamponade.

Reddy and Curtiss [6] subsequently revised their original tamponade physiology model. In the revision, the RV and LV filling pressures rise but do not equilibrate with pericardial pressure in phase 1. This finding contrasts with the previous concept that LV filling pressure does not rise until the RV filling pressures equilibrated with the pericardial pressure. During phase 1, cardiac output may decline and systolic blood pressure may fall with inspiration below baseline values, but diagnostic criteria for pulsus paradoxus are not met. Pericardiocentesis during this phase, decreases pericardial and right atrial pressure with minimal change in arterial systolic pressure and no change in cardiac output. The onset of phase 2 occurs when pericardial pressure equilibrates with RV but not LV filling pressure. Pericardiocentesis during phase 2 leads to a decrease in pericardial, right atrial, and LV filling pressures with a decrease in respiratory variations in systolic blood pressure and a moderate increase in cardiac output. In phase 3, both LV and RV filling pressures equilibrate with intrapericardial pressure. Pericardiocentesis during phase 3 decreases pericardial, right atrial, and LV filling pressures with normalization of the exaggerated inspiratory decrease in arterial systolic pressure and a prominent increase in cardiac output. In contrast to the original concept, the inspiratory fall in arterial systolic pressure (pulsus paradoxus) is exaggerated from the onset of pericardial effusion and progressively increases during each phase. In summary, rather than an all-or-none phenomenon, cardiac tamponade should be viewed as a syndrome with a continuum of hemodynamic abnormalities with a resultant spectrum of clinical presentations and hemodynamic findings.

PRESSURE WAVEFORMS IN CARDIAC TAMPONADE: RIGHT ATRIAL AND VENOUS PRESSURE

The normal pressure waveform in the right atrium displays three positive waves, A, C, and V, and two negative waves, X- and Y-descents. The A-wave is caused by atrial systole; the C-wave is caused by tricuspid valve displacement toward the right atrium during early ventricular systole. The A- and C-waves are followed by a negative deflection, the X-descent, associated with decline in intrapericardial pressure at the beginning of ventricular systole and movement of the tricuspid apparatus toward the ventricular apex. The V-wave reflects passive atrial filling in late ventricular systole and is followed by Y-descent, coinciding with the opening of the atrioventricular valves and early ventricular diastole.

The venous blood flow into the right atrium is near zero during atrial systole and rises to a maximum during ventricular systole (coinciding with the X-descent), then falls and rises to a second smaller peak in diastole (corresponding to the Y-descent in the RA waveform). During inspiration, the pressure in vena cavae falls (superior vena cava and intrathoracic portion of the inferior vena cava) as the flow increases [7,8].

The positive deflection in RA waveform coinciding with the R-wave in electrocardiogram (ECG) is labeled as the A-wave and the positive deflection coinciding with the T-wave on ECG is labeled as the V-wave. During simultaneous right and left heart pressure waveform

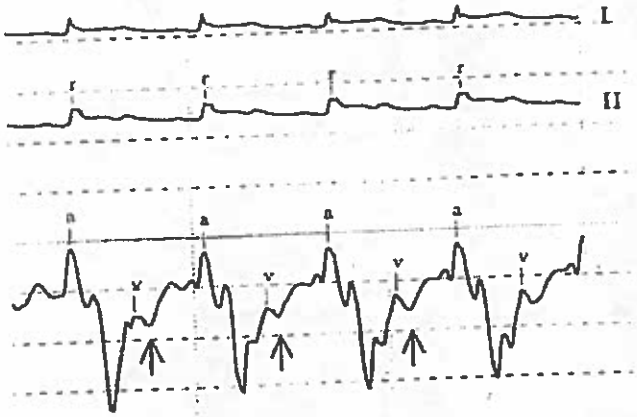

Fig. 1. Right atrial pressure wave form (50 mm Hg scale) in a patient with cardiac tamponade showing a blunted Y-descent (black arrow).

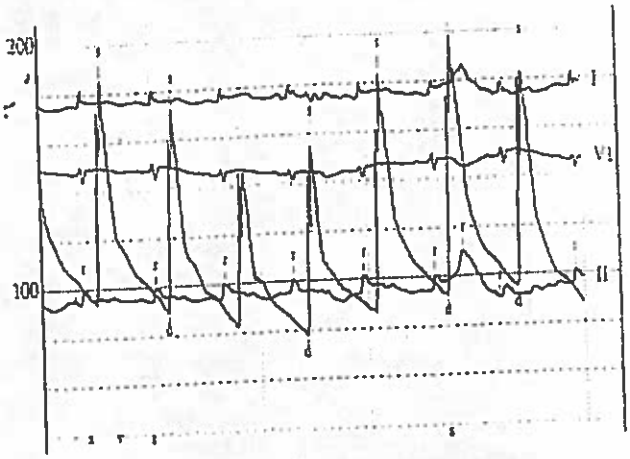

Fig. 2. Aortic pressure tracing (200 mm Hg scale) demonstrating a marked pulsus paradoxus of 40 mm Hg.

recording, V-wave in the pulmonary capillary wedge pressure (PCWP) waveform precedes or bisects the down slope of LV systolic pressure waveform.

In cardiac tamponade, the RA pressure waveform has an attenuated or an absent Y-descent (Fig. 1). Absent Y-descent is secondary to diastolic equalization of pressures in RA and RV and lack of effective flow across the tricuspid valve in early ventricular diastole. The caval (venous) flow also becomes monophasic and is confined to ventricular systole, corresponding to the X-descent. Similar to RA, the Y-descent in venous pressure waveform (during ventricular diastole) is also absent or transformed into a positive wave. The vena cava flow during ventricular systole is maintained by RA transmural pressure (RA pressure minus the intrapericardial pressure). Specifically, as the cardiac volume is reduced during ventricular systole and blood is ejected into the great arteries, the right intra-atrial pressure falls in excess of the intrapericardial pressure, producing a pressure gradient for forward venous blood flow. During ventricular diastole, the cardiac volume increases, limiting the early diastolic surge of venous return.

PULMONARY ARTERY PRESSURE AND FLOW

In normal subjects during inspiration, the transmural pulmonary artery pressure (intra-arterial PA pressure minus the intrapericardial pressure) and pulmonary artery flow increase. In subjects with tamponade, inspiratory increase in the blood flow velocity in the pulmonary artery systolic pressure is exaggerated.

INTRAPERICARDIAL PRESSURE

The unstretched pericardium usually contains less then 50 cc of pericardial fluid. When measured using a fluid-filled catheter system, pericardial pressure is zero or negative relative to atmospheric pressure, and virtually identical with intrathoracic pressure. Pericardial pressure correlates well with the intrathoracic pressure throughout the respiratory cycle. Changes in intrapericardial pressure are dependent on both the volume and acuity of accumulation of pericardial content. Pericardial pressure-volume curves are different with varying slopes based on the chronicity of pericardial fluid collection [9]. In acute cardiac tamponade, usually seen in trauma or in patients with iatrogenic perforation during invasive procedures, even minor increases in the pericardial cavity fluid volume lead to a marked increase in pericardial pressure and acute hemodynamic compromise. Chronic accumulation of pericardial fluid, such as in patients with uremia or connective tissue disorders, allows gradual stretching of the pericardial sac such that large pericardial collection can occur without significant elevation in intrapericardial pressure.

PULSUS PARADOXUS

The term "pulsus paradoxis" was coined to describe paradoxically absent radial pulse despite the presence of heart tones [10]. Pulsus paradoxus, an exaggeration of the normal respiratory physiology and its effects on the intracardiac pressure, is defined as a decline of more than 10–12 mm Hg in the systolic blood pressure during quiet inspiration compared with expiration [11]. Although the original description was based on palpation of the radial pulse, at present time pulsus paradoxus is usually assessed at bedside using sphygmomanometer-measured brachial artery pressure or direct intra-arterial pressure recording, the latter being the most sensitive and accurate of the three methods (Fig. 2). Another criterion of pulsus paradoxus is 10%

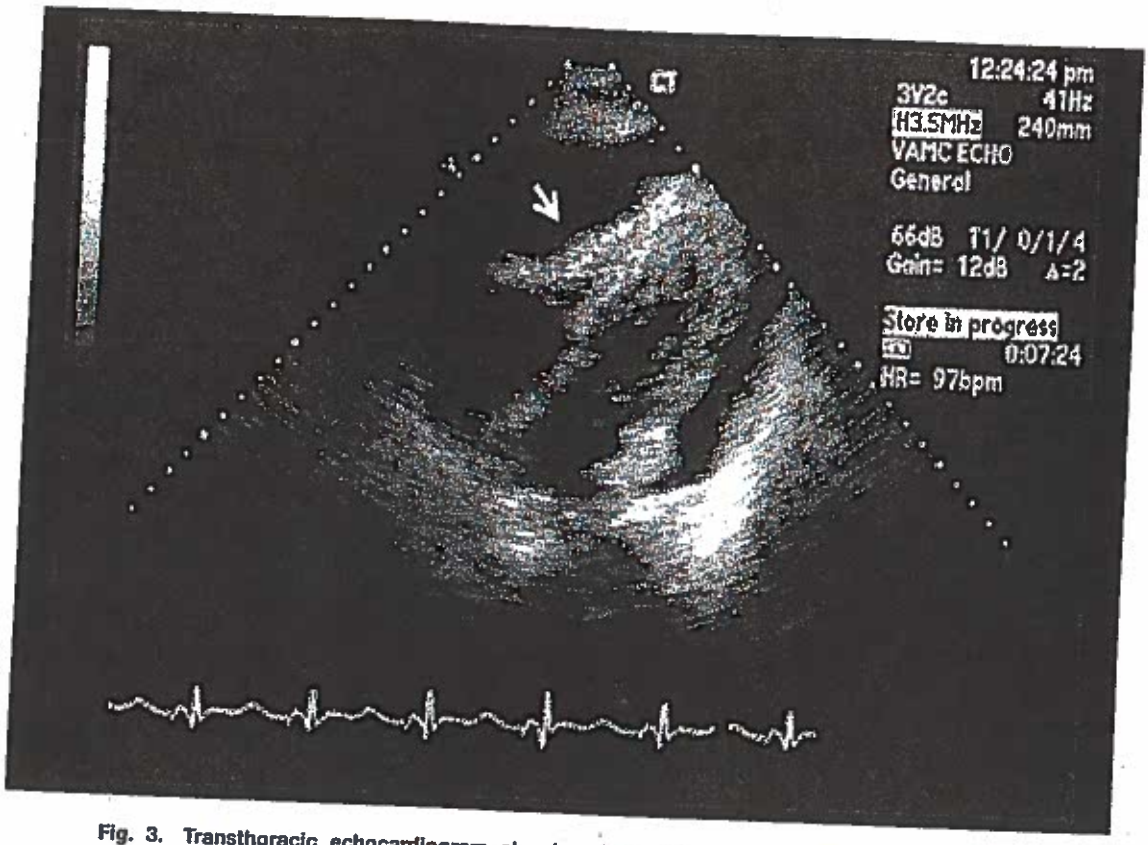

Fig. 3. Transthoracic echocardiogram showing diastolic right ventricular collapse (white arrow) with circumferential pericardial effusion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

decrease in arterial systolic pressure during inspiration (percentage decrease in arterial systolic pressure = expiratory arterial systolic pressure − inspiratory systolic pressure/expiratory systolic pressure × 100) [12].

In normal subjects, inspiration with resultant fall in intrathoracic and pleural pressure produces a gradient between the extrathoracic and intrathoracic veins with resultant increase in venous return to the right-sided cardiac chambers (RA and RV) [11]. Since the heart is in a confined space defined by the pericardium, increased RV volume produces a shift in the intraventricular septum, making the LV cavity smaller at the expense of the enlarged RV. At the same time, pulmonary vascular blood pooling occurs during inspiration, further decreasing LA and LV filling. Inspiration also decreases transaortic pressure and hence LV afterload. All of the above translates into a reduced LV stroke volume, LV ejection time, and systolic blood pressure during inspiration. Experimental studies in animals showed that pulsus paradoxus does not occur in the setting of cardiac tamponade when the RV is bypassed or the volume of the right heart is kept constant [13].

Though pulsus paradoxus is a frequent sign in patients with phase 3 cardiac tamponade, it has been described in multiple other conditions, including RV infarction [14], pulmonary embolism [15], chronic obstructive pulmonary disease (COPD) exacerbation [16], severe LV systolic dysfunction, pleural effusion [17], tense ascites [18], constrictive pericarditis [19], and external cardiac compression [20]. An inspiratory decline in blood pressure of 10 mm Hg has even been noted in normal subjects [7]. In patients with emphysema, a pulsus paradoxus has been hypothesized to result from increased right ventricular filling pressures due to pulmonary hypertension, when an inspiratory effort results in further buildup of pressure within the right ventricle. The hearts of patients with emphysema also have a limited ability to expand outward due to hyperexpanded lungs; consequently, high RV filling pressures during inspiration result in bowing of the interventricular septum, producing a pulsus paradoxus.

Certain preexisting cardiac conditions preclude occurrence of pulsus paradoxus despite the presence of all the other classic features of cardiac tamponade. These conditions include LV hypertrophy, pulmonary artery obstruction [21], large atrial septal defect, severe aortic regurgitation, loculated pericardial effusion, chronic

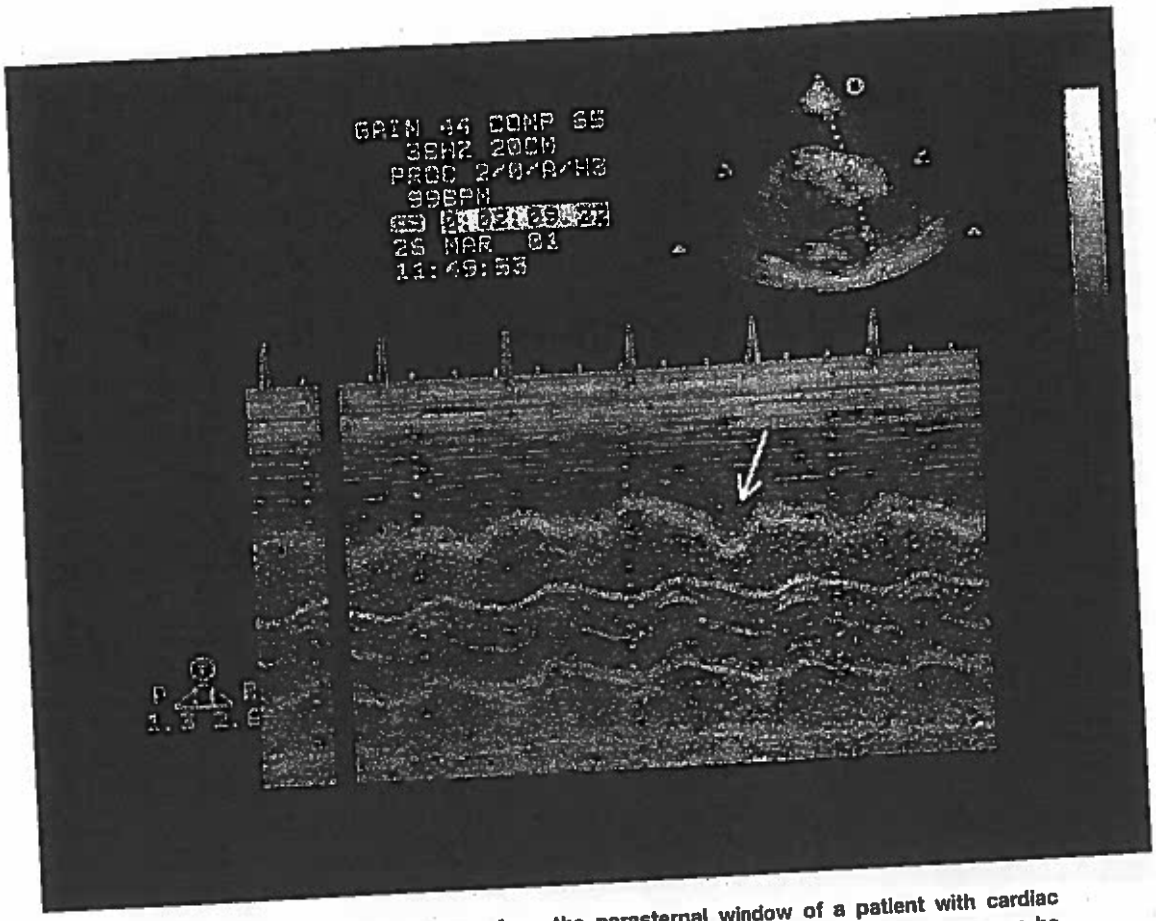

Fig. 4. M-mode echocardiogram from the parasternal window of a patient with cardiac tamponade. There is diastolic right ventricular collapse (white arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

renal failure [4], and severe hypotension. In patients with elevated left ventricular diastolic filling pressures above and beyond right ventricular filling pressures, such as in a patient with severe aortic regurgitation, elevated pressure in the left ventricle checks the inspiratory increase in right ventricular volume [7,11,22]. Therefore, during inspiration, the interventricular septum is not capable of bowing into the left ventricle, consequently preventing inspiratory decline in the systemic blood pressure with a resultant lack of pulsus paradoxus. Patients with severe aortic stenosis and cardiac tamponade may similarly lack pulsus paradoxus due to elevated left ventricular end-diastolic pressure from LV hypertrophy. Patients with a large atrial septal defect in the setting of coexisting tamponade frequently may not demonstrate a pulsus paradoxus thought to be due to the equalization of blood volumes in both atria from the atrial septal defect. Consequently, the normal inspiratory increase in systemic venous return is balanced by a decrease in left-to-right shunt, resulting in unchanged right and left ventricular end-diastolic pressures and volumes during the respiratory cycle [7,11,22,23].

Patients with systemic hypotension may have so low a blood pressure as to make a pulsus paradoxus difficult to detect. In a patient suffering from significantly impaired left ventricular systolic function and a pericardial effusion, the appearance of a pulsus paradoxus may actually be an extremely ominous sign. These patients with minimal left ventricular reserve have significantly elevated left ventricular filling pressure. Thus, the development of a pulsus paradoxus in these patients signifies markedly high right-sided pressures.

In summary, two conditions are prerequisite for the production of a pulsus paradoxus in tamponade: significant pericardial effusion with elevated pericardial pressures restraining ventricular diastolic filling, and differential filling of left and right ventricle during respiratory cycle. If either of these two components is missing, pulsus paradoxus will usually be absent.

COMPENSATORY MECHANISMS

During early phases of cardiac tamponade, increase in heart rate compensates for reduced stroke volume and car-

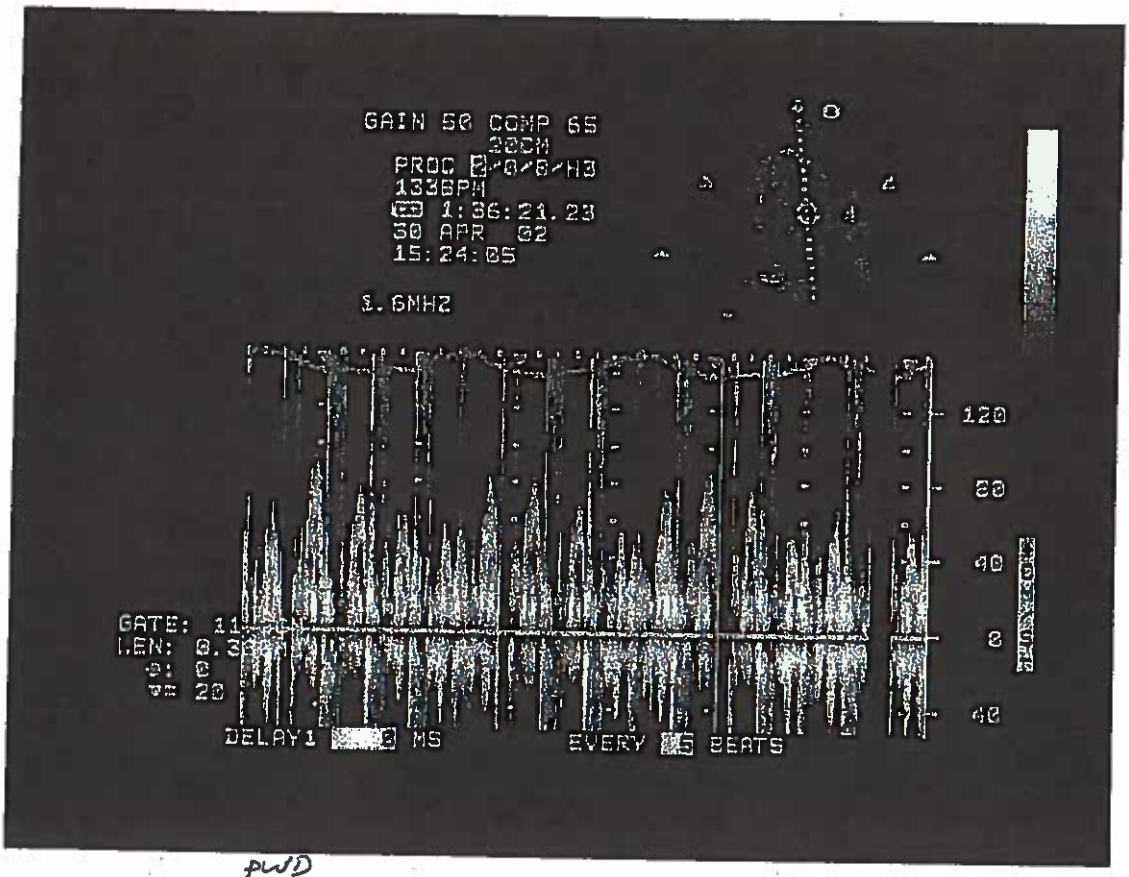

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Fig. 5. Pulsed-wave Doppler recording at the level of mitral valve from the four-chamber apical view. There is pronounced respiratory variation (> 25%) in the Doppler signal through the respiratory cycle. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

diac output is maintained. In chronic pericardial effusions, renal compensatory mechanisms such as salt and water retention attempt to increase intravascular volumes [24].

NONINVASIVE TESTING

Transthoracic echocardiography plays a vital role in the diagnosis and management of pericardial effusion and tamponade. When the pericardial space is filled with fluid, it is detected as an echo-free space that persists throughout the cardiac cycle, although a localized posterior effusion may be evident only in systole. Pericardial effusion size can be graded using transthoracic echocardiography. One such grading system defined moderate pericardial effusion as an echo-free space of 10–20 mm (both anterior and posterior) during diastole and > 20 mm as a large effusion [25]. It should be noted that a small echo-free space is frequently observed over the anterior RV free wall in asymptomatic patients due to the anterior fat pad. As the effusion enlarges, various M-mode and 2D echocardiographic signs are used to determine hemodynamic significance and compromise. Specifically, early diastolic collapse of the RV, late diastolic collapse of the RA (Figs. 3 and 4), abnormal ventricular septal motion (more commonly seen in constrictive pericarditis), exaggerated respiratory variability in mitral inflow velocity (lowest velocity during inspiration; Fig. 5) and tricuspid inflow velocity (highest during inspiration), inspiratory decrease and expiratory increase in pulmonary vein diastolic forward flow, respiratory variation in ventricular chamber size, and aortic outflow velocity (echocardiographic pulsus paradoxus; Fig. 6). Since echocardiography is portable, readily available, and easy to use, it is often the initial study performed to evaluate the size, location, and the degree of hemodynamic impact of the pericardial effusion. Also, echocardiography can be used to guide pericardiocentesis with excellent safety and efficacy. In a Mayo Clinic experience, there was only 1 death in more than 1,000 procedures performed. Echocardiography is also the preferred modality to confirm resolution or recurrence of pericardial effusion [26].

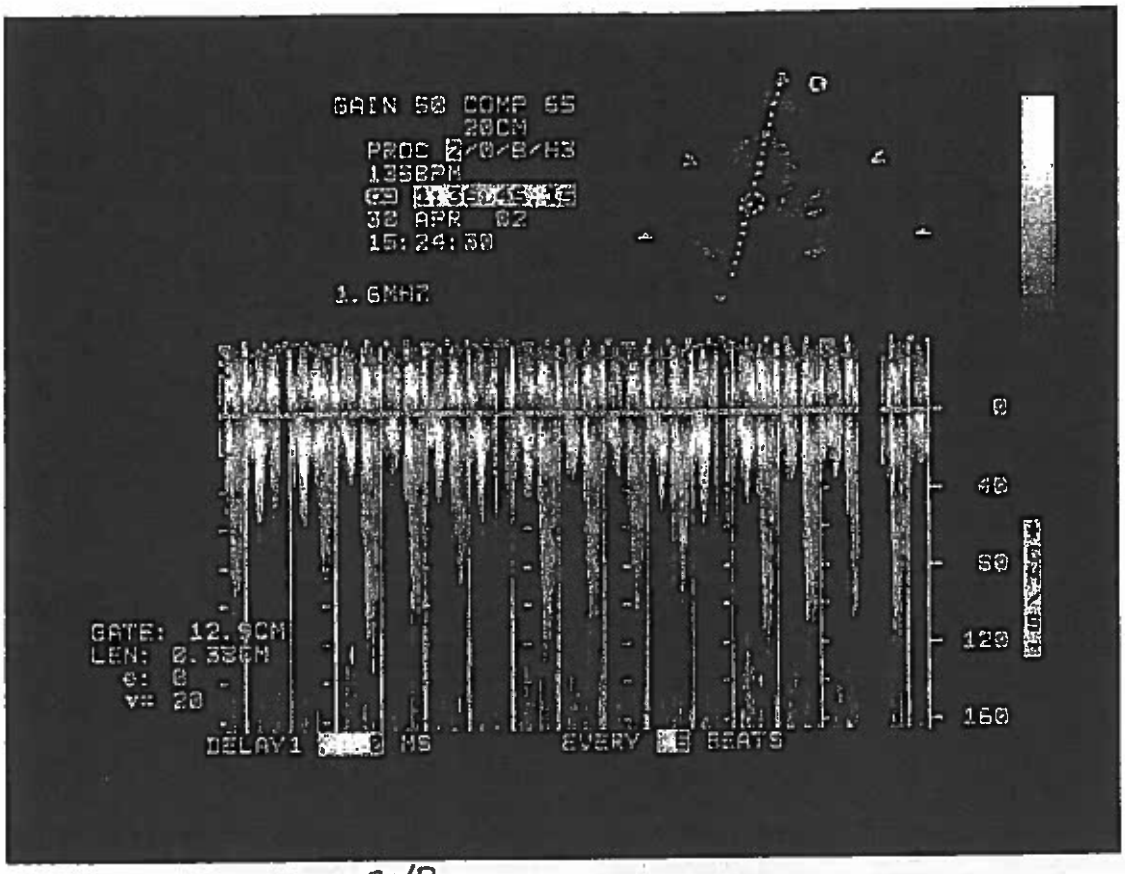

Fig. 6. Continuous-wave Doppler recording across the aortic valve (four-chamber apical view) showing respiratory variation in aortic outflow velocity, an echocardiographic equivalent of pulsus paradoxus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com].

EFFUSIVE-CONSTRICTIVE PERICARDITIS

Persistently elevated right atrial pressure after a successful pericardiocentesis suggests the diagnosis of effusive-constrictive pericarditis. These hemodynamic changes result from persistent visceral pericardial constraint caused by uremia, infection, malignancy, tuberculosis, radiation, or organizing fibrous material [27]. These patients may demonstrate Kussmaul's sign (increased venous pulsation or right atrial pressure with inspiration) in addition to pulsus paradoxus. After pericardial fluid removal, right atrial and ventricular diastolic pressures remain elevated despite an echocardiographically confirmed empty pericardial space and a low or negative pericardial pressure. Postevacuation hemodynamics resembles those of a pure constrictive physiology with a prominent Y-descent and a dip-and-plateau pattern of the RV diastolic waveform. In a recent large series of patients undergoing simultaneous hemodynamic evaluation and pericardiocentesis, effusive-constrictive physiology was noted in 8% of patients [28]. Many of the effusive-constrictive patients were asymptomatic in this series and gradually normalized their hemodynamics. If symptoms persist in a patient with hemodynamic features suggestive of effusive-constrictive pericarditis, the preferred treatment is surgery (total pericardiectomy with removal of visceral pericardium).

POSTSURGERY CARDIAC TAMPONADE

Pericardial effusions and organizing hematomas occur despite having a partially open pericardium after cardiac surgery [29], and delayed presentation has been reported after minimally invasive CABG surgery [30]. In a series of 510 patients, incidence of tamponade after cardiac surgery was 2%, with 90% of patients having atypical clinical and hemodynamic presentation of cardiac tamponade [31]. The diagnosis and management of postoperative tamponade is very challenging, since effusion and hematomas may be loculated and confined posteriorly. Pulsus paradoxus may be absent in as many as 50% of patients; a high index of suspicion is required for the prompt diagnosis and management. On echocardio-

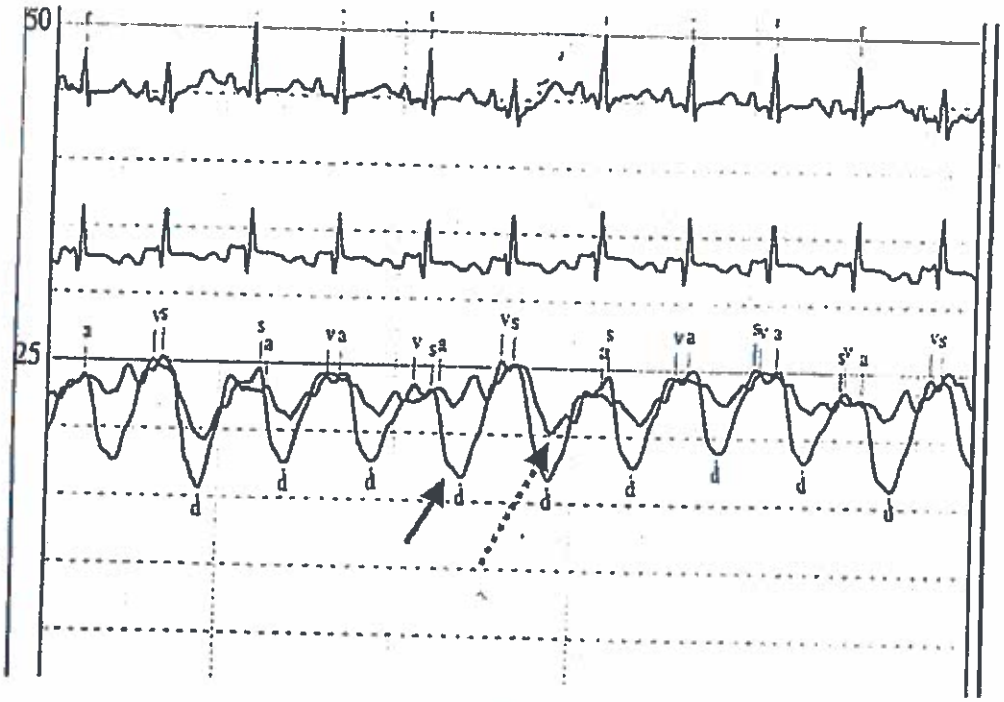

Fig. 7. Right atrial (dashed arrow) and intrapericardial (solid arrow) pressure waveforms showing equalization of pressures in a patient with phase 3 cardiac tamponade (50 mm Hg scale).

graphy, posterior effusions or hematomas can present with isolated left-sided chamber collapse without traditional signs of right-sided chamber diastolic collapse. In a study comparing isolated right- versus left-sided pericardial effusion in an animal model, the right-sided effusion led to more hemodynamic compromise compared with isolated left-sided effusion [32]. Percutaneous drainage is challenging, usually requiring echocardiographic guidance and surgical reexploration is often necessary in hemodynamically unstable patients.

LOW-PRESSURE TAMPONADE

Low-pressure tamponade may occur in a patient with hypovolemia during the setting of compressive pericardial effusion. In its acute form, low-pressure tamponade can occur following a penetrating cardiac wound; in a chronic form, it can occur from prolonged dehydration. Clinical findings may demonstrate a low to normal blood pressure with an absence of jugular venous distention or pulsus paradoxus [33]. In suspected cases, the administration of fluids can stabilize a rapidly declining patient in preparation for a pericardial drainage procedure. If a low-pressure tamponade is suspected, a fluid bolus prior to invasive hemodynamic measurement may help unmask occult tamponade or constrictive pericarditis hemodynamics.

CARDIAC TAMPONADE WITH COEXISTENT LV/RV DYSFUNCTION

The clinical diagnosis of tamponade in a patient with preexisting significant LV dysfunction can often be difficult [34]. In such patients, the left ventricular end-diastolic pressure may be elevated higher than the right ventricular end-diastolic pressure and the intrapericardial pressure. Similarly, in patients with isolated right heart failure (e.g., COPD) and elevated right end-diastolic pressure, the intrapericardial pressure will increase to equal the LV end-diastolic pressure but remain lower than the RV filling pressures. Both RV and LV dysfunction may lead to absent pulsus paradoxus. The hemodynamic diagnosis of tamponade in patients with LV dysfunction can be made when the RA and intrapericardial pressures equilibrate and track each other throughout the respiratory cycle. Likewise, in a patient with predominantly right heart failure and a high RV diastolic pressures, the PCWP and intrapericardial pressure track each other throughout the respiratory cycle.

MANAGEMENT OF CARDIAC TAMPONADE

The treatment of cardiac tamponade is based on clinical presentation and may involve pericardial fluid removal by percutaneous pericardiocentesis, balloon pericardiotomy, or surgical pericardial window. Fluid

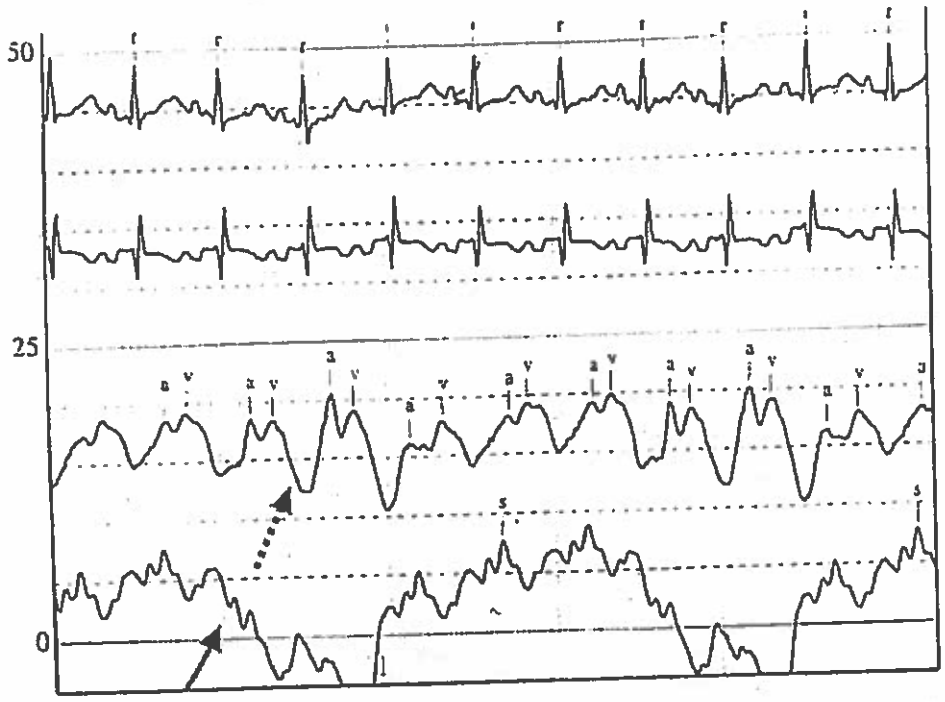

Fig. 8. The separation of right atrial (dashed arrow) and intrapericardial (solid arrow) pressure tracing (50 mm Hg scale) after pericardial fluid drainage. Note the return of respiratory variation in the intrapericardial pressure tracing. Persistent elevation in the right atrial pressure is suggestive of effusive-constrictive physiology.

resuscitation allows early hemodynamic stabilization. For percutaneous pericardiocentesis, fluoroscopic [29], echocardiographic [35], or combined guidance is used based on the operator's experience and preference. A common technique is use of fluoroscopic guidance in patients with large pericardial effusion and use of echocardiographic and/or fluoroscopic guidance in patients with a small or localized effusion. If the patient's clinical condition permits, complete right heart catheterization is performed prior to pericardiocentesis. Continuous femoral artery pressure may be recorded to allow for confirmation of pulsus paradoxus and for hemodynamic monitoring during pericardiocentesis. Pericardial space is entered via subxiphoid approach unless the effusion is loculated. Simultaneous right atrial, pulmonary artery wedge, intrapericardial, and femoral artery pressures are recorded. Cardiac output by thermodilution and arterial and mixed venous blood samples (pulmonary artery) are obtained before and after the pericardiocentesis. A bedside echocardiogram may be performed simultaneously or immediately following the pericardiocentesis. A comprehensive hemodynamic assessment pre- and postpericardiocentesis offers several advantages. One, it confirms the hemodynamic severity of the pericardial effusion and presence of cardiac tamponade by demonstrating equalization of diastolic pressures and pericardial pressures (Fig. 7). Two, it confirms the relief of tamponade physiology after drainage. Three, it excludes coexisting causes of right atrial hypertension and effusive-constrictive pericarditis, which may be present in up to 40% of medical patients with tamponade [36]. Four, fluoroscopic guidance and hemodynamic monitoring enhance the safety of procedure.

Cardiac tamponade physiology is relieved if pericardial pressure falls to subatmospheric levels (at or below 0 mm Hg; Fig. 8); right atrial pressure falls to normal and a Y-descent appears in the RA waveform (indicative of normal atrial emptying); pulsus paradoxus is relieved or significantly reduced. If after pericardiocentesis a patient persists to have jugular venous distention despite pericardial pressure of less then 0 mm Hg and right atrial pressure is normal, a superior vena cava obstruction should be considered. In patients with poor LV function after pericardiocentesis, monitoring should focus on development of pulmonary edema mainly due to an abrupt increase in the pulmonary blood flow and left heart filling [37]. If the PCWP remains elevated after complete drainage, the operator should consider preexisting heart muscle disease. Complete drainage is usually accomplished when no more fluid can be aspirated.

Large-volume pericardiocentesis has been reported to cause transient LV systolic dysfunction [38] and severe RV dysfunction leading to cardiogenic shock [39]. Other

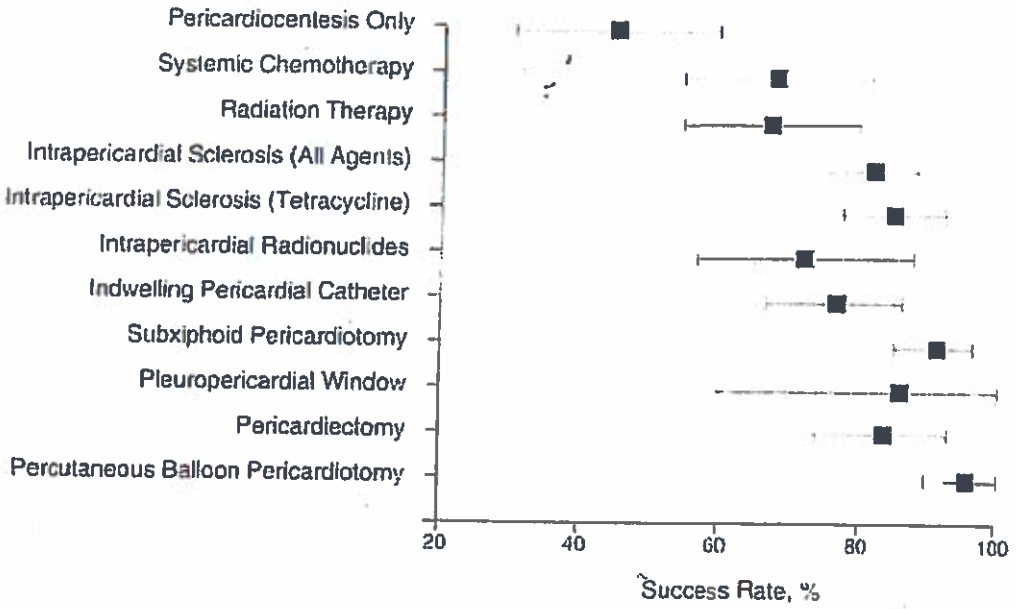

Fig. 9. Success rates for different treatment modalities of recurrent malignant pericardial effusions Reprinted with permission from Vaitkus et al. [41].

complications from pericardiocentesis involve transient arrhythmias, cardiac arrest, right ventricular perforations, and occasional death [40]. Risk of complications varies from 2.4% to 4.8% and depends on the size and location of fluid, operator experience, and echocardiographic guidance [36,40–43]. Pericardiocentesis in patients with a large pericardial effusion without signs of tamponade physiology has a low diagnostic yield and unclear clinical benefit [44].

MANAGEMENT OF RECURRENT PERICARDIAL EFFUSION

Pericardial fluid reaccumulation is highly dependent on the etiology of the effusion [41,43]. Prolonged drainage with an in-dwelling catheter reduces the chance of reaccumulation within 90 days to 12%, with a rare recurrence (1%) after 90 days [43]. Management options for recurrent pericardial effusions, usually malignant in etiology, include subxiphoid pericardiotomy with or without sclerotherapy, repeat pericardiocentesis with instillation of sclerosing agents, or percutaneous balloon pericardiotomy [45,46]. Briefly, the technique involves accessing the pericardial space under fluoroscopic and echocardiographic guidance with a needle, followed by placement of a stiff wire in the pericardial space, localization of fibrous pericardium by feeling and marking the point of resistance during pullback of a inflated balloon in the pericardium, deflating the balloon and positioning it across the previously marked point of entry into the pericardium, and finally dilation (balloon diameter in 18 mm range), creating a tear in the fibrous parietal pericardium. An in-dwelling drainage catheter is left in place along with prophylactic antibiotic administration. This procedure has a low complication rate that includes pleural effusion, RV trauma, and rarely balloon fragmentation. Balloon pericardiotomy remains an attractive option with a high success rate and comparable results to surgical pericardial window in a patient population with significant comorbidities (Fig. 9).

In conclusion, hemodynamics plays an invaluable role in the diagnosis and treatment of patients with pericardial effusion and cardiac tamponade [47]. Complementary use of noninvasive and invasive hemodynamic with a careful review of patient's clinical condition facilitates optimal management of this challenging cardiac emergency.

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ASE/SCA Guidelines for Performing a Comprehensive Intraoperative Multiplane Transesophageal Echocardiography Examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography

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Since the introduction of transesophageal echocardiography (TEE) to the operating room in the early 1980s,[1-4] its effectiveness as a clinical monitor to assist in the hemodynamic management of patients during general anesthesia and its reliability to make intraoperative diagnoses during cardiac operations has been well established.[5-26] In recognition of the increasing clinical applications and use of intraoperative TEE, the American Society of Echocardiography (ASE) established the Council for Intraoperative Echocardiography in 1993 to address issues related to the use of echocardiography in the operating room. In June 1997, the Council board decided to create a set of guidelines for performing a comprehensive TEE examination composed of a set of anatomically directed cross-sectional views. The Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography has endorsed these guidelines and standards of nomenclature for the various anatomically directed cross-sectional views of the comprehensive TEE examination. This document, therefore, is the collective result of an effort that represents the consensus view of both anesthesiologists and cardiologists who have extensive experience in intraoperative echocardiography.

The writing group has several goals in mind in creating these guidelines. The first is to facilitate training in intraoperative TEE by providing a framework in which to develop the necessary knowledge and skills. The guidelines may also enhance quality improvement by providing a means to assess the technical quality and completeness of individual studies. More consistent acquisition and description of intraoperative echocardiographic data will facilitate communication between centers and provide a basis for multicenter investigations. In recognition of the increasing availability and advantages of digital image storage, the guidelines define a set of cross-sectional views and nomenclature that constitute a comprehensive intraoperative TEE examination that could be stored in a digital format. These guidelines will encourage industry to develop echocardiography systems that allow quick and easy acquisition, labeling, and storage of images in the operating room, as well as a simple mechanism for side-by-side comparison of views made at different times.

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The following discussion is limited to a description of a method to perform a comprehensive intraoperative echocardiographic examination and does not address specific diagnoses, which is beyond the scope of a journal article. It describes how to examine a patient with "normal" cardiac structures to establish a baseline for later comparison. A systematic and complete approach ensures that unanticipated or clinically important findings will not be overlooked. Routinely performing a comprehensive examination also increases the ability to recognize normal structures and distinguish normal variants from pathologic states, thereby broadening experience and knowledge more rapidly. The description of the examination in the guidelines is based on multiple imaging plane (multiplane) TEE technology because it represents the current state of the art and is the type of system most commonly used. Compared with single plane or biplane imaging, multiplane TEE provides the echocardiographer with a greater ability to obtain images of cross-sections with improved anatomic orientation to the structures being examined.[27-31]

The writing group recognizes that individual patient characteristics, anatomic variations, pathologic features, or time constraints imposed on performing the TEE examination may limit the ability to perform every aspect of the comprehensive examination. Whereas the beginner should seek a balance between a fastidiously complete, comprehensive examination and expedience, an experienced echocardiographer can complete the recommended examination in <10 minutes. The TEE examination should be recorded on videotape or stored in a digital format so that individual studies can be archived and retrieved for review when necessary. The writing group also recognizes that there may be other entirely acceptable approaches and views of an intraoperative TEE examination, provided they obtain similar information in a safe manner.

Patient Safety

Although safe when properly conducted, in rare circumstances, TEE can cause serious and even fatal complications.[32-37] An effort should be made to detect preexisting esophageal or gastric problems before performing TEE. Contraindications to TEE include esophageal stricture, diverticulum, tumor, and recent esophageal or gastric surgery. The TEE transducer should be inspected for defects and cracks in the waterproof covering before insertion. The mouth should be examined for preexisting injuries and loose teeth. The TEE probe may be inserted into an anesthetized, tracheally intubated patient with or without the use of a laryngoscope by displacing the mandible anteriorly and inserting the probe gently in the midline. Flexing the neck will help in some cases. If blind insertion of the probe is not easy, a laryngoscope can be used to expose the glottis and permit direct passage of the probe posteriorly into the esophagus. Once in the esophagus, the transducer should never be forced through a resistance. The tip of the transducer should be allowed to return to the neutral position before advancing or withdrawing the probe, and excessive force should never be applied when moving the transducer in the esophagus or flexing the tip with the control wheels. Cleaning and decontamination of the probe should be performed after each use.

General Principles

When examining the heart with TEE, the transducer is first moved into the desired location, and then the probe is manipulated to orient the imaging plane to obtain the desired cross-sectional image. This is accomplished by watching the image develop as the probe is manipulated, rather than by relying on the depth markers on the probe or the multiplane angle icon. Although the most common transducer location and multiplane angle are provided for each cross-sectional image, final adjustment of the image is based on the anatomic structures that are displayed. It is recognized that there is individual variation in the anatomic relationship of the esophagus to the heart; in some patients, the esophagus is adjacent to the lateral portion of the atrioventricular groove, whereas in others it is directly posterior to the left atrium (LA). This relationship is taken into consideration when developing each of the desired cross-sectional views. When possible, each structure is examined in multiple imaging planes and from more than one transducer position. An echocardiograph produces a two-dimensional or tomographic imaging plane. Manipulating the probe or the transducer to move the imaging plane through the entire three-dimensional extent of a structure permits it to be examined completely.

Instrument settings and adjustments are important for optimizing image quality and the diagnostic capabilities of TEE. Many TEE probes can obtain image with more than one transducer frequency. Increasing the imaging frequency improves resolution but decreases penetration. Structures closer to the probe, such as the aortic valve (AV), are imaged best at a higher frequency, whereas structures farther away from the probe, such as the apical regions of

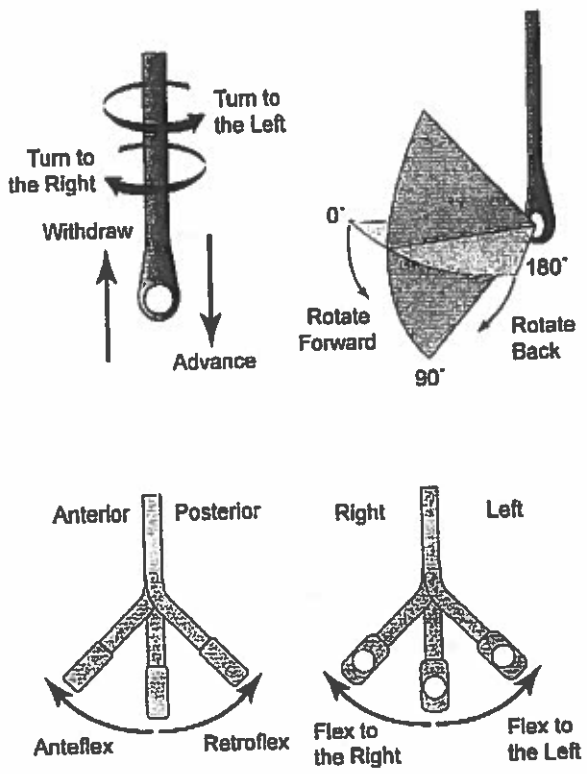


Figure 1 Terminology used to describe manipulation of the probe and transducer during image acquisition.

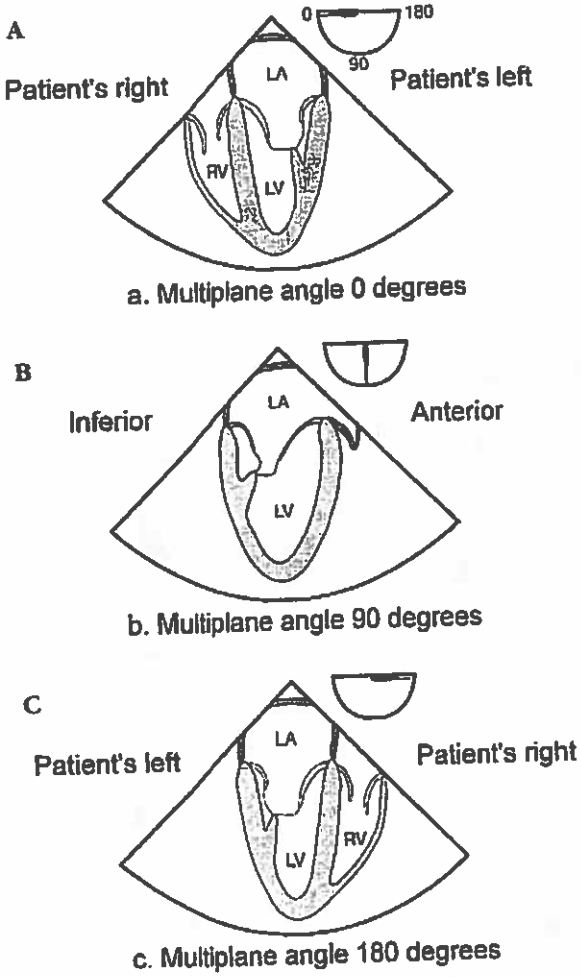


Figure 2 Conventions of image display followed in the guidelines. Transducer location and the near field (vertex) of the image sector are at the top of the display screen and far field at the bottom. A, Image orientation at multiplane angle 0 degrees. B, Image orientation at multiplane angle 90 degrees. C, Image orientation at multiplane angle of 180 degrees. *LA*, Left atrium; *LV*, left ventricle; *RV*, right ventricle.

the left ventricle (LV), are imaged best at a lower frequency. The depth is adjusted so that the structure being examined is centered in the display, and the focus is moved to the area of interest. Overall image gain and dynamic range (compression) are adjusted so that the blood in the chambers appears nearly black and is distinct from the gray scales representing tissue. Time compensation gain adjustments are set to create uniform brightness and contrast throughout the imaging field. The color flow Doppler (CFD) gain is set to a threshold that just eliminates any background noise within the color sector. Decreasing the size and depth of the color sector increases the aliasing velocity and frame rate. Decreasing the width of the two-dimensional imaging sector also increases the frame rate.

The following terminology is used to describe manipulation of the probe and transducer during image acquisition (Figure 1). It is assumed that the patient is supine in the standard anatomic position, and the imaging plane is directed anteriorly from the esophagus through the heart. With reference to the heart, superior means toward the head, inferior toward the feet, posterior toward the spine, and anterior toward the sternum. The terms right and left denote the patient's right and left sides, except when the text refers to the image display.

Pushing the tip of the probe more distal into the esophagus or the stomach is called advancing the transducer, and pulling the tip in the opposite direction more proximally is called withdrawing. Rotating the anterior aspect of the probe clockwise within the esophagus toward the patient's right is called turning to the right, and rotating counterclockwise is

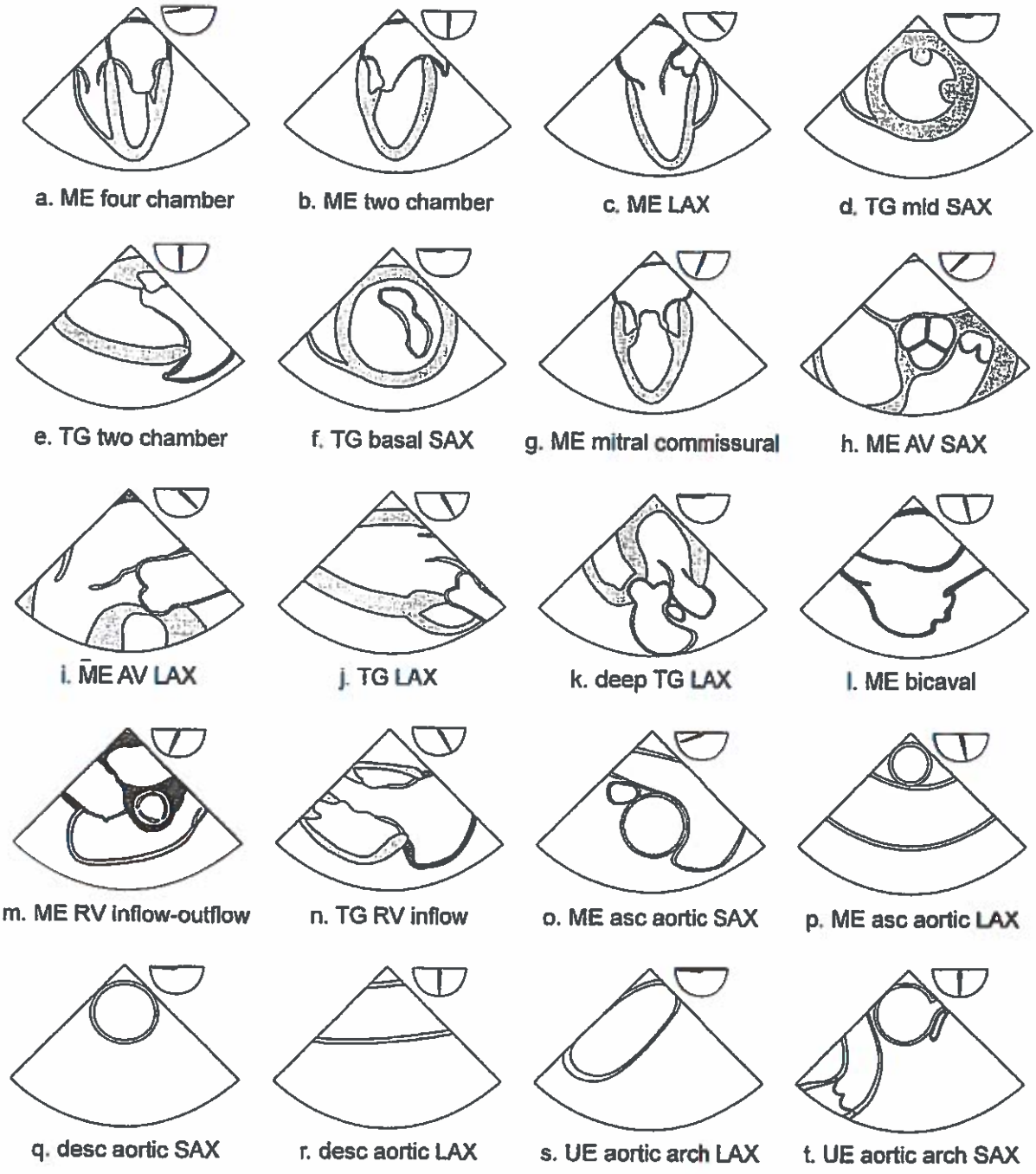


Figure 3 20 cross-sectional views composing the recommended comprehensive transesophageal echocardiographic examination. Approximate multiplane angle is indicated by the icon adjacent to each view. *ME,* Mid esophageal; *LAX,* long axis; *TG,* transgastric; *SAX,* short axis; *AV,* aortic valve; *RV,* right ventricle; *asc,* ascending; *desc,* descending; *UE,* upper esophageal.

Table 1 Recommended transesophageal echocardiography cross sections

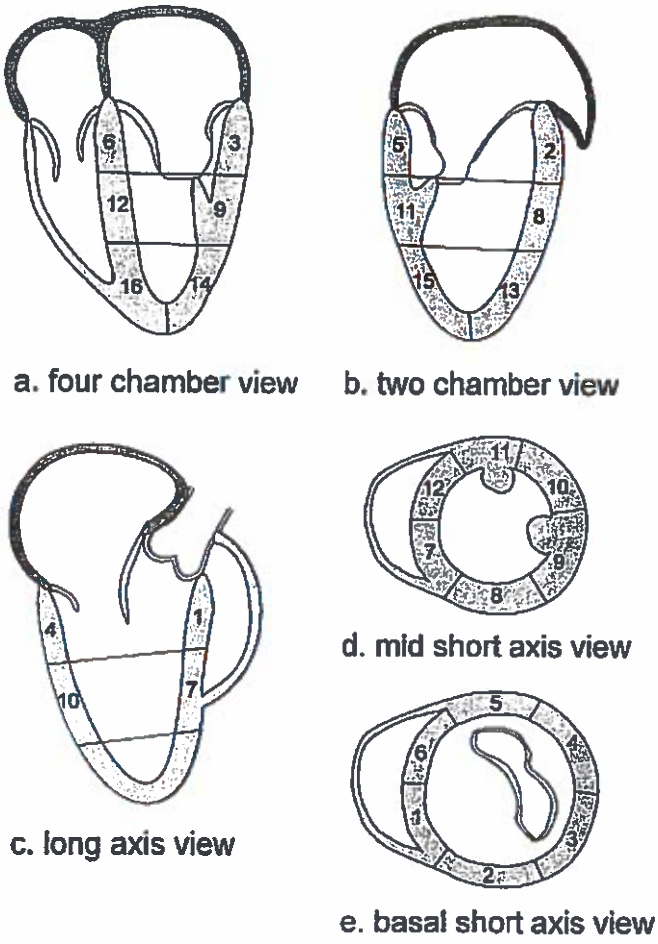
Window (depth from incisors)	Cross section (panel in Figure 3)	Multiplane angle range	Structures imaged
Upper esophageal (20-25 cm)	Aortic arch long axis (s)	0°	Aortic arch, left brachio v
	Aortic arch short axis (t)	90°	Aortic arch, PA, PV, left brachio v
Mid esophageal (30-40 cm)	Four-chamber (a)	0°-20°	LV, LA, RV, RA, MV, TV, IAS
	Mitral commissural (g)	60°-70°	MV, LV, LA
	Two-chamber (b)	80°-100°	LV, LA, LAA, MV, CS
	Long axis (c)	120°-160°	LV, LA, AV, LVOT, MV, asc aorta
	RV inflow-outflow (m)	60°-90°	RV, RA, TV, RVOT, PV, PA
	AV short axis (h)	30°-60°	AV, IAS, coronary ostia, LVOT, PV
	AV long axis (i)	120°-160°	AV, LVOT, prox asc aorta, right PA
	Bicaval (l)	80°-110°	RA, SVC, IVC, IAS, LA
	Asc aortic short axis (o)	0°-60°	Asc aorta, SVC, PA, right PA
	Asc aortic long axis (p)	100°-150°	Asc aorta, right PA
	Desc aorta short axis (q)	0°	Desc thoracic aorta, left pleural space
	Desc aorta long axis (r)	90°-110°	Desc thoracic aorta, left pleural space
Transgastric (40-45 cm)	Basal short axis (f)	0°-20°	LV, MV, RV, TV
	Mid short axis (d)	0°-20°	LV, RV, pap mm
	Two-chamber (e)	80°-100°	LV, MV, chordae, pap mm, CS, LA
	Long axis (j)	90°-120°	LVOT, AV, MV
	RV inflow (n)	100°-120°	RV, TV, RA, TV chordae, pap mm
Deep transgastric (45-50 cm)	Long axis (k)	0°-20° (anteflexion)	LVOT, AV, asc aorta, arch

Brachio v, Brachiocephalic vein; *PA*, pulmonary artery; *PV*, pulmonic valve; *LV*, left ventricle; *LA*, left atrium; *RV*, right ventricle; *RA*, right atrium; *MV*, mitral valve; *TV*, tricuspid valve; *IAS*, interatrial septum; *LAA*, left atrial appendage; *CS*, coronary sinus; *AV*, aortic valve; *LVOT*, left ventricular outflow tract; prox, proximal; *RVOT*, right ventricular outflow tract; *SVC*, superior vena cava; *IVC*, inferior vena cava; *RPA*, right pulmonary artery; *asc*, ascending; *desc*, descending; *pap mm*, papillary muscles.

called turning to the left. Flexing the tip of the probe anteriorly with the large control wheel is called anteflexing, and flexing it posteriorly is called retroflexing. Flexing the tip of the probe to the patient's right with the small control wheel is called flexing to the right, and flexing it to the patient's left is called flexing to the left. Finally, axial rotation of the multiplane angle from 0 degrees towards 180 degrees is called rotating forward, and rotating in the opposite direction towards 0 degrees is called rotating back.

The following conventions of image display are followed in the guidelines (Figure 2). Images are displayed with the transducer location and the near field (vertex) of the image sector at the top of the display screen and the far field at the bottom. At a multiplane angle of 0 degrees (the horizontal or transverse plane), with the imaging plane directed anteriorly from the esophagus through the heart, the patient's right side appears in the left of the image display (Figure 2, *A*). Rotating the multiplane angle forward to 90 degrees (vertical or longitudinal plane) moves the left side of the display inferiorly, toward the supine patient's feet (Figure 2, *B*). Rotating the multiplane angle to 180 degrees places the patient's left side to the left of the display, the mirror image of 0 degrees (Figure 2, *C*).

The comprehensive, intraoperative TEE examination recommended by the writing group consists of a series of 20 cross-sectional views of the heart and great vessels (Table 1 and Figure 3). The nomenclature is as consistent as possible with previous recommendations of the ASE Committee on Nomenclature and Standards[38] and commonly accepted terminology for transthoracic echocardiography (TTE).[39] The views are designated by the transducer location (ie, the echo window), a description of the imaging plane (eg, short axis, long axis), and the main anatomic structure in the image. When used without an associated structure, the term "short axis" refers to views of the left ventricle in short axis (transgastric mid short axis view and transgastric basal short axis view). When used without an associated structure, the term "long axis" refers to views of the LV that also include the aortic valves and mitral valves (MV) (mid esophageal long axis view, transgastric long axis view, and deep transgastric long axis view). When possible, terms corresponding to the analogous TTE views are used; thus, the mid esophageal four-chamber view may be thought of as a TEE analog of the apical four-chamber view of TTE. Table 1 also includes the typical range of probe depth and multiplane angle needed to obtain each view to serve as a starting point in its acquisition. Many of the same views are also used for the CFD and spec-



Basal Segments	Mid Segments	Apical Segments
1= Basal Anteroseptal	7= Mid Anteroseptal	13= Apical Anterior
2= Basal Anterior	8= Mid Anterior	14= Apical Lateral
3= Basal Lateral	9= Mid Lateral	15= Apical Inferior
4= Basal Posterior	10= Mid Posterior	16= Apical Septal
5= Basal Inferior	11= Mid Inferior	
6= Basal Septal	12= Mid Septal	

Figure 4 16-segment model of the left ventricle. **A**, Four-chamber views show the three septal and three lateral segments. **B**, Two-chamber views show the three anterior and three inferior segments. **C**, Long axis views show the two anteroseptal and two posterior segments. **D**, Mid short axis views show all six segments at the mid level. **E**, Basal short axis views show all six segments at the basal level.

tral Doppler examination to image the flow through the chambers and valves of the heart or to obtain the velocity profiles of pulmonary venous inflow, transmitral flow, and left ventricular outflow. The writing group recognizes the complexity of any attempt to fully characterize three-dimensional structures using a limited set of two-dimensional images and acknowledges that an examination may need to include modifications or variations of the recommended cross-sections to optimally characterize an individual's anatomy or pathology.

The order in which the examination proceeds will vary from examiner to examiner. Examination of a specific structure need not be performed continuously or completed before moving on to the next structure but may be broken up into different parts

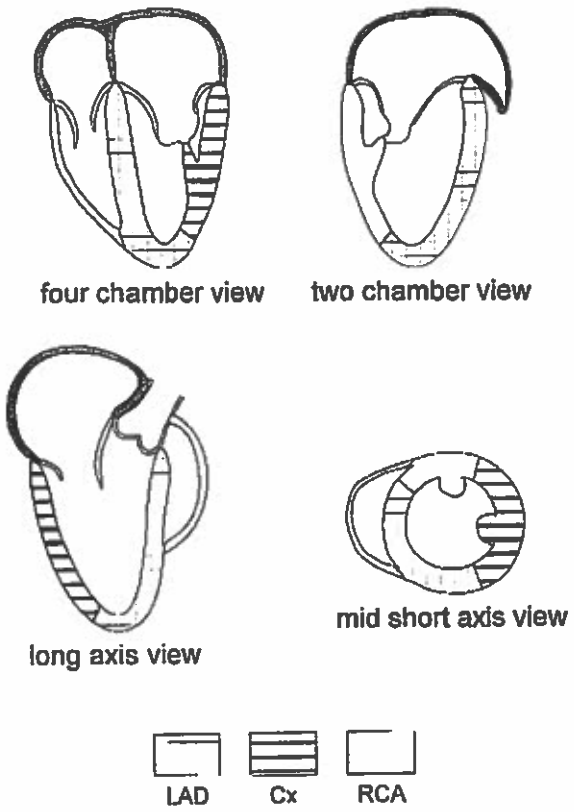


Figure 5 Typical regions of myocardium perfused by each of the major coronary arteries to the left ventricle. Other patterns occur as a result of normal anatomic variations or coronary disease with collateral flow. *LAD*, Left anterior descending; *Cx*, circumflex; *RCA*, right coronary artery.

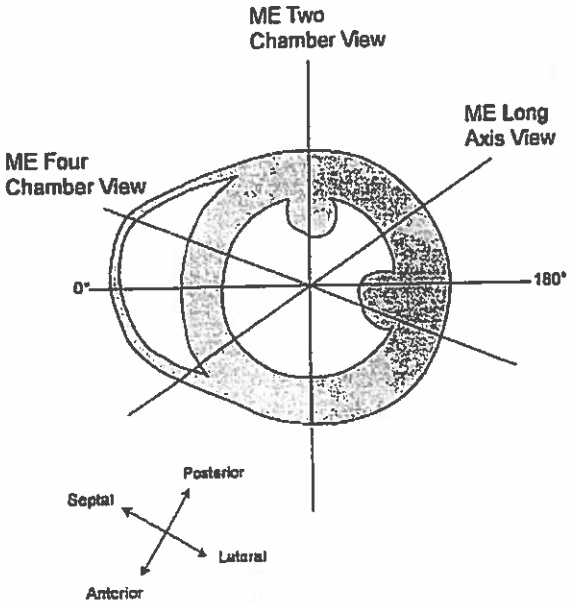


Figure 6 Short axis drawing of the left ventricle at the mid papillary level illustrating how it is transected by the mid esophageal views. Rotating from multiplane angle 0 degrees to 180 degrees moves the imaging plane axially through entire left ventricle. *ME*, Mid esophageal.

of the study for greater efficiency. For example, many will find it more practical to obtain all the mid esophageal views before proceeding to the transgastric views. In general, an intraoperative examination should begin with the structure that is the primary clinical question, often the valve or chamber being operated on. If hemodynamic instability or some other interruption fragments the TEE examination, at least the main objective of the study will be accomplished. The cross-sectional views described are generally obtainable in most patients, but as a result of individual anatomic variation, not all views can be developed in all patients. Most of the structures to be examined, however, are present in more than one cross-section, permitting a complete and comprehensive examination in most patients.

The guidelines will proceed by describing the examination of the individual structures of the heart and great vessels, emphasizing the recommended cross-sections that demonstrate each particular structure. An equally valid approach is to describe each of the cross-sections, emphasizing the structures that are displayed. This conceptualization of a comprehensive intraoperative examination is represented in Table 1 and Figure 3, which list each of the cross-sectional views. In practice, performance of the examination will become a fusion of the structural and cross-sectional approaches tailored to individual preferences and training.

Left Ventricle

Segmental models of the LV are needed to accurately describe the location and extent of regional wall motion abnormalities detected by echocardiography. All segmental models must balance complexity and descriptive power with practicality. The guidelines use a 16-segment model of the LV based on the recommendations of the Subcommittee on Quantification of the ASE Standards Committee.[40] This model divides the LV into three levels from base to apex: basal, mid, and apical. The basal and mid levels are each divided circumferentially into six segments, and the apical level into four (Figure 4). The coronary artery that usually perfuses each segment is shown in Figure 5. In current clinical practice, analysis of LV segmental function is based on a qualitative visual

assessment of the motion and thickening of a segment during systole. The recommended qualitative grading scale for wall motion is: 1 = normal (>30% thickening), 2 = mildly hypokinetic (10% to 30% thickening), 3 = severely hypokinetic (<10% thickening), 4 = akinetic (does not thicken), 5 = dyskinetic (moves paradoxically during systole). This grading scale has been used extensively in the intraoperative echocardiography literature.[5,7,41-55] All 16 segments are examined by obtaining five cross-sectional views of the LV, three through the mid esophageal window and two through the transgastric window.

To obtain the mid esophageal views of the LV, the transducer is positioned posterior to the LA at the mid level of the MV. The imaging plane is then oriented to pass simultaneously through the center of the mitral annulus and the apex of the LV. The LV is usually oriented within the patient's chest with its apex somewhat more inferior than the base, so the tip of the probe may require retroflexion to direct the imaging plane through the apex. The depth is adjusted to include the entire LV, usually 16 cm. The mid esophageal four-chamber view (Figure 3, *A*) is now obtained by rotating the multiplane angle forward from 0 degrees to between 10 and 20 degrees, until the AV is no longer in view and the diameter of the tricuspid annulus is maximized. The mid esophageal four-chamber view shows the basal, mid, and apical segments in each of the septal and lateral walls (Figure 4, *A*). The mid esophageal two-chamber view (Figure 3, *B*) is developed by rotating the multiplane angle forward to between 80 and 100 degrees until the right atrium (RA) and right ventricle (RV) disappear. This cross-section shows the basal, mid, and apical segments in each of the anterior and inferior walls (Figure 4, *B*). Finally, the mid esophageal long axis view (Figure 3, *C*) is developed by rotating the multiplane angle forward to between 120 and 160 degrees, until the LV outflow tract (LVOT), AV, and the proximal ascending aorta come into view. This view shows the basal and mid anteroseptal segments, as well as the basal and mid posterior segments (Figure 4, *C*). With the imaging plane properly oriented through the center of the mitral annulus and the LV apex, the entire LV can be examined, without moving the probe, by simply rotating forward from 0 to 180 degrees. Figure 6 illustrates how the mid esophageal views transect the LV. It can be difficult to image the apex of the LV with TEE in some patients, especially if the LV is enlarged or has an apical aneurysm.

The transgastric views of the LV are acquired by advancing the probe into the stomach and anteflexing the tip, until the heart comes into view. At a multiplane angle of 0 degrees, a short axis view of the LV will appear, and the probe is then turned to the right or left as needed to center the LV in the display. The image depth is adjusted to include the entire LV, usually 12 cm. Next, the multiplane angle is rotated forward to 90 degrees to show the LV in long axis with the apex to the left and the mitral annulus to the right of the display. The anteflexion of the probe is adjusted until the long axis of the LV is horizontal in the display (Figure 3, *E*). The level of the LV over which the transducer lies is noted (basal, mid, or apical), and the probe is advanced or withdrawn as needed to reach the mid papillary level. Now, the multiplane angle is rotated back to between 0 and 20 degrees, until the circular symmetry of the chamber is maximized to obtain the transgastric mid short axis view (Figure 3, *D*). This cross-section shows the six mid level segments of the LV and has the advantage of simultaneously showing portions of the LV supplied by the right, circumflex, and left anterior descending coronary arteries and is the most popular view for monitoring LV function (Figure 5). The transgastric mid short axis view is used for assessing LV chamber size and wall thickness at end diastole,

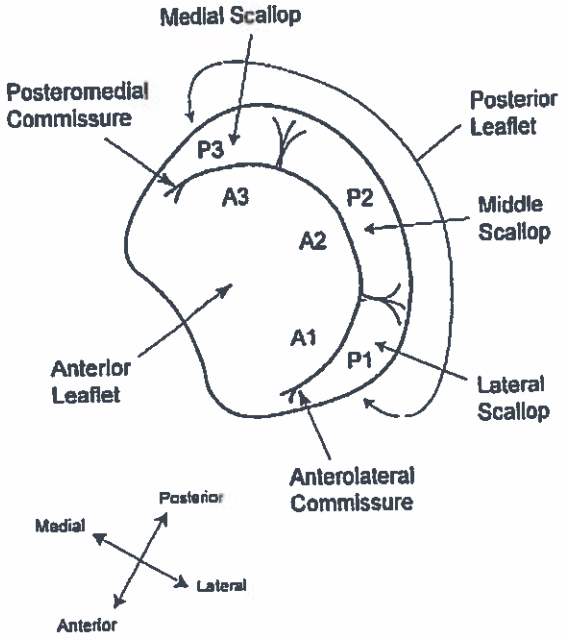


Figure 7 Anatomy of mitral valve. *A1*, Lateral third of the anterior leaflet; *A2*, middle third of the anterior leaflet; *A3*, medial third of the anterior leaflet; *P1*, lateral scallop of the posterior leaflet; *P2*, middle scallop of the posterior leaflet; *P3*, medial scallop of the posterior leaflet.

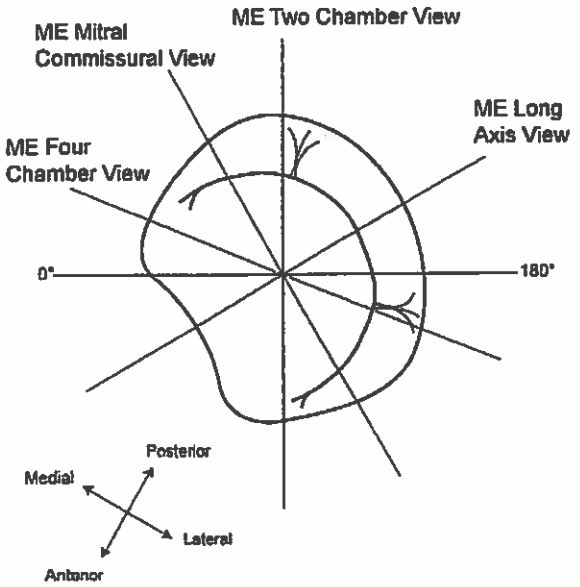


Figure 8 Short axis drawing of the mitral valve illustrating how it is transected by mid esophageal views. Rotating from multiplane angle from 0 degrees to 180 degrees moves the imaging plane axially through the entire mitral valve. *ME*, Mid esophageal.

which is best determined by measuring at the onset of the R wave of the electrocardiogram. Normal LV short axis diameter is <5.5 cm, and LV wall thickness is <1.2 cm. End diastolic and end systolic areas of the LV chamber may be measured in this cross-section for calculation of fractional area change as an index of LV systolic function. The transgastric two-chamber view (Figure 3, *E*) is developed by rotating the multiplane angle forward to approximately 90 degrees, until the apex and the mitral annulus come into view. The probe is turned to the left or right as needed to maximize the length of the LV chamber in the image. This view shows the basal and mid segments of the inferior and anterior walls, but usually not the apex.

The transgastric basal short axis view (Figure 3, *F*) is obtained by withdrawing the probe from the transgastric mid short axis view until the MV appears. It shows all six basal segments of the LV. When advancing or withdrawing the probe to different ventricular levels, it is helpful to do so from the transgastric two-chamber view, which shows the position of the transducer in relation to the long axis of the LV. When the desired level is reached, the short axis view is obtained by rotating the multiplane angle back toward 0 degrees.

Mitral Valve

The MV is composed of the anterior and posterior leaflets, chordae tendinae, papillary muscles, annulus, and LV walls. The two leaflets are joined at the anterolateral and posteromedial commissures, each of which is associated with a corresponding papillary muscle. The posterior leaflet consists of three scallops: lateral (P1), middle (P2), and medial (P3). For descriptive purposes, the anterior leaflet is divided into 3 parts: lateral third (A1), middle third (A2), and medial third (A3) (Figure 7).

The MV is examined with TEE by using four mid esophageal and two transgastric views. The mid esophageal views of the MV are all developed by first positioning the transducer posterior to the mid level of the LA and directing the imaging plane through the mitral annulus parallel to the transmitral flow. Again, because the apex of the LV is located inferior to the base of the heart in many patients, retroflexion of the probe tip is often necessary. The multiplane angle is then rotated forward to develop the mid esophageal four-chamber view. In this cross-section the posterior mitral leaflet P1 is to the right of the image display, and the anterior mitral leaflet A3 is to the left. As the multiplane angle is rotated forward to about 60 degrees, a transition in the image occurs beyond which the posterior leaflet is to the left of the display, and the anterior leaflet is to the right. At this transition angle, the imaging plane is parallel to the line that intersects the two commissures of the MV, to form the mid esophageal mitral commissural view (Figure 3, *G*). In this view, A2 is seen in the middle of the LV inflow tract with the posterior leaflet on each side; P1 is to the right of the display, and P3 is to the left. Beginning from a point where the imaging plane transects the middle of the valve, turning the probe to the right moves the plane toward the medial side of the MV through the base of the anterior leaflet, whereas turning the probe to the left moves the plane toward the lateral side through P2 of the posterior leaflet. Next, the multiplane angle is rotated forward to develop the mid esophageal two-chamber view. Now the posterior leaflet (P3) is to the left of the display and the anterior leaflet (A1) is to the right. Finally, the multiplane angle is rotated forward to the mid esophageal long axis view. In this view, the posterior mitral leaflet (P2) is to the left of the display, and the anterior mitral leaflet (A2) is to the right. As with the LV, proper orientation of the imaging plane from the mid esophageal window through the center of the mitral annulus permits the entire MV to be examined without moving the probe by rotating forward from 0 to 180 degrees, and both

structures are easily examined simultaneously. Figure 8 illustrates how the mid esophageal views transect the MV.

The mid esophageal views of the MV are repeated with CFD, ensuring that the color sector includes the left atrial portion of any mitral regurgitation jet as well as the ventricular aspect of the valve to detect any flow convergence caused by mitral regurgitation. This is easily accomplished by rotating the multiplane angle backward from the mid esophageal long axis view through the two-chamber, mitral commissural and four-chamber views. The transmitral flow velocity profile is examined using spectral pulsed wave Doppler (PWD) to evaluate LV diastolic function in the mid esophageal four-chamber or mid esophageal long axis view by placing the sample volume between the tips of the open mitral leaflets. The sample volume size is kept as small as possible (3-5 mm) and the Doppler beam aligned such that the angle between the beam and the presumed direction of transmitral flow is as close to 0 as possible.

The two transgastric views of the MV are developed by advancing the probe until the transducer is level with the base of the LV. The transgastric basal short axis view provides a short axis view of the MV and is generally obtained at a multiplane angle of 0 degrees by further anteflexing the probe and withdrawing slightly to achieve a plane slightly above (superior to) the transgastric mid short axis view. Better short axis cross-sections of the MV often are obtained with the transducer slightly deeper in the stomach and with more anteflexion in order to orient the imaging plane as parallel to the mitral annulus as possible. Often, however, the cross-section obtained is not perfectly parallel to the annulus, in which case the probe is withdrawn to image the posteromedial commissure in short axis, then advanced slightly to image the anterolateral commissure. In these views of the MV, the posteromedial commissure is in the upper left of the display, the anterolateral commissure is to the lower right, the posterior leaflet is to the right of the display, and the anterior leaflet is to the left. These short axis views of the MV are very useful for determining which portion of the leaflet is abnormal or has abnormal flow. It is also important to examine the transgastric mid short axis view to detect wall motion abnormalities adjacent to the papillary muscles or hypermobility at the papillary muscles indicating rupture of the papillary muscle or its components. The transgastric two-chamber view is developed from the same probe position by rotating the multiplane angle forward to about 90 degrees and is especially useful for examining the chordae tendinae, which are perpendicular to the ultrasound beam in this view. The chordae to the posteromedial papillary muscle are at the top of the display, and those to the anterolateral papillary muscle are at the bottom. Both of the transgastric views of the MV are repeated using CFD.

Aortic Valve, Aortic Root, and Left Ventricular Outflow Tract

The AV is a semilunar valve with three cusps located close to the center of the heart. The aortic root is not a specific structure, per se, but includes the AV annulus, cusps, sinuses of Valsalva, coronary artery ostia, sinotubular junction, and proximal ascending aorta. The LVOT is the outflow portion of the LV just inferior to the AV. All these structures are examined in detail with TEE by using four cross-sections.

The mid esophageal AV short axis view (Figure 3, *H*) is obtained from the mid esophageal window by advancing or withdrawing the probe until the AV comes into view and then turning the probe to center the AV in the display. The image depth is adjusted to between 10 to 12 cm to position the AV in the middle of the display. Next, the multiplane angle is rotated forward to approximately 30 to 60 degrees until a symmetrical image of all three cusps of the aortic valve comes into view. This cross-section is the only view that provides a simultaneous image of all three cusps of the AV. The cusp adjacent to the atrial septum is the noncoronary cusp, the most anterior cusp is the right coronary cusp, and the other is the left coronary cusp. The probe is withdrawn or anteflexed slightly to move the imaging plane superiorly through the sinuses of Valsalva to bring the right and left coronary ostia and then the sinotubular junction into view. The probe is then advanced to move the imaging plane through and then proximal to the AV annulus to produce a short axis view of the LVOT. The mid esophageal AV short axis view at the level of the AV cusps is used to measure the length of the free edges of the AV cusps and the area of the AV orifice by planimetry. CFD is applied in this cross-section to detect aortic regurgitation and estimate the size and location of the regurgitant orifice.

The mid esophageal AV long axis view (Figure 3, *I*) is developed by keeping the AV in the center of the display while rotating forward to a multiplane angle of 120 to 160 degrees until the LVOT, AV, and proximal ascending aorta line up in the image. The LVOT appears toward the left of the display and the proximal ascending aorta toward the right. The cusp of the AV that appears anteriorly or toward the bottom of the display is always the right coronary cusp, but the

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cusp that appears posteriorly in this cross-section may be the left or the noncoronary cusp, depending on the exact location of the imaging plane as it passes through the valve. The mid esophageal AV long axis view is the best cross-section for assessing the size of the aortic root by measuring the diameters of the AV annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta, adjusting the probe to maximize the internal diameter of these structures. The diameter of the AV annulus is measured during systole at the points of attachment of the aortic valve cusps to the annulus and is normally between 1.8 and 2.5 cm. The mid esophageal AV long axis view is repeated with CFD to assess flow through the LVOT, AV, and proximal ascending aorta and is especially useful for detecting and quantifying aortic regurgitation.

The primary purpose of the two transgastric views of the AV is to direct a Doppler beam parallel to flow through the AV, which is not possible from the mid esophageal window. They also provide good images of the ventricular aspect of the AV in some patients. The transgastric long axis view (Figure 3, *J*) is developed from the transgastric mid short axis view by rotating the multiplane angle forward to 90 to 120 degrees until the AV comes into view in the right side of the far field. Sometimes, turning the probe slightly to the right is necessary to bring the LVOT and AV into view.

The deep transgastric view is obtained by advancing the probe deep into the stomach and positioning the probe adjacent to the LV apex. The probe is then anteflexed until the imaging plane is directed superiorly toward the base of the heart, developing the deep transgastric long axis view (Figure 3, *K*). The exact position of the probe and transducer is more difficult to determine and control deep in the stomach, but some trial and error flexing, turning, advancing, withdrawing, and rotating of the probe develops this view in most patients. In the deep transgastric long axis view, the aortic valve is located in the far field at the bottom of the display with the LV outflow directed away from the transducer. Detailed assessment of valve anatomy is difficult in this view because the LVOT and AV are so far from the transducer, but Doppler quantification of flow velocities through these structures is usually possible. Multiplane rotation from this cross-section can achieve images of the aortic arch and great vessels in the far field in some patients.

Doppler quantification of blood flow velocities through the LVOT and AV are performed using the transgastric long axis view or the deep transgastric long axis view. Blood flow velocity in the LVOT is measured by positioning the PWD sample volume in the center of the LVOT just proximal to the AV. Flow velocity through the AV is measured by directing the CWD beam through the LVOT and across the valve cusps. Normal LVOT and AV flow velocities are less than 1.5 meter/second. CFD imaging of the LVOT and AV is useful in directing the Doppler beam through the area of maximum flow when making these velocity measurements.

Left Atrium, Left Atrial Appendage, Pulmonary Veins, and Atrial Septum

Given its anatomic location immediately anterior to the esophagus, the LA is the cardiac chamber that is most consistently and easily imaged. Examination of the LA is initiated with the mid esophageal four-chamber view with the image depth adjusted to approximately 10 cm to maximize the LA size in the display. Withdrawing and advancing the probe several centimeters generates images of the entire LA from its most superior to inferior extent. Near its superior and lateral aspect, the LA is seen to join the left atrial appendage (LAA). The left upper pulmonary vein (LUPV), which enters the LA just lateral to the LAA from an anterior to posterior trajectory, is identified by withdrawing slightly and turning the probe to the left. The left lower pulmonary vein (LLPV) is then identified by turning slightly farther to the left and advancing 1 to 2 cm. The LLPV enters the LA just below the LUPV, courses in a more lateral to medial direction, and is less suitable for Doppler quantification of pulmonary venous blood flow velocity being nearly perpendicular to the ultrasound beam. In some patients, the LUPV and LLPV join and enter the LA as a single vessel. The right upper pulmonary vein (RUPV) is imaged by turning the probe to the right at the level of the LAA. Like the LUPV, the RUPV can be seen entering the LA in an anterior to posterior direction. The right lower pulmonary vein, which enters the LA nearly at a right angle to the Doppler beam, is then located by advancing the probe 1 to 2 cm and turning slightly to the right. The interatrial septum (IAS) is examined next at the mid esophageal level by turning the probe slightly to the right of midline and advancing and withdrawing the probe through its entire superior-inferior extent. The IAS consists of the thin fossa ovalis centrally and thicker limbus regions anteriorly and posteriorly. The IAS is examined with CFD to detect interatrial shunts. Decreasing the scale (Nyquist limit) of the CFD is useful for detecting low velocity flow through an atrial septal defect or patent foramen ovale. Ten milliliters of saline agitated with a small amount of air

leaflet of the TV to the right. These views are repeated with CFD to detect flow abnormalities of the TV.

The transgastric views of the TV are obtained by advancing the probe into the stomach and developing the transgastric RV inflow view as previously described. This cross-section shows the TV in the middle of the display with the RV to the left and the RA to the right. This view also usually provides the best images of the tricuspid chordae tendinae because they are perpendicular to the ultrasound beam. A short axis view of the TV is developed by withdrawing the probe slightly toward the base of the heart until the tricuspid annulus is in the center of the display and rotating the multiplane angle backwards to approximately 30 degrees. In this cross-section the anterior leaflet of the TV is to the left in the far field, the posterior leaflet is to the left in the near field, and the septal leaflet is to the right side of the display. These views are repeated with CFD of the valve.

Right Atrium

The examination of the RA is initiated from the mid esophageal four-chamber view, which allows direct comparison of the relative sizes of the right and left atria. The probe is turned to the right to bring the RA into the center of the display and the image depth adjusted to maximize the size of the RA in the display. The probe is then advanced and withdrawn to examine its entire inferior to superior extent. The mid esophageal bicaval view is next developed by rotating the multiplane angle forward to between 80 and 110 degrees until the SVC appears in the right side of the display and the IVC in the left. This view also provides good images of the right atrial appendage, seen to emanate from the superior, anterior aspect of the RA. The probe is turned to the right and the left from the medial to the lateral borders of the RA to complete the exam.

The RA wall is typically thinner than the LA wall. The Eustachian valve, a normal structure of variable size, is seen at the junction of the IVC and the RA. It is formed by a fold of endocardium that arises from the lower end of the crista terminalis and stretches across the posterior margin of the IVC to become continuous with the border of the fossa ovalis. Occasionally, the Eustachian valve has mobile, serpigenous filaments attached to it, termed the Chiari network, which is considered to be a normal variant.[56] From the mid esophageal four-chamber view the IVC and SVC are examined by advancing or withdrawing the probe from their junctions with the RA to their more proximal portions. If present, central venous catheters or pacemaker electrodes entering the RA from the SVC can be seen with the mid esophageal bicaval view.

Coronary Sinus

The coronary sinus is located in the atrioventricular groove along the posterior surface of the heart and empties into the RA at the most inferior and posterior extent of the atrial septum adjacent to the septal leaflet of the TV. It is imaged in long axis by slightly advancing or retroflexing the probe from the mid esophageal four-chamber view to move the imaging plane through the inferior wall of the LA. A short axis image of the coronary sinus is seen in the mid esophageal two-chamber view to the left of the display in or just superior to the atrioventricular groove. Withdrawing the probe from the transgastric basal short axis view until the coronary sinus appears in long axis is another approach to imaging this structure.

Pulmonic Valve and Pulmonary Artery

Like the AV, the PV is a trileaflet, semilunar valve. Its leaflets, however, are thinner and farther from the esophagus, and therefore are more difficult to image with TEE. The orientation of flow through the PV is roughly perpendicular to flow through the AV and directed from anteriorly to posteriorly and slightly from the patient's right to left. TEE views of the PV are made from three cross-sections. The mid esophageal AV short axis view provides a view of the PV and main PA to the right side of the display. The multiplane angle is rotated back toward 0 degrees and the probe anteflexed or withdrawn slightly to display the bifurcation of the main pulmonary artery with the right PA at the top of the display coursing off to the patient's right. The left PA arches over the left mainstem bronchus after bifurcating from the main PA and is often difficult to visualize with TEE as the airway comes between it and the esophagus. The mid esophageal RV inflow-outflow view displays the PV in long-axis and is useful for detecting pulmonic regurgitation by CFD. The main PA and the PV are seen in the upper esophageal aortic arch short axis view (Figure 3, *T*, see below for description of view) in the left side of the display by turning the probe until these structures come into view. Retroflexing the probe will often improve the view of the PV. The upper esophageal aortic arch short axis view usually allows the Doppler beam to be aligned parallel to flow through the PV and main PA and is therefore useful for measuring blood flow velocities through these structures.

Thoracic Aorta

Most of the thoracic aorta can be routinely imaged with multiplane TEE because it is adjacent to the esophagus as it passes vertically through the mediastinum. However, because the air filled trachea is interposed between the esophagus and the distal ascending aorta and proximal aortic arch, these regions usually cannot be visualized with TEE.[57] Epiaortic scanning can be used to examine these areas through a median sternotomy by covering a high frequency transducer with a sterile sheath and placing it directly on the ascending aorta in the surgical field.

The proximal and mid ascending aorta is seen with TEE through the proximal portion of the mid esophageal window with a probe depth of approximately 30 cm from the incisors, placing the transducer at the level of the right pulmonary artery. The mid esophageal ascending aortic short axis view (Figure 3, *O*) is developed by locating the ascending aorta in the center of the image and adjusting the multiplane angle until the vessel appears circular, usually between 0 and 60 degrees. The probe is advanced and withdrawn in the esophagus to examine different levels of the aorta. The multiplane angle is rotated forward to between 100 and 150 degrees to develop the mid esophageal ascending aortic long axis view (Figure 3, *P*), in which the anterior and posterior walls of the aorta appear parallel to one another. The diameter of the ascending aorta at the sinotubular junction and at specified distances from the sinotubular junction or the AV annulus is measured from the long axis and short axis images.

TEE examination of the descending thoracic aorta is accomplished by turning the probe to the left from the mid esophageal four-chamber view until the circular, short axis image of the vessel is located in the center of the near field of the display producing the descending aortic short axis view (Figure 3, *Q*). The image depth is decreased to 6 to 8 cm to increase the size of the aorta in the display and the focusing depth moved to the near field to optimize image quality. The multiplane angle is rotated forward from 0 to between 90 and 110 degrees to yield circular, oblique, and eventually the descending aortic long axis view (Figure 3, *R*) in which the walls of the descending aorta appear as two parallel lines. The entire descending thoracic aorta and upper abdominal aorta are examined by advancing and withdrawing the probe within the esophagus. The esophagus is located anterior to the aorta at the level of the diaphragm and then winds around within the thorax until it is posterior to the aorta at the level of the distal arch. As the probe is advanced within the esophagus starting from the distal arch, it is turned to the left (posteriorly) to keep the descending aorta in view. The mid and distal abdominal aorta usually are not seen because it is difficult to maintain contact between the transducer and the aorta within the stomach.

Because of the changing relationship between the esophagus and the descending thoracic aorta and lack of internal anatomic landmarks, it is difficult to designate anterior and posterior or right to left orientations of the descending thoracic aorta in the TEE images. One approach to anatomically localize abnormalities within the descending thoracic aorta is to describe the location of the defect as a distance from the origin of the left subclavian artery and its location on the vessel wall relative to the position of the esophagus (eg, the wall opposite the esophagus). Another approach is to record the depth of the lesion from the incisors. The presence of an adjacent structure, such as the LA or the base of the LV, may also designate a level within the descending aorta.

The aortic arch is imaged with the multiplane angle at 0 degrees by withdrawing the probe while maintaining an image of the descending thoracic aorta until the upper esophageal window is reached, at approximately 20 to 25 cm from the incisors, to develop the upper esophageal aortic arch long axis view (Figure 3, *S*). Because the mid aortic arch lies anterior to the esophagus, as the tip of the probe is withdrawn farther, it needs to be turned to the right (anterior) to keep the vessel in view. The proximal arch is to the left of the display and the distal arch to the right. The multiplane angle is rotated forward to 90 degrees to develop the upper esophageal aortic arch short axis view (Figure 3, *T*), and the probe is turned to the right to move the imaging plane proximally through the arch and to the left to move distally.

In some individuals, withdrawing the transducer farther from the upper esophageal aortic arch long axis view can image the proximal left subclavian artery and left carotid artery. The right brachiocephalic artery is more difficult to image because of the interposition of the air filled trachea. As the transducer is withdrawn, it is turned to the left to follow the left subclavian artery distally. The left internal jugular vein lies anterior to and to the left of the common carotid artery and sometimes is seen. In the upper esophageal aortic arch short axis view the origin of the great vessels often is identified at the superior aspect of the arch to the right of the display. The visualization rate of the arch vessels by TEE is lowest

for the right brachiocephalic artery and highest for the left subclavian artery. The left brachiocephalic vein is also often seen anterior to the arch in views of the aortic arch.

Conclusion

Recent advances in echocardiographic instrumentation have increased the diagnostic capabilities of TEE, but have also increased the number of possible approaches for performing a routine TEE examination. Guidelines recommending a methodology for performing a comprehensive intraoperative multiplane TEE examination based on a series of 20 anatomically referenced cross-sectional images are described to promote training in TEE, assist assessment of quality and completeness of individual studies, and facilitate comparison of studies performed at different centers. When possible, the cross-sectional imaging planes were chosen to correspond to those used in transthoracic echocardiography, and an effort was made to choose nomenclature consistent with the recommendations of the ASE Committee on Nomenclature and Standards. We hope that acceptance of a format for performing, acquiring, and archiving intraoperative multiplane TEE examinations will promote a more objective approach to describing the echocardiographic findings that are used to make management decisions and increase the benefit that can be achieved with TEE in the operating room.

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REVIEW ARTICLE

Temporary epicardial pacing after cardiac surgery: a practical review
Part 1: General considerations in the management of epicardial pacing

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Summary

Epicardial wires allow temporary pacing after cardiac surgery. Pacing is often the best, and sometimes the only method of treating temporary rhythm disturbances in this context. Temporary epicardial pacing has evolved from simple one-chamber systems to dual chamber, biatrial, and even biventricular systems. The first part of this two-part review provides an overview of the management of temporary epicardial pacing systems. Factors influencing the placement of the various types of epicardial wires and the routine care of a pacemaker-dependent patient are outlined, followed by a description of the diagnostic use of pacing wires, how to remove wires, and when to consider transition to permanent pacing. Special circumstances such as compatibility with magnetic resonance imaging and intra-aortic balloon pumps are also discussed. The second part of this review will describe the various pacing modes, and solutions to common pacing problems using various adjustable parameters.

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Knowledge of epicardial pacing is required for the intra- and postoperative management of patients undergoing cardiac surgery. While the majority of patients do not require pacing to facilitate separation from cardiopulmonary bypass, it is difficult to select those who may subsequently require pacing during their early postoperative course. Although decisions regarding placement of epicardial wires are seldom made solely by anaesthetists, and indeed much of the management of pacing systems is performed by nursing staff in the ICU, it is essential that anaesthetists have a sound understanding of the indications for, and management of, epicardial pacing. Optimisation of epicardial pacing systems can markedly affect cardiovascular stability, and so the pacemaker interacts with every other therapy controlled by the anaesthetist.

Indications for temporary pacing

Specific electrophysiological conditions that may benefit from temporary pacing are listed in Table 1. Whereas many of these indications are universally accepted (such as third degree heart block), some have yet to achieve consensus. For example, in non-operative patients with congestive cardiac failure with intraventricular conduction delay, it has been recognised for some time that in permanent pacing there is benefit to delivering the pacemaker stimuli to both ventricles [1]. The relative timing of left and right ventricular pacing impulses is usually optimised using echocardiography. This technique has not been widely employed after cardiac surgery to date, but anecdotally can improve cardiac output after valve replacement surgery by 10–30% [2]. No currently available temporary pulse generator can differentially pace left and right ventricles. A satisfactory result can be obtained by connecting both left and right wires to the same output terminals of the pulse generator. As patients with increasingly small physiological reserve are considered for surgery, and as the technological challenge is small, this method of pacing may gain popularity. If so, a pulse generator capable of independently pacing each ventricle may become available.

Table 1 Electrophysiological abnormalities that may benefit from temporary cardiac pacing [25, 26].

Conduction abnormality
Prolonged AV delay (common after cardiac surgery; artificially shortening this using AV sequential pacing may improve mechanical coupling between the atria and ventricles)
AV block: third degree, or type II second degree
During the insertion of a pulmonary artery catheter in a patient with left bundle branch block (although this is noted to be controversial)
Bifasicular block with first degree block
New onset bifasicular block (indicative of active ischaemia)
Prolonged QT syndrome in the presence of significant bradycardia (to prevent torsades de pointes)
Tachycardia
AV junctional tachycardia (common after cardiopulmonary bypass): may be terminated by a brief period of pacing, which can then be discontinued
To terminate re entrant SVT or VT
Type I atrial flutter (rate < 320–340 beats.min^{-1})
Prophylactic
Bradycardia-dependent ventricular tachycardia
Prophylaxis of atrial fibrillation
Other
Sinus bradycardia (as an alternative to pharmacologic treatment)
To restore AV mechanical synchrony in underlying third degree block, AV junctional or ventricular rhythms
Hypertrophic obstructive cardiomyopathy (in particular if effective in reducing systolic anterior motion of the anterior mitral leaflet)
Following heart transplantation

Another new potential role for temporary epicardial pacing is in the prevention of atrial fibrillation, which is extremely common in the period immediately following cardiac surgery (40% in some series). The incidence can be reduced by prophylactic simultaneous pacing of both right and left atria [3]. Bi-atrial pacing in this context was recently recommended by the American College of Chest Physicians [4], but has not yet gained widespread adoption.

Set against the physiological advantage and extra safety afforded by one or more epicardial wires is the small, but definite, risk they entail. Complications of epicardial wires include infection, myocardial damage, perforation, tamponade, and disruption of coronary anastomoses [5, 6]. Unfortunately, these risks have never been well quantified. Many studies have shown that the majority of patients never require pacing. In the light of this, some centres limit their use of epicardial wires to patients requiring pacing immediately prior to chest closure, for indications such as bradycardia with low cardiac output, nodal or junctional arrhythmias, or AV block [7]. Whereas in one study only 2.6% of patients without diabetes, preoperative arrhythmia or the need for pacing to separate from bypass required pacing in the postop period [8], many centres find this risk unacceptably high, and implant at least ventricular wires in all patients. Given the multiple inputs to surgical decision-making, this question is unlikely to be answered in a sufficiently powered randomised controlled trial.

Epicardial pacing wires: atrial and/or ventricular placement

Epicardial pacing wires were historically placed only on the right ventricle. In this position they allow ventricular stimulation, which is usually not as mechanically efficient as endogenous depolarisation. More importantly, there is no co-ordinated atrial contraction. Many patients, especially those with reduced ventricular compliance (as occurs in ischaemia), have a substantially reduced cardiac output in the absence of atrial contraction to assist in ventricular preloading. One study found a 25% increase in cardiac output with atrial or A-V sequential pacing compared to ventricular pacing [9], and the effect was particularly pronounced in patients with low ejection fractions [10]. For this reason, placing wires on the right atrium is often also desirable, but this must be balanced with the risks described above.

Epicardial wires are manufactured with a small needle on one end. This is used to embed the wire in the myocardium, after which the needle is cut off. Some wires are coiled to assist fixation; others can be clipped or loosely sutured in place. A larger needle on the other end of the wire is used to penetrate the body wall, bringing the wire to the surface. The lead should be sufficiently well anchored in the myocardium to avoid premature dislodgement, while still allowing eventual removal by gentle traction. Although the right ventricle is the most commonly used location, there is no agreement on optimal wire position, or even whether the intended position should be tested intra-operatively while there is still the opportunity for repositioning. There are competing influences: some positions give a better haemodynamic profile, and others preserve the longevity of the wires [11]. This question could form the subject of a separate review, and as the decision will seldom rest with the anaesthetist or intensivist, it will not be discussed further here.

Epicardial pacing wires: unipolar and bipolar

Two epicardial wire systems are in common use: unipolar and bipolar (Figs 1 and 2). A unipolar system consists of a single wire (the negative anode) attached to the epicardium, with the positive electrode attached at a distance in the subcutaneous tissues. Which wire is which must be clearly marked at the ends protruding through the skin. The alternative bipolar system involves a single wire with two conductors insulated from one another, which both

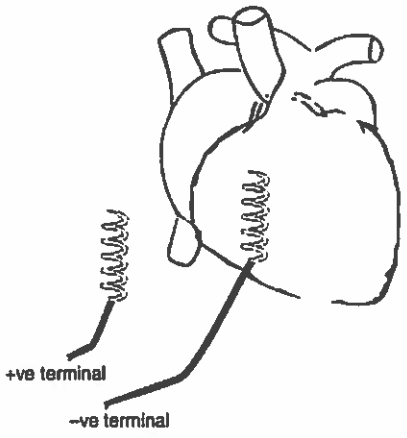

Figure 1 Unipolar epicardial pacing electrodes.

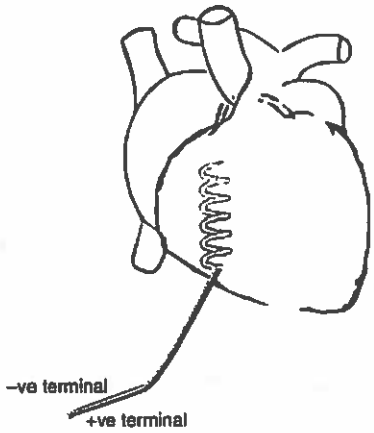

Figure 2 Bipolar epicardial pacing electrodes.

run to the epicardial surface. The negative anode is usually the more distal. The ends of the conductors are 8 mm apart in one commonly used wire (the Medtronic bipolar coaxial 6495: Medtronic, Minneapolis, MN). As the current must travel a much shorter distance between electrode tips, the electrical potential required to bring the myocardium to threshold is less than in the unipolar system. This makes bipolar electrodes more suitable for use in dual chamber applications, as the likelihood of between-chamber interference is less when smaller potential differences are applied. As explained below, epicardial wires are also used by pacemakers to sense endogenous electrical activity. The smaller current path of bipolar electrodes makes them less susceptible to electrical interference when performing the sensing function. The larger current in a unipolar system creates much larger pacing spikes on the surface ECG.

By informal convention, wires attached to the right atrium are brought out through the skin on the right of the sternum, and those from the right ventricle emerge on the left. Again, the wire that should be connected to the negative terminal of the pulse generator (epicardial for unipolar; distal epicardial for bipolar) should be marked; this is achieved by colour coding wires or with adhesive tags, according to local convention.

A major problem with all epicardial wires is the development of an inflammatory reaction around the wire/myocardium interface. Inflammation is accelerated when higher energy is applied, which is one reason to limit pacemaker energy output. Unfortunately, the only remedy for increased resistance is the application of increased current or voltage – which further increases the inflammation. As bipolar electrodes require less energy to begin with, they may have a greater longevity in pacing compared to a unipolar system [12, 13]. Epicardial wires usually fail to sense and capture after a few days. Increases in stimulation threshold typically occur after 4 days in both atrial and ventricular wires [14], and failure to pace is observed in > 60% right and > 80% left atrial wires after 5 days [15]. Other than minimising the initial energy delivered to the wire, techniques employed to extend wire longevity include variations in placement site (which must be balanced against haemodynamic optimisation) and the use of steroids. High dose systemic steroids are sometimes given to patients whose permanent pacemaker wires exhibit rapidly increased thresholds in the first few days. However, for patients with permanent pacing systems, this has largely been replaced by the use of steroid-eluting endovascular pacing wires. At present, steroid-eluting epicardial wires are only available for permanent placement in paediatrics. The efficacy of systemic steroids in extending the longevity of temporary pacing wires has not been studied.

Diagnostic use of pacing wires

If not required for the transmission of a pacemaker impulse, atrial pacemaker wires can be used to create an atrial electrogram (AEG). Though seldom used, in some circumstances the atrial electrogram may be the best method of differentiating atrial and junctional arrhythmias, and in defining the nature of an AV block.

On many modern ECG recorders, there are three leads made specifically for this purpose: two for the bipolar atrial wires and a third for a skin electrode on the patient's flank. When the AEG channel is set to lead I, the potential between the tips of the two atrial electrodes is recorded (a 'bipolar' recording). This shows a large deflection with atrial depolarisation, but almost no signal with ventricular depolarisation. When set to lead II or III, the potential between one of the wires and the skin electrode is recorded (a 'unipolar' recording). In comparison to the bipolar recording, a larger ventricular signal is recorded. Alternatively, on an

ECG machine without specific AEG leads, the connectors that usually go to the right and left arm leads can instead be attached to the bipolar atrial pacing wires. In this arrangement, a bipolar AEG will be similarly recorded in lead I, and a unipolar AEG in leads II or III. The only disadvantage of this system is the inability to record simultaneously from the standard chest leads; for this reason some recommend connecting the pacing wires to the chest leads instead.

Analysis of the AEG is useful in a number of situations, particularly in some forms of heart block. Sinus node exit block (resulting in dropped P waves), second degree AV block, and third degree block with isorhythmic AV dissociation are all more easily diagnosed. The AEG allows timing of sinus depolarisation as opposed to P wave activity and also the identification of sinus or other atrial activity that might otherwise be lost within an ectopic depolarisation. A more detailed treatment of the use of AEGs is presented elsewhere [16].

Alternatives to epicardial pacing wires

Epicardial wires are not the only means of temporary pacing after cardiac surgery. Alternative means of delivering the potential difference from the pacemaker box to the myocardium include a temporary transvenous wire, an electrode attached to an oesophageal probe, and transcutaneous electrodes. It is possible to pace the atrium using a temporary transvenous 'J-tip' wire lodged in the right atrial appendage, but this is technically difficult to place. Temporary transvenous wires are more commonly used to stimulate ventricular depolarisation. Oesophageal and transcutaneous pacing may depolarise large areas of the myocardium simultaneously, but the effect is usually similar to ventricular pacing. If pacing is an anticipated requirement after cardiac surgery, epicardial wires are the preferred technique. They more reliably sustain capture and are less prone to dislodgement and infection than a temporary transvenous wire, and do not require sedation as often do transcutaneous pacing or an oesophageal probe.

General care of a patient with epicardial wires

Epicardial pacemaker wires are a low resistance connection to the heart. This creates the potential for microshock-induced arrhythmia, particularly ventricular fibrillation. Patients must be nursed in a cardiac-protected electrical environment, which implies adequately isolated electrical equipment and measures to prevent build-up of static electricity (absence of carpet, for example). Wires should only be handled with non-conductive gloves, and a large metal object (the bed, for example) should be touched first to discharge static potential prior to touching the wires. The wires should be protected in a non-conductive container (for example, a plastic syringe barrel) when not in use.

To minimise unwanted electrical interference, by default, modern digital ECG monitors apply a high frequency filter to the incoming signal. In most cases this filters out the brief pacemaker spike, making it difficult to tell whether a pacing stimulus is being delivered. This can be overcome on most modern monitors by selecting the 'pacemaker' mode, which will record each spike, often highlighted with a marker. The small skin potentials created by bipolar leads in particular may be difficult to detect, and it may be necessary to inspect a variety of leads. Extracardiac, high frequency interference may become problematic, in which case the monitor can be returned to its usual mode after pacing diagnostics have occurred.

Electrical pacemaker output does not necessarily equate to mechanical capture of the myocardium, and as such it is helpful to have a monitor demonstrating the timing of cardiac contraction. An arterial pressure tracing or pulse oximeter waveform are the most readily available, and can usually be printed next to the ECG on a cardiac rhythm strip. This is much more helpful than attempts at analysing the moving screen image. If attempting to find pacing settings that produce optimal cardiac output, it is also helpful to have a high time-resolution monitor of cardiac output, such as echocardiography, continuous cardiac output pulmonary artery catheter, mixed venous oxygen, or one of the pulse contour analysis devices.

Pacemaker-dependent patients are at risk of pacemaker system failure or pacemaker-generated arrhythmia, and as a minimum should have continuous ECG monitoring and immediate access to a cardiac defibrillator with the capacity for transcutaneous pacing.

Daily checks

Every day (and ideally with each change of nursing shift), a number of checks should be made on the pacing system. If the patient is cardiovascularly unstable for reasons unrelated to pacing, these other problems should be addressed before altering any pacing settings.

Underlying rhythm

The need for ongoing pacing should be regularly reassessed. This is best done by turning down the pacing rate and allowing the endogenous rhythm to appear. This is a better strategy than turning down the pacing energy output until capture is lost, as there may be no underlying rhythm at all. It is occasionally impossible to re-establish capture once it has been lost –

leading to potential disaster if the underlying rhythm is inadequate.

Sensitivity

The 'sensitivity' (as numerically represented on the pacing generator) is the minimum current that the pacemaker is able to sense. A lower number thus corresponds to a greater sensitivity. This paradox causes considerable confusion.

To check the sensitivity, the pacemaker rate should be set below the endogenous rate (if present), and placed in VVI, AAI or DDD modes. An explanation of the various pacing modes is presented in part 2 of this review. The sensitivity number is increased (making the pacemaker *less* sensitive) until the sense indicator stops flashing. Pacing should then occur asynchronously in the chamber being tested. This should not be allowed to persist for too long because there is a risk of precipitating atrial or ventricular fibrillation if the pacing spike is delivered late in the repolarisation phase (an artificial 'R-on-T'). The sensitivity number is then turned down (making the pacemaker more sensitive) until the sense indicator flashes with each endogenous depolarisation (in time with the P or R wave on the surface ECG). The number at which this first occurs is the pacing threshold. Most institutional protocols recommend leaving the pacing generator set at half the pacing threshold, to allow for detection of abnormally small signals, and for the possibility that perilead fibrosis over the course of the day will reduce the current transmitted to the pacemaker.

If there is no endogenous rhythm, it is impossible to determine the pacemaker sensitivity, in which case the sensitivity is typically set to 2 mV.

As explained in Part 2 of this review, if the sensitivity value is too low (i.e. the pacemaker is too sensitive), there may be inappropriate sensing of far field signals such as R or T waves, which may inappropriately inhibit pacing.

Capture threshold

The capture threshold is the minimum pacemaker output required to stimulate an action potential in the myocardium. The capture threshold should not be checked if there is no underlying rhythm (which will have been established in the first step of these checks), for fear of losing and not being able to regain capture. If this is the case, careful continuous attention should be paid to the development of occasional missed beats, which (other causes having been excluded) will indicate a rise in the capture threshold and a need to increase the pacing output.

If it is safe to check the pacing threshold, the pacemaker rate should be set above the patient's endogenous rate, such that the chamber of interest is being consistently paced. The pacemaker energy output is then reduced until a QRS complex no longer follows each pacing spike. This is the capture threshold. Typically, the output is left at twice the threshold, again to allow a margin of safety. However, if the threshold is > 10 mA, the margin of safety is set to a lesser value, so as not to accelerate fibrosis at the lead/myocardium interface.

Rate

Cardiac output is the product of stroke volume and heart rate. After a point, as heart rate increases, stroke volume falls, so each patient will have an optimal heart rate for cardiac output. However, increased cardiac output driven by heart rate comes at the cost of increased oxygen consumption. In practice, the optimal heart rate is rarely accurately titrated to cardiac output and is usually left at 80–90 beats.min^{-1} after the above adjustments are made. As a transition to complete reliance on endogenous rhythm, some advocate a period of 'backup' pacing (with the pacemaker set at around 40 beats.min^{-1}), which allows the patient to remain in an endogenous rhythm until the point of significant haemodynamic compromise. This approach has the advantage of allowing the sensing threshold of the pacemaker to be continuously monitored. If full pacing is again required, it can be commenced with the confidence that the pacing threshold will not have become too excessive.

Other pacing variables

The battery indicator should be checked. The appropriate pacing mode for the patient should be reassessed as described in part 2 of this review. The less commonly adjusted variables, such as the maximum tracking rate, AV interval, and post ventricular (pacing spike) atrial refractory period (PVARP) should be noted. These are also described in part 2. In practice, once these have been set (or left on automatic) and the pacemaker is functioning well in the desired mode, there is no reason to retest regularly whether they remain optimal.

Pulse generators in common use

The Medtronic 5388 (Medtronic, Minneapolis, MN) and St Jude Medical 3085 (St Jude Medical, Sylmar, CA) are examples of currently marketed dual chamber temporary pulse generators, and the St Jude 3077 (St Jude Medical) and Medtronic 5348 (Medtronic) are single chamber devices (Fig. 3). The manufacturers' instructions for setting the various parameters are readily available in electronic format [17–19]. The different pacing modes and other variables that can be adjusted are the subject of the second part of this review. Typical settings are shown in Table 2.

pacing. Whether a patient with epicardial wires in place, which are not being used, may have an MRI scan is more controversial. There is at least theoretical concern that a current could be induced in the epicardial wire by either the pulsating movement of the wire in the magnetic field, or the effect of the MRI radiofrequency pulse. Such a current could potentially precipitate an arrhythmia [22]. Energy transfer to the wire will also cause heating, with an increase of up to 20 °C at the electrode tip [23]. For this reason, most authorities agree that MRI is not advisable while epicardial leads remain in place. In contrast, patients with retained epicardial wires that have been cut off at the skin (and hence have no long 'antennae') have undergone MRI safely [24].

Intra-aortic balloon pump (IABP)

If the IABP is timed according to a cardiac monitor with the high frequency filter disabled (to allow pacing spikes to become visible), the spikes may be misinterpreted by the IABP as QRS complexes. In the case of isolated ventricular pacing, the adverse effect of this small timing difference can be easily overcome by manual adjustment of the IABP timing parameters. However, if both atrial and ventricular spikes are misread as two QRS complexes, this will not be possible to correct. Either the IABP should be timed according to the arterial pulse, or the high frequency filter applied. This problem is lessened with bipolar leads, which have a smaller ECG representation than unipolar leads.

Conclusion

The first part of this review has concentrated on the selection and routine management of temporary epicardial pacing systems. The second part will describe the indications for the various pacing modes and the optimal methods of troubleshooting the most common problems.

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REVIEW ARTICLE

Temporary epicardial pacing after cardiac surgery: a practical review
Part 2: Selection of epicardial pacing modes and troubleshooting

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Summary

The first part of this two-part review discussed the indications for various types of epicardial pacing systems and an overview of the routine care of a pacemaker-dependent patient. Dual chamber temporary pulse generators now feature many of the refinements developed initially for use in permanent pacemakers. Few of these are utilised in the immediate postoperative period, often solely due to lack of familiarity with all but basic functions. The second part of the review deals with the selection of pacing modes. Troubleshooting real and apparent pacemaker malfunctions, including manual adjustment of parameters such as the AV interval, post atrial refractory period and upper rate limit, to avoid over- and undersensing, cross-talk and pacemaker-mediated tachycardia will also be addressed.

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Epicardial pacing has evolved considerably from simple single chamber systems with very few adjustable parameters, to complex dual chamber systems that incorporate most of the functions of permanent pacemakers. Dual chamber pacing in particular produces many technical challenges that are not immediately apparent. Fortunately, knowledge of the algorithms used by manufacturers to overcome these challenges is seldom required in the context of temporary epicardial pacing. It is tempting to ignore the complexity of modern temporary pulse generator design and fall back on suboptimal modes of pacing should any complication arise. This is an unfortunate approach, as there is often substantial benefit to be gained from adjusting the pulse generator settings correctly. How often temporary epicardial pacemakers require troubleshooting is not known [1]. The only published figure is a 0.4% incidence in 1675 patients over 18 months [2]. Most pacemaker texts deal with permanent pacemakers and only briefly cover much of the knowledge required to operate a temporary epicardial pacing system.

Pacing settings and specific indications: antibradycardia modes

Permanent pacemakers are classified using the North American Society of Pacing and Electrophysiology (now the Heart Rhythm Society)/British Pacing and Electrophysiology Group Generic Code (the NBG code), which (as revised in 2002) [3] consists of five 'positions' (Table 1). Aspects of permanent pacing relevant to anaesthesia were recently reviewed [4]. Only the first three NBG positions are relevant to temporary epicardial pacemakers. A description of pacing modes that ends with a description of the NBG code is clearly incomplete, as only a few of the theoretical possibilities make logical sense or are of any clinical use. The pacing modes applicable to temporary epicardial pacing are described below.

Single chamber pacing modes

If wires leading to only a single chamber (atrium or ventricle) are in place, then the pacemaker can be used in

Table 1 NBG code. Only the first three positions are relevant to temporary epicardial pacemakers.

I	II	III	IV	V
Chamber paced O = none A = atrium V = ventricle D = dual (A + V)	Chamber sensed O = none A = atrium V = ventricle D = dual (A + V)	Response to sensing O = none T = triggered I = inhibited D = dual (T + I)	Rate modulation O = none R = rate modulation	Multi site pacing O = none A = atrium V = ventricle D = dual (A + V)

one of only five modes: AOO, VOO, AAI, VVI, or VVT.

AOO (atrial asynchronous)

Pacing spikes are delivered to the atrium at a set rate, regardless of electrical activity in either chamber of the heart. Stimulation of ventricular contraction in this mode relies on intact conduction through the AV node. There is usually a mechanical advantage in preserving the physiological relationship of atrial to ventricular contraction. There is a risk in asynchronous atrial pacing that a pacing spike might be delivered in the repolarisation phase of an endogenous beat, which may precipitate atrial fibrillation. The refractory period of the AV node should prevent the depolarisation from being conducted to the ventricle, which should prevent VF. Because of this risk of atrial fibrillation, use of AOO is usually restricted to stable bradycardia, where the pacemaker rate reliably exceeds the endogenous rate. If this is the case, the pacemaker spike should always occur before any endogenous impulse would have been generated.

Indications

- Bradycardia with intact AV node conduction, in situations where synchronous modes are contra-indicated. This rarely means anything other than during use of electrocautery, which can interfere with sensing.

Limitations

- Contra-indicated in atrial tachycardia, atrial fibrillation/flutter (due to inability to capture the atrium), and AV node block.

VOO (ventricular asynchronous)

Analogous to AOO, pacing spikes are delivered to the ventricle, regardless of the endogenous electrical activity of the heart. As in the atrium, there is a risk that a ventricular pacing spike might be delivered while the ventricle is in the repolarisation phase of an endogenous beat. This is the classic 'R-on-T' phenomenon, known to precipitate ventricular fibrillation (VF).

Indications

- Bradycardia without reliable AV node conduction, in situations where synchronous modes are contra-indicated (e.g. with electrocautery).
- In an emergency, to preserve cardiac output in the case of malfunction of pacing in one of the more sophisticated pacemaker modes, while the cause of the malfunction is rectified. For this reason, some pulse generators have this as a 'rapid access' function.

Limitations

- Competition with intrinsic rhythm; possibility of R-on-T VF.

AAI (atrial demand)

The pulse generator has a sensing 'timing cycle', which is determined by the rate set on the pacemaker. If no endogenous depolarisation is sensed by the end of this timing cycle, a pacing spike is delivered to the atrium. However, if an endogenous depolarisation is sensed, no spike is delivered, and the timing cycle begins again. There is one further level of complexity to appreciate. After an atrial depolarisation (either endogenous or a pacing spike), a pacemaker atrial refractory 'blanking' period begins, during which there is essentially no sensing at all. A depolarisation occurring during this time does not reset the timing cycle. This is required to prevent atrial after-depolarisations resetting the timing cycle.

Ventricular ectopics are potentially problematic during AAI pacing, as no ventricular depolarisations are sensed. The atrial stimulus can potentially be conducted to the ventricle whilst it is in the repolarisation phase of a ventricular ectopic endogenous beat, precipitating R-on-T VF. Fortunately, this is usually prevented by the AV node, which has entered its refractory period following the ventricular ectopic, and so blocks transmission of the atrial impulse.

Indications

- Bradycardia, with an endogenous atrial rhythm (or frequent ectopics) sufficiently quick to compete with the pacemaker rate.

Limitations

- As for AOO, AAI is contra-indicated in atrial tachycardia, atrial fibrillation/flutter (due to inability to capture the atrium), and AV node block.

VVI (ventricular demand)

VVI is the same as AAI, except the sensing and pacing is in the ventricle. As with VOO, during a paced beat there is no co-ordinated atrial contraction, which can significantly reduce cardiac output.

Indications

- Similar to AAI, but where there is no reliable AV node conduction to the ventricle.
- Bradycardia with AV block, sick sinus syndrome, atrial fibrillation, atrial flutter.
- Overdrive suppression of ectopic beats.

Limitations

- No atrial contribution to ventricular preload.

Dual chamber pacing modes

If wires leading to both atrium and ventricle are in place, the pacemaker can be used in one of the single chamber modes listed above, in addition to any of the following: DOO, DVI, DDI, DDD and, in some pulse generators, VDD. DDD is by far the most useful and commonly used, but understanding its timing cycles is facilitated by a preliminary discussion of DOO, DVI and DDI.

DOO (AV sequential asynchronous)

First the atrium and then the ventricle receive a pacing spike, with the spikes separated by a programmed AV delay (simulating the delay in the AV node during an endogenous beat, and improving mechanical efficiency). There is the same risk of R-on-T VF as in the other asynchronous modes (AOO and VOO). While mechanical efficiency is better than in VOO, the ventricular spike spreads throughout the ventricle in an abnormal manner compared to that of an endogenous impulse through an intact conducting system. Mechanical efficiency of the ventricular contraction is usually less. AOO is thus preferred if the conducting system is intact.

Indications

- As for VOO, but in particular in patients who derive substantial haemodynamic benefit from the contribution of atrial contraction to ventricular preload.

DVI (AV sequential, ventricular inhibited)

In the absence of any intrinsic cardiac depolarisation, the pacemaker behaves like a DOO. There is no sensing in the atrium. When an endogenous ventricular depolarisation is sensed (following either an atrial pacing spike or endogenous atrial depolarisation), the ventricular spike is inhibited. If a ventricular depolarisation is sensed at a time before the delivered atrial spike should have arrived, it is assumed that there has been an endogenous depolarisation in the atrium that has been conducted to the ventricle. As this endogenous rhythm is likely to be mechanically more efficient than pacing, the timing cycle is reset, delaying the next atrial spike and allowing the possibility of ongoing conducted endogenous atrial depolarisations completely inhibiting atrial and ventricular output.

There is a possibility that the atrial spike will not be inhibited when in fact there is an endogenous atrial rate. This may lead to competition if the atrium is beating at a faster rate, which (as in AOO etc.) can precipitate atrial fibrillation. For this reason, DDI or DDD are preferable to DVI in patients with atrial rates high enough to compete with the pacing rate.

There is another potential problem with all ventricular sensing modes. If the ventricular sensitivity is too high, it is possible that the atrial depolarisation might be inappropriately sensed as ventricular activity and the ventricular spike inhibited. If there is no AV conduction, there will be no ventricular contraction. This is called *cross-talk* and is discussed in detail in the next section.

There is one particular use for DVI pacing. If a ventricular paced beat is conducted retrogradely up the AV node, an atrial sensing wire might interpret this as endogenous atrial activity, which in DDI and DDD modes would precipitate a release of a ventricular spike. This is pacemaker-mediated tachycardia (discussed below), which has a number of solutions. The solution requiring the least understanding of timing cycles is to switch the pacemaker to DVI, ideally while consideration is given to a better remedy.

Indications

- Seldom used. Immediate treatment of pacemaker-mediated tachycardia.

Limitations

- Contra-indicated in atrial tachyarrhythmias.
- Risk of precipitating atrial fibrillation.

DDI (AV sequential, non-P-synchronous, with dual chamber sensing)

DDI improves on DVI by adding atrial sensing. This prevents the possibility of the atrial pacing spike competing with an endogenous atrial rhythm. The maximum rate of delivery of pacing spikes is the same as the minimum rate set on the pulse generator. (NB: the 'minimum rate' is commonly just referred to as the 'rate'

of the pacemaker, but this must be distinguished from the upper rate limit, discussed later). This is the difference between DDI and DDD (below). The maximal rate in DDD is not the set lower rate limit; instead the ventricular pacing spikes can be delivered at a higher rate so as to 'track' atrial activity. DDI is thus better than DDD in the context of rapid atrial arrhythmias, as in DDD the ventricle will potentially be paced too rapidly. Indeed, most permanent pacemakers set to DDD will automatically change to DDI if a too-rapid atrial rate is detected. Temporary pulse generators will not do this (but do have an automatic defence against tracking of a too-rapid atrial rhythm (see below)). Postoperatively, patients so commonly develop atrial tachyarrhythmias (many of whom will have been paced in DDD) that at least one pulse generator (the Medtronic 5388: Medtronic, Minneapolis, MN) identifies DDI with a unique indicator to facilitate rapid changeover to this mode.

Indications

- As for DDD pacing, but in patients with paroxysmal atrial tachyarrhythmias.

Limitations

- Compared to DDD, with no atrial tracking there may be no increase in pacemaker rate in the context of physiologically appropriate sinus tachycardia.

DDD (AV universal)

This is the most commonly used mode in patients with both atrial and ventricular wires. The pacemaker waits for an endogenous atrial depolarisation. If none is sensed, an atrial spike is delivered. The pacemaker then waits for an endogenous ventricular depolarisation, in response to either the atrial pacing spike or endogenous atrial depolarisation, should this have occurred. If there is no endogenous ventricular depolarisation, a ventricular pacing spike is delivered.

As explained above, there is a risk of ventricular tracking of atrial tachyarrhythmias in DDD. Most temporary pulse generators address this risk by allowing the setting of a 'maximum tracking rate' or 'upper rate limit', as explained in detail below.

Indications

- All indications for pacing, with the exception of atrial tachyarrhythmias.

VDD (P wave synchronous)

This mode is unusual amongst the dual chamber modes in that only the ventricle is paced. The pulse generator inhibits its ventricular spike in response to a sensed ventricular depolarisation. A sensed atrial depolarisation, however, triggers a ventricular spike if an endogenous ventricular depolarisation is not sensed. If there is no endogenous atrial depolarisation, a ventricular pacing spike is delivered.

Indications

- The specific indication for VDD is AV node block with an intact sinus node. The pacemaker acts as a conduit around the AV node. There is the same risk of tracking an atrial tachy-arrhythmia as in DDD, and the same safeguards must be in place to prevent this.

A summary of the various antibradycardia pacing modes and their indications is presented in a decision-tree approach in Figure 1.

Triggered modes

Triggered modes (VAT, AAT, DAT) are more commonly employed in permanent pacemakers in special circumstances, but are available in some temporary external pulse generators (e.g. the Oscor PACE 203H, Oscar Inc, Palm Harbor, FL, USA). Triggered modes prevent inappropriate inhibition from oversensing (such as with electrocautery) [5], but in practice asynchronous modes are more commonly used for this indication.

Whenever contemplating overdrive pacing, it is essential to confirm that the atrial output of the pulse generator is indeed connected to the atrial wires, as such rapid pacing of the ventricle is likely to precipitate ventricular tachycardia. Even if the wires are correctly attached, the current may be high enough to stimulate the ventricle directly: this must be checked by setting the pacemaker 10–15 beats above the ventricular rate and ensuring the ventricle does not track [7].

Pacing settings and specific indications: antitachycardia modes

Tachyarrhythmias are common following cardiac surgery. The presence of epicardial pacing wires allows many of these to be effectively treated by means other than pharmacotherapy or DC cardioversion. The exceptions are ventricular and atrial fibrillation and sinus tachycardia, which cannot be controlled by pacing. When attempting overdrive pacing, ventricular tachycardia or fibrillation may result and so DC cardioversion must be immediately available.

AV junctional tachycardia

AV junctional tachycardia (with rates around 100–120 beats.min^{-1}) is common following cardiac surgery [5], and is effectively managed using atrial (AOO or AAI) or AV sequential overdrive pacing (DOO or DDD). The pacing rate is increased to around 120% of the endo-

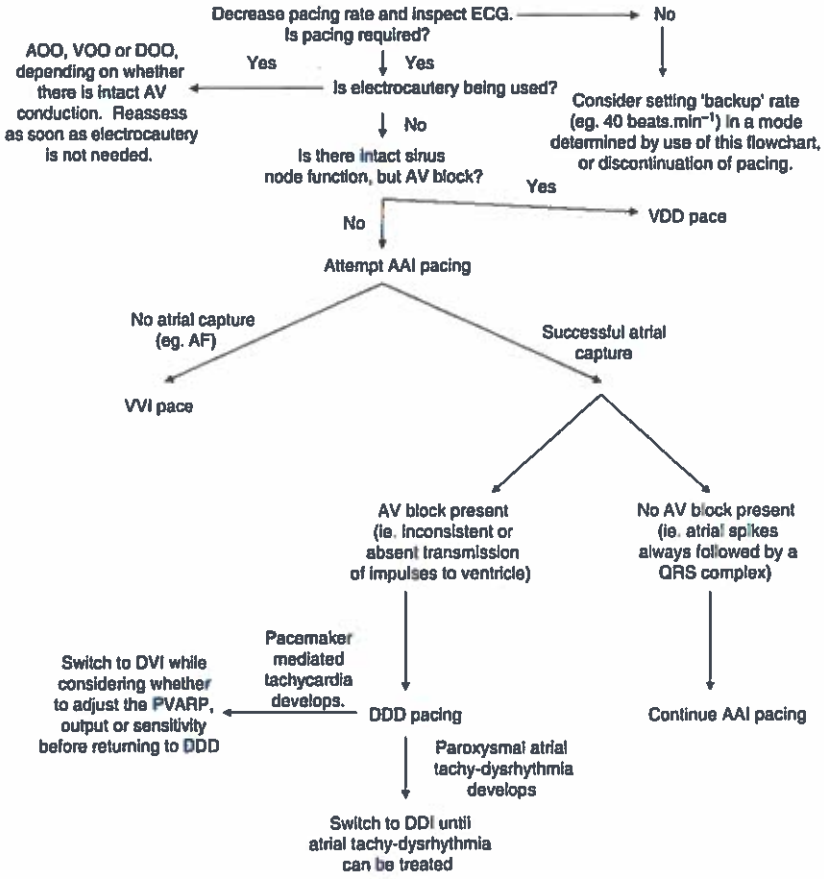

Figure 1 Decision tree approach to setting the dual chamber epicardial pacing mode.

genous rate. Once 1 : 1 capture of the myocardium is achieved, the pacemaker rate is gradually reduced. As the pacemaker rate falls below the endogenous sinus rate, a stable sinus rhythm is often established.

Paroxysmal re-entrant SVT

Paroxysmal re-entrant supraventricular tachycardia can also be terminated by atrial pacing: either 'underdrive' pacing (at less than the SVT rate) if the pacing spike induces a refractory period in the segment of the myocardium forming the re-entrant loop; or 'overdrive', where the atrial pacemaker is set above the SVT rate in a manner similar to that described for AV junctional tachycardia. The myocardium in the re-entrant limb is depolarised by an anterograde pacing spike before re-entrant depolarisation of the preceding beat arrives; when it does arrive, the myocardium is in its refractory state, so the re-entrant pathway is effectively blocked. After capture, the rate can be gradually reduced to the desired target [6].

Atrial flutter

Overdrive pacing is effective in type I atrial flutter (< 320–340 beats.min^{-1}), but not in type II with rates in excess of this [5]. The pacemaker is set to just above the flutter rate and then gradually increased until the atrial complexes on the surface ECG change morphology. Typically, this will be 10–20 beats.min^{-1} faster than the flutter rate [6] and indicates the flutter has been terminated. The pacemaker is then slowed to an acceptable rate, or below the endogenous sinus rate. Failure of this technique is usually attributable to insufficiently rapid pacing rates, insufficient duration of atrial pacing, or insufficient stimulus strength.

Supraventricular tachycardias with rapid ventricular response: failure to revert to sinus rhythm

Occasionally after attaining 1 : 1 capture with overdrive pacing, sinus rhythm is not re-established on turning down the rate and the SVT with rapid ventricular response persists. In this situation it may be preferable to induce atrial fibrillation by rapid atrial pacing (up to 800 beats.min^{-1}, depending on the pulse generator). Termination of rapid atrial pacing will sometimes lead to sinus rhythm where other techniques have not [6]. If not, remaining in electrically induced rapid atrial fibrillation

may be preferable if the AV block is sufficiently high to make the ventricular rate slower than that when in SVT.

Ventricular tachycardia

There is some suggestion that either underdrive or overdrive ventricular pacing can terminate ventricular tachycardia [6], but there is a risk of precipitating VF by doing this. DC cardioversion remains the accepted standard of care for VT.

Common pacing system faults

Failure to pace

'Failure to pace' occurs when there is no electrical output at the pacing wire tips when the set pacing mode calls for such an output. This is distinguished from 'failure to capture' (below) by the absence of pacing spikes in the surface ECG, and a heart rate less than that set on the pacemaker as the minimum rate. Failure to pace can be due to:

- lead malfunction or an unstable connection between the lead and the pulse generator;
- insufficient power in the pulse generator (which should be apparent from the battery indicator).
- Cross-talk inhibition (see below).
- Oversensing (as distinct from cross-talk). Any electrical potential across the sensing wires can be misinterpreted as endogenous depolarisation, with resulting inhibition of the pacing spike. Such potentials can be caused by electromagnetic interference (from electrocautery, or even mobile telephones [8]), skeletal muscle activity (including fasiculations caused by suxamethonium), or intermittent contact between the pacing wires, which can generate small 'make and break' potentials [9].
- (Apparent failure to pace) Detection of endogenous extrasystoles, which are of insufficient amplitude to register on the surface electrode, but which inhibit pacemaker output.

An appropriate first response to failure to pace is to switch to an asynchronous mode. The first two cases above can be distinguished by noting that no pacemaker spikes are delivered after making this change.

Failure to capture

'Failure to capture' is when there is electrical output at the pacemaker wire tips (confirmed by visible pacing spikes on the ECG), but this does not cause a cardiac contraction, as shown by the absence of a mechanical cardiac impulse on the arterial pressure or pulse oximeter waveform. The cause is an increase in the resistance at the wire/myocardium interface, most commonly due to fibrosis around the pacemaker lead. Additional factors contributing to increased threshold may be:

- myocardial ischaemia;
- electrolyte imbalance, particularly hyperkalaemia, acidosis and alkalosis;
- following defibrillation;
- medications, including flecainide, moricizine, propafenone, sotalol, and possibly beta blockers, lidocaine, procainamide, quinidine and verapamil [9].

Failure to capture (or a progressively increasing pacing energy requirement) is the commonest problem encountered with temporary epicardial pacing. Correction of any of the exacerbating causes listed above should be attempted. Reversing the polarity of both bipolar and unipolar lead systems may help. In a bipolar lead system, the distal (negative) electrode usually develops fibrosis first. If this occurs, the proximal electrode may remain adequate to use as a unipolar electrode (now connected to the negative terminal), with a return electrode inserted into the subcutaneous tissues. Clearly these techniques are at best a temporary solution to impending irrecoverable failure to capture. If the threshold is progressively increasing and the patient is dependent on the pacemaker, it is wise to place an alternative means of stimulus delivery (such as a temporary transvenous wire) before capture is entirely lost.

Failure to sense

In essence the same mechanisms of failure to capture can cause failure to sense [9]. True failure to sense must be distinguished from normal pacemaker function with inappropriate settings, such as over-long refractory periods.

Uncommon pacemaker faults

Cross-talk

In a dual chamber system with atrial and ventricular pacing and ventricular sensing (DVI, DDD, DDI), it is possible that the atrial pacemaker spike will be sensed by the ventricular wire, misinterpreted as a ventricular depolarisation and thereby inhibit the ventricular pacemaker output. In the absence of AV conduction, this will lead to ventricular standstill. In atrial sensing systems, the ventricular spike can be similarly misinterpreted, leading to inhibition of the atrial spike; however, ventricular pacing persists, making this less serious. Of more concern is the system that allows such atrial sensing 'cross-talk' to trigger a ventricular pacemaker spike. This will cause a form of pacemaker-mediated tachycardia, which is discussed in detail in the next section.

The simplest approaches to eliminating cross-talk are to:

- reduce the sensitivity (increase the lowest power that is sensed) in the atrial or ventricular channel; or
- reduce the power delivered to the ventricular or atrial pacing wire.

However, given the possibility of ventricular standstill, manufacturers have incorporated a number of features to guard against inappropriate inhibition of output in the ventricular wires.

A modification of dual chamber pacing – 'committed pacing' – whereby an atrial spike is always followed by a ventricular spike, regardless of endogenous ventricular activity. This mode was developed for use in unipolar systems, where the large atrial spike is commonly misinterpreted as endogenous ventricular activity. However, as unipolar dual chamber systems are now rarely used, most temporary and permanent pulse generators do not function in this manner.

A ventricular blanking period immediately after atrial depolarisation in which ventricular depolarisation is ignored by the pacemaker. Only after this period passes does the pacemaker become alert for a ventricular depolarisation. If one occurs, it is assumed to be a conducted beat; if not, a ventricular spike is delivered. A problem might occur if a premature ventricular complex occurred within the ventricular blanking period. The pacemaker spike (having not been inhibited) could theoretically fall within the T wave of the premature beat, causing R-on-T fibrillation. In practice, the spike is almost always delivered sooner than the repolarisation phase of a premature complex that has fallen within the blanking period.

Ventricular safety pacing. If the ventricular lead senses depolarisation after the blanking period, but before the period in which it looks for ventricular depolarisation normally transmitted through the AV node (i.e. the 'cross-talk sensing window') the pacemaker assumes that there is either cross-talk or a PVC. Not knowing which, it emits a ventricular spike a little earlier than the usual AV delay. If the problem is cross-talk, this leads to mild AV dyssynchrony rather than ventricular standstill; if the problem was a PVC, the spike is emitted sufficiently early to arrive before the repolarisation phase of the PVC.

Most temporary pacemakers employ a fixed ventricular blanking period and default to set parameters for ventricular safety pacing. As such, cross-talk is rarely if ever problematic as long as reasonable sensitivity and output is set.

Pacemaker-mediated tachycardia

This is a potential problem in only VDD or DDD pacing. The simplest form is far-field atrial sensing of a ventricular pacing spike, which is interpreted as an endogenous atrial depolarisation, leading to another ventricular impulse. This is overcome by use of an atrial blanking period, during which the atrial channel will not sense any depolarisation. Temporary pace generators have a preset atrial blanking period that should be sufficient to guard against this.

A more difficult problem exists when there is retrograde conduction between the ventricle and atrium, through either the AV node or an accessory pathway. More than 50% of patients receiving permanent dual chamber pacemakers are susceptible to such conduction [9] and there is no reason to suspect patients with temporary epicardial wires will be any less prone. The conduction may be intermittent and so may not be appreciated when the pulse generator is first set. In addition, it is often only a premature ventricular contraction that is initially conducted back up into the atrium. This may be sensed in the atrial wire as an endogenous atrial depolarisation, which (after the AV delay) triggers another ventricular depolarisation. This 'endless loop' continues with a periodicity that is the sum of the programmed AV delay and the time taken for retrograde conduction.

This problem is overcome by having an adjustable post ventricular (pacing spike) atrial refractory period, the PVARP. The atrial sensing channel must be refractory when the retrograde depolarisation arrives. The PVARP is set to a default value in all pacing generators. However, as the speed of conduction in the retrograde pathway is variable between individuals, *it is not uncommon to need to adjust the PVARP.* The disadvantage of setting a very long PVARP is that it limits the maximum rate of atrial tracking. This limitation would rarely be clinically significant in the ICU patient, and is more a concern for physiological rate response in permanent pacemakers.

As briefly touched on in the previous section, there is a simpler, but in some circumstances less ideal, solution to pacemaker-mediated tachycardia. The re-entrant pathway will be terminated if the mode is switched to VVI or DVI, but this may incur the penalty of losing AV synchrony.

Other causes of inappropriate tachycardia

Tracking of atrial tachyarrhythmias

In dual chamber modes with atrial tracking (DDD or VDD) the pacemaker emits a ventricular spike for every atrial impulse detected. In the absence of a protection mechanism, a tracked rapid atrial arrhythmia would rapidly lead to VF. All pacemakers must incorporate a means of protection against this possibility. Permanent pacemakers may be programmed to switch automatically to DDI mode when a set upper atrial rate is exceeded. DDI can be manually set on the temporary pulse generator, but as there will be an inevitable delay before this can be done, temporary pulse generators must incorporate an upper rate limit as well. This is described in detail below.

Oversensing (as distinct from cross-talk)

Oversensing can cause failure to pace, as already described. In DDD, external electrical impulses can also

be misinterpreted as atrial activity, causing pacemaker-mediated tachycardia. If the electrical interference is likely to continue, it may be necessary to reduce the sensitivity of the pacemaker (i.e. increase the sensitivity threshold) or switch to an asynchronous mode.

Portions of pacemaker timing cycles that can be manually adjusted

All modern temporary pace generators will default to timing settings that are adequate in the vast majority of patients. Most of these will be automatically adjusted when the rate is altered. For this reason, it is possible to remain ignorant of much of the following and still adequately manage a pacemaker-dependent patient. However, there will be circumstances in which manual adjustment of one of the following will be the only alternative to pacing in a haemodynamically suboptimal mode. Some of the concepts below have been touched on in the above sections.

AV delay

This is the interval following an atrial depolarisation before a ventricular spike is delivered. It allows the atrial contraction sufficient time to empty blood into the ventricle before ventricular contraction. As such, it allows the pacemaker to perform the function of the AV node. The patient's AV node may be able to conduct an impulse. If the set pacemaker AV interval is longer than the time to conduct through the patient's AV node, the ventricular pacing spike is inhibited; if it is shorter, the spike will be delivered, regardless of whether the atrial impulse would have eventually made it through the node.

Many permanent pacemakers, but no temporary pulse generators, use a 'differential' AV interval for atrial paced and endogenous depolarisations. The spread of depolarisation is more rapid following an endogenous depolarisation, and so the AV interval that follows an endogenous depolarisation is shorter than that following an atrial pacing spike to achieve the same mechanical delay between atrial and ventricular contraction.

The AV delay is shortened in ventricular safety pacing as described above. Cross-talk is detected by noticing that the AV delay is consistently shorter than that which is set on the pacemaker. The sensitivity and output of the pacemaker should be adjusted, as ventricular safety pacing usually produces a suboptimal cardiac output.

Many permanent pacemakers feature 'AV interval hysteresis'. Whenever set to a mode such that both atrial and ventricular spikes are being delivered, the system periodically extends the AV delay to look for a conducted R wave; if one is detected, the AV delay is automatically reset to a longer interval to allow endogenous conduction. However, if an R wave is missed, the system reverts to the original AV interval, allowing pacing to continue. As this automatic feature is not available on temporary pulse generators, it may be worth occasionally manually checking for AV node function in this fashion, especially if the patient remains pacemaker dependent and a permanent pacemaker is being considered.

There will be an optimal AV delay for each patient. Whereas the default value is usually sufficient, in the borderline patient, titration of the AV delay to a near-instantaneous measure of cardiac output (such as the time-velocity integral at the aortic valve (by echo), the value provided by pulse contour analysis, or the mixed venous oxygen saturation) may be warranted. In a series of only 13 patients undergoing cardiac surgery, the optimal AV delay varied between 0.100 and 0.225 s [10].

Post ventricular atrial refractory period

This has been discussed in detail above (under 'pacemaker-mediated tachycardia'). It sets how early after a ventricular impulse (paced or sensed) that a sensed atrial depolarisation can trigger a ventricular spike, and is the timing parameter that most often needs adjustment.

VA interval (atrial escape interval)

This is the interval from a ventricular sensed or paced event to an atrial paced event. The lower rate limit (i.e. the set pacemaker rate) is the sum of the AV interval plus the VA interval. In DDD and VDD, an endogenous atrial depolarisation after the PVARP, but before the end of the atrial escape interval, will be sensed, inhibiting atrial output and starting the AV interval timer. The VA interval is determined by the AV interval and the lower rate limit settings and (as it is not independently adjustable) is mentioned here only to facilitate understanding.

Duration of pulse

The ability of the pacemaker to bring the myocardium to action potential is determined by both current intensity and duration of pacing stimulus. The relationship between these two is expressed as a strength–duration curve (Fig. 2). In many temporary pulse generators, the pulse duration is fixed at around 1.5 ms, which is on the flat part of the curve. Further increases in pulse duration would not reduce the current required for depolarisation. Reducing the pulse duration may reduce fibrosis (and delay failure to capture), and in permanent pacemakers is an even more important consideration as this will also conserve battery life. In practice, the pulse duration in temporary pacemakers is rarely altered, even if this option is present.

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