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Discontinuing Cardiopulmonary Bypass

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KEY POINTS

1. The key to successful weaning from cardiopulmonary bypass (CPB) is proper preparation.
2. After rewarming the patient, correcting any abnormal blood gases, and inflating the lungs, make sure to turn on the ventilator.
3. To prepare the heart for discontinuing CPB, optimize the cardiac rate, rhythm, preload, myocardial contractility, and afterload.
4. The worse the heart's condition, the more gradually CPB should be weaned. If hemodynamic values are not adequate, immediately return to CPB. Assess the problem, and choose an appropriate pharmacologic, surgical, or mechanical intervention before trying to terminate CPB again.
5. Perioperative ventricular dysfunction usually is caused by myocardial stunning and is a temporary state of contractile dysfunction that should respond to positive inotropic drugs.
6. In addition to left ventricular dysfunction, right ventricular failure is a possible source of morbidity and mortality after cardiac surgical procedures.
7. The presence of diastolic dysfunction during the postbypass period may contribute to impaired chamber relaxation and poor compliance, resulting in reduced ventricular filling during separation.
8. Epinephrine is frequently chosen as an inotropic drug when terminating CPB because of its mixed α- and β-adrenergic stimulation.
9. Milrinone is an excellent inodilator drug that can be used alone or combined with other drugs such as epinephrine for discontinuing CPB in patients with poor ventricular function and diastolic dysfunction.
10. In patients with high preload and/or elevated systemic vascular resistance, vasodilators such as nitroglycerin, nicardipine, clevidipine, or nitroprusside may improve ventricular function.
11. Variable gene expression and genetic polymorphism in patients presenting for cardiac surgical procedures may provide the foundation for individualized tailoring of pharmacology based on molecular genotyping in the future.
12. Intraaortic balloon pump counterpulsation increases coronary blood flow during diastole and unloads the left ventricle during systole. These effects can help in weaning patients with poor left ventricular function and severe myocardial ischemia.

Cardiopulmonary bypass (CPB) has been used since the 1950s to facilitate surgical procedures of the heart and great vessels, and is a critical part of most cardiac operations. Managing patients undergoing CPB remains one of the defining characteristics of cardiac surgery and cardiac anesthesiology (see Chapters 31–35). Discontinuing CPB is a necessary part of every operation involving extracorporeal circulation. Through this process, the support of the circulation by the bypass pump and oxygenator is transferred back to the patient's heart and lungs. This chapter reviews important considerations for discontinuing CPB and presents an approach to managing this critical component of a cardiac operation, which may be routine and easy or extremely complex and difficult. The key to success in discontinuing CPB is proper preparation. The period during and immediately after weaning from CPB usually is busy for the anesthesiologist, and having to do tasks that could have been accomplished earlier in the operation is not helpful. The preparations for removing a patient from CPB may be organized into several parts: general preparations, preparing the lungs, preparing the heart, and final preparations.

General Preparations

Temperature

Because at least moderate hypothermia is used during CPB in most cardiac surgical cases, it is important that the patient is sufficiently rewarmed before attempts are made to wean the patient from CPB (Table 36.1).[1–3] Initiation of rewarming is a good time to consider whether additional drugs must be given to keep the patient anesthetized and to prevent shivering. Monitoring the temperature of a highly perfused tissue such as the nasopharynx is useful to help prevent overheating of the brain during rewarming. Cerebral hyperthermia may lead to neurologic injury and postoperative cognitive dysfunction. The central nervous system receives a greater proportion of warm blood, thus resulting in a more rapid increase in temperature compared with other sites such as the bladder, rectum, or axilla. This situation may lead to inadequate rewarming and temperature dropoff after CPB as the heat continues to distribute throughout the body.[4]

TABLE 36.1 General Preparations for Discontinuing Cardiopulmonary Bypass

Temperature	*Laboratory Results*
Adequately rewarm before weaning from CPB	Correct metabolic acidosis
Avoid overheating the brain	Optimize hematocrit
Start measures to keep patient warm after CPB	Normalize potassium
Use fluid warmer, forced air warmer	Consider giving magnesium or checking magnesium level
Warm operating room	Check calcium level and correct deficiencies

CPB, Cardiopulmonary bypass.

BOX 36.1 PREPARING THE LUNGS FOR DISCONTINUING CARDIOPULMONARY BYPASS

- Suction trachea and endotracheal tube.
- Inflate lungs gently by hand.
- Ventilate with 100% oxygen.
- Treat bronchospasm with bronchodilators.
- Check for pneumothorax and pleural fluid.
- Consider the need for positive end-expiratory pressure, intensive care unit ventilator, and nitric oxide.

Different institutions have various protocols for rewarming, but the important point is to warm gradually, avoiding hyperthermia of the central nervous system while providing enough heat to the patient to prevent significant dropoff after CPB (see Chapters 31 and 32). After CPB, the tendency is for the patient to lose heat, and measures to keep the patient warm (eg, fluid warmers, a circuit heater-humidifier, and forced-air warmers) should be set up and turned on before weaning from CPB is begun. The temperature of the operating room may need to be increased as well; this is probably an effective measure to keep a patient warm after CPB, but it may make the scrubbed and gowned personnel uncomfortable.

Laboratory Results

Arterial blood gases should be measured before the patient is weaned from CPB, and any abnormalities should be corrected. Severe metabolic acidosis depresses the myocardium and necessitates correction before separation from bypass.[5] The optimal hematocrit for weaning from CPB is controversial and probably varies from patient to patient.[6,7] It makes sense that sicker patients with lower cardiovascular reserve may benefit from a higher hematocrit (optimal is considered to be 30%), but the risks and adverse consequences of transfusion must be considered as well. The hematocrit should be measured and optimized before the patient is weaned from CPB (see Chapters 34 and 35). The serum potassium (K^+) level should be measured before weaning from CPB and may be high because of cardioplegia or low, especially in patients receiving loop diuretics. Hyperkalemia may make establishing an effective cardiac rhythm difficult and can be treated with sodium bicarbonate, ($NaHCO_3$), calcium chloride ($CaCl_2$), or insulin, but the levels usually decrease quickly after cardioplegia has been stopped. Low serum K^+ levels should be corrected before CPB is discontinued, especially if arrhythmias are present. Administration of magnesium (Mg^{2+}) to patients on CPB decreases postoperative arrhythmias and may improve cardiac function, and many centers routinely give all CPB-treated patients magnesium sulfate.[8,9] Theoretic disadvantages include aggravation of vasodilation and inhibition of platelet function.[10] If Mg^{2+} is not given routinely, the level should be checked before weaning from CPB, and deficiencies should be corrected. The ionized Ca (Ca^{2+}) level should be measured, and significant deficiencies should be corrected before discontinuing CPB. Many centers give all patients a bolus of $CaCl_2$ just before coming off CPB because it transiently increases contractility and systemic vascular resistance (SVR).[11] However, investigators have argued that this practice is to be avoided because Ca^{2+} may interfere with catecholamine action and aggravate reperfusion injury.[12]

Preparing the Lungs

As the patient is weaned from CPB and the heart starts to support the circulation, the lungs again become the site of gas exchange, by delivering oxygen and eliminating carbon dioxide. Before weaning from CPB, the patient's lung function must be restored (Box 36.1). The trachea should be suctioned and, if necessary, lavaged with saline solution to clear secretions. If the abdomen appears to be distended, the stomach should be suctioned so that gastric distention does not impair ventilation after CPB. The lungs are reinflated by hand gently and gradually, with sighs using up to 30 cm H_2O pressure, and then mechanically ventilated with 100% oxygen. Care should be taken not to allow the lungs to injure an in situ internal mammary artery graft as they are reinflated. The compliance of the lungs can be judged by their feel with hand ventilation; stiff lungs suggest more difficulty with oxygenation or ventilation after CPB. If visible, both lungs should be inspected for residual atelectasis, and they should be rising and falling with each breath. Ventilation alarms and monitors should be activated. If prolonged expiration or wheezing is detected, bronchodilators should be given. The surgeon should inspect both pleural spaces for pneumothorax, which should be treated by opening the pleural space. Examining the lung fields by transesophageal echocardiography (TEE) may assist in the detection of pleural effusions. This imaging technique is primarily performed by examining the lung fields just to the right and left of the heart in the midesophageal four-chamber view at 0 degrees. Any fluid present in the pleural spaces should be removed before attempting to wean the patient from CPB.

The apneic period during CPB has been suggested to contribute to ventilator-associated pneumonia and postoperative pulmonary dysfunction through a variety of mechanisms.[13,14] Continuing mechanical ventilation during CPB has been proposed as another option to attenuate the post-CPB impairment of lung function.[13,15] Results of several small trials that used continued ventilation during CPB were mixed, with some trials showing benefit and others showing no outcome difference.[1] At present, the evidence for intraoperative lung protection strategies such as continued ventilation is lacking and awaits larger randomized trials. In its most severe form, pulmonary dysfunction after CPB may require positive end-expiratory pressure, an intensive care unit–type ventilator, or nitric oxide (see Chapters 37, 39, and 41). If needed, this equipment should be obtained before attempting to wean the patient from CPB.

Preparing the Heart

Management of Intracardiac Air

During the bypass period, the heart is empty, cooled, and usually electrically silent to minimize consumption of adenosine triphosphate (ATP). Air is often introduced into the heart during the operation and can eventually cause deleterious effects during separation from CPB and in the postoperative period. TEE can be helpful in identifying and locating air in the heart and assisting in de-airing before CPB is discontinued. On TEE, air is often seen as echo-dense or bright foci floating to the highest point within the chamber.[1,16]

The time to begin looking with TEE for intracardiac air on CPB is usually after all the chambers and the aorta are closed and the aortic cross-clamp is removed. It is essential to identify macroscopic accumulations of air within the left side of the heart to minimize systemic emboli. With the patient in the supine position, air often is visualized in the left atrium along the interatrial septum, left atrial (LA) appendage, and near the entry points of the pulmonary veins. In the left ventricle and aortic root, air often accumulates along the apical portion

of the interventricular septum and right coronary sinus of Valsalva.[1] To scan for intracardiac air systematically, it may be useful to start in the midesophageal four-chamber view at 0 degrees and fully examine all aspects of the left atrium and ventricle, with special attention to the interatrial and interventricular septum. From this image plane, it may be useful to change the multiplane angle to approximately 120 to 145 degrees, to provide an additional image sector to examine the apical septum for air-fluid levels. As the heart ejects, close inspection of the left ventricular (LV) outflow tract (LVOT) and aortic root at this image plane may facilitate visualization of air emboli, mandating aggressive aspiration of the aortic root vent.

Although a correlation with the amount of intracardiac air seen with TEE and neurologic outcome has not been shown, one of the major concerns with systemic air emboli after CPB is the potential for cerebral injury (see Chapter 40). It is reasonable to proceed with the assumption that the less air pumped into the systemic circulation during and after CPB, the better. Another adverse consequence is the passage of air into the coronary circulation that leads to myocardial ischemia. In the supine patient, the right coronary artery takes off from the highest point of the aortic root, and intracoronary air is most commonly manifested by dramatic inferior ST-segment elevation and acute right-sided heart dysfunction. Saphenous vein grafts typically are anastomosed to the anterior aspect of the ascending aorta and are susceptible to air emboli as well. If this occurs while the patient is still on CPB or before decannulation, it is a simple matter to go back on CPB and wait a few minutes until the air clears from the coronary circulation, the ST segments normalize, and ventricular function improves before trying to wean the patient from CPB again. If, however, coronary air embolization occurs after decannulation, the hemodynamic status can quickly deteriorate to cardiac arrest. Smaller air emboli can be moved through the coronary vessels by acutely increasing the blood pressure with a vasopressor while dilating the coronary arteries with nitroglycerin (NTG). Perhaps the worst-case scenario is when a macroscopic air bubble in the left side of the heart is shaken loose while moving the patient from the operating table at the end of the case; acute right-sided heart failure (HF) and circulatory collapse may occur either then or while the patient is being transported to the intensive care unit.

Numerous maneuvers may be used to de-air the chambers.[1,17] They may include shaking the vented heart on partial CPB to jar loose any pockets of air, elevating and aspirating LV air directly from the apex, applying positive pressure to the lungs to squeeze air out of the pulmonary veins, and tipping the table from side to side to help the passage of bubbles through the heart to the ascending aorta where they are released through a vent. Additional air may appear in the left side of the heart during weaning from CPB as increasing flow through the pulmonary veins flushes air out from the lungs into the left atrium. Passage of air from the left atrium to the left ventricle may be facilitated with the head and right-side-down position, as well as from the left ventricle to the ascending aorta with the head and right-side up. It may be impossible to evacuate every last trace of air from the left side of the heart before discontinuing CPB, especially tiny bubbles trapped in the trabeculae of the left ventricle; it therefore becomes a matter of judgment and experience to know when enough is enough. The persistence of a macroscopic air-fluid level in the left side of the heart visible with TEE, however, suggests that more de-airing probably is needed before closing the vent in the ascending aorta and weaning from CPB. After adequate de-airing, preparing the heart to resume its function of pumping blood involves optimizing the determinants of cardiac output (CO). The five hemodynamic parameters that can be controlled are rate, rhythm, preload, contractility, and afterload (Table 36.2).

TABLE 36.2 Preparing the Heart for Discontinuing Cardiopulmonary Bypass

Hemodynamic Parameters	*Preparation*
Heart rate	Rate should be between 75 and 95 beats/min in most cases Treat slow rates with electrical pacing Treat underlying causes of fast heart rates Heart rate may decrease as the heart fills Control fast supraventricular rates with drugs, and then pace as needed Always have pacing immediately available during heart operations
Rhythm	Normal sinus rhythm is ideal Defibrillate if necessary when temperature >30°C Consider antiarrhythmic drugs if ventricular fibrillation persists more than a few minutes Try synchronized cardioversion for atrial fibrillation or flutter Look at the heart to diagnose atrial rhythm Try atrial pacing if atrioventricular conduction exists Try atrioventricular pacing for heart block
Preload	End-diastolic volume is the best measure of preload and can be seen with TEE Filling pressures provide a less direct measure of preload Consider baseline filling pressures Assess RV volume with direct inspection Assess LV volume with TEE Cardiac distention may cause MR and TR
Contractility	Carefully examine heart for air and employ de-airing maneuvers Assess and quantify RV function with direct inspection and TEE Assess and quantify LV function with TEE Inspect for new regional wall motion abnormalities Inspect for new or worsening valvular abnormalities Quantify cardiac output by TEE or PAC Assess need for inotropic agent
Afterload	Systemic vascular resistance is a major component of afterload Keep MAP between 60 and 80 mm Hg at full CPB flow Consider a vasoconstrictor if the MAP is low and a vasodilator if the MAP is high

CPB, Cardiopulmonary bypass; *LV,* left ventricular; *MAP,* mean arterial pressure; *MR,* mitral regurgitation; *PAC,* pulmonary artery catheter; *RV,* right ventricular; *TEE,* transesophageal echocardiography; *TR,* tricuspid regurgitation.

Heart Rate

Establishing an effective heart rate (HR) is a critical prerequisite and major determinant of CO. In most situations for adult patients, the HR should be between 75 and 95 beats/minute for weaning from CPB. It may be prudent to establish electrical pacing early in the weaning process to ensure a means to control the HR precisely. Lower rates theoretically may be desirable for hearts with residual ischemia or incomplete revascularization. Higher HRs may be needed for hearts with limited stroke volume (SV) such as after ventricular aneurysmectomy. Slow HRs are best treated with electrical pacing, but β-agonist or vagolytic drugs also may be used to increase the HR. Tachycardia before weaning from CPB is more worrisome and difficult to manage, and treatable causes such as inadequate anesthesia, hypercarbia, and ischemia should be identified and corrected. The HR often decreases as the heart is filled in the weaning process, and electrical pacing always should be immediately available during cardiac operations to treat sudden bradycardias. Supraventricular tachycardias should be electrically cardioverted if possible, but drugs such as β-antagonists or Ca^{2+} channel antagonists may be needed to control the ventricular rate if these arrhythmias persist, most typically in patients with chronic atrial fibrillation. If drug therapy decreases the HR too much, pacing may be used.

Rhythm

The patient must have an organized, effective, and stable cardiac rhythm before attempts are made to wean the patient from CPB. This rhythm can occur spontaneously after removal of the aortic cross-clamp, but the heart may resume electrical activity with ventricular fibrillation. If the blood temperature is greater than 30°C, the heart may be defibrillated with internal paddles applied directly to the heart by using 10 to 20 J. Defibrillation at lower temperatures may be unsuccessful

because extreme hypothermia can cause ventricular fibrillation.[18,19] If ventricular fibrillation persists or recurs repeatedly, antiarrhythmic drugs such as lidocaine, amiodarone, or Mg^{2+} may be administered to help achieve a stable rhythm. It is not unusual for the rhythm to remain unstable for several minutes immediately after cross-clamp removal, but persistent or recurrent ventricular fibrillation should prompt concern about impaired coronary blood flow. Because it provides an atrial contribution to ventricular filling and a normal, synchronized contraction of the ventricles, normal sinus rhythm is the ideal cardiac rhythm for weaning from CPB.[20] Atrial flutter or fibrillation, even if present before CPB, often can be converted to normal sinus rhythm with synchronized cardioversion, especially if antiarrhythmic drugs are administered. It often is helpful to look directly at the heart when any question exists about the cardiac rhythm. Atrial contraction, flutter, and fibrillation are easily seen on CPB when the heart is visible. Ventricular arrhythmias should be treated by correcting underlying causes such as K^+ or Mg^{2+} deficits and, if necessary, by administering antiarrhythmic drugs such as amiodarone.[9] If asystole or complete heart block occurs after cross-clamp removal, electrical pacing with temporary epicardial pacing wires may be needed to achieve an effective rhythm before weaning from CPB. If atrioventricular conduction is present, atrial pacing should be attempted because, as with normal sinus rhythm, it provides atrial augmentation to filling and synchronized ventricular contraction. Atrioventricular sequential pacing is used in patients with heart block, which may be temporarily present for 30 to 60 minutes as the myocardium recovers after cardioplegia and cross-clamp removal. Ventricular pacing remains the only option if no organized atrial rhythm is present, but this sacrifices the atrial "kick" to ventricular filling and the more efficient synchronized ventricular contraction of the normal conduction system[21,22] (see Table 36.2).

Preload

Once control of the rate and rhythm is established, priming the heart with volume or preload is the next step. Preload is the amount of stretch on the myocardial muscle fibers just before contraction. In the intact heart, the best measure of preload is end-diastolic volume. Less direct clinical measures of preload include LA pressure (LAP), pulmonary artery occlusion pressure, and pulmonary artery diastolic pressure, but the relationship between end-diastolic pressure and volume during cardiac surgical procedures may be poor[23,24] (see Chapters 6, 13, and 38). TEE is a useful tool for weaning from CPB because it provides direct visualization of the end-diastolic volume and contractility of the left ventricle[25,26] (see Chapters 14–16). TEE may also provide a means to calculate serial CO measurements during volume loading of the heart. In addition, diastolic filling indices (transmitral and pulmonary venous inflow) may assist in assessing fluid responsiveness and elevations in LA and LV filling pressures.[27,28] The process of weaning a patient from CPB involves increasing the preload (ie, filling the heart from its empty state on CPB) until an appropriate end-diastolic volume is achieved. When preparing to discontinue CPB, some thought should be given to the appropriate range of preload for the individual patient. The filling pressures before CPB may indicate what they need to be after CPB; a heart with high filling pressures before CPB may require high filling pressures after CPB to achieve an adequate preload.

Contractility

The contractile state of both the right and left sides of the heart should be considered individually before attempting to wean from CPB. The decision to institute inotropic support after CPB is complex, and intraoperative use of inotropes may be associated with higher mortality rates.[29] Some of the factors associated with the low CO syndrome (LCOS) or the need for inotropic support after CPB include preexisting right ventricular (RV) or LV dysfunction,[30–36] diastolic dysfunction,[37,38] elevated LV end-diastolic pressure (LVEDP),[30,32] advanced age,[30,32,34] prolonged CPB time,[37] and long aortic cross-clamp time[30,35,37] (Table 36.3). Assessment of the right ventricle may be easily attainable because the right-sided chambers are directly visible to the anesthesiologist. Direct visualization of the left ventricle is difficult, and TEE may be the only modality by which to visualize left-sided heart function directly. Both right-sided and left-sided heart function and the corresponding atrioventricular valves should be systematically examined by TEE. The use of TEE during gradual weaning from the pump may provide essential information on chamber filling and the contractile state.

TABLE 36.3 Summary of Factors Associated With the Use of Inotropic Drug Support or Low Cardiac Output Syndrome

Variable	*Odds Ratio*	*Reference*
Age (>60 y)	4.3	Butterworth et al., 1998[31]
Aortic cross-clamp time >90 min	2.32	Muller et al., 2002[36]
Bypass time (min)	3.40	Bernard et al., 2001[37]
CABG + MVR	3.607	McKinlay et al., 2004[35]
Cardiac index <2.5 L/m^2 per min	3.10	Ahmed et al., 2009[30]
CHF (NYHA class >II)	1.85	Muller et al., 2002[36]
CKD (stage 3–5; GFR <60 mL/1.73 m^2 per min	3.26	Ahmed et al., 2009[30]
COPD	1.85	Muller et al., 2002[36]
Diastolic dysfunction	4.31	Bernard et al., 2001[37]
Ejection fraction (%) <40	2.76	Ahmed et al., 2009[30]
Emergency operation	9.15	Ding et al., 2015[34]
Female sex	2.0	Alganrni et al., 2011[33]
LVEDP >20 mm Hg	3.58	Ahmed et al., 2009[30]
Myocardial infarction	2.01	Muller et al., 2002[36]
Moderate-to-severe mitral regurgitation	2.277	McKinlay et al., 2004[35]
Regional wall motion abnormality	4.21	McKinlay et al., 2004[35]
Repeat operation	2.38	McKinlay et al., 2004[35]

CABG, Coronary artery bypass graft; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *COPD,* chronic obstructive pulmonary disease; *GFR,* glomerular filtration rate; *LVEDF,* left ventricular end-diastolic pressure; *MVR,* mitral valve repair or replacement; *NYHA,* New York Heart Association.

A brief evaluation of cardiac function including both RV and LV contractility is achieved by a series of scan planes at the midesophageal level and advancing the probe into the transgastric position. The goal is to ascertain quickly the suitability of the heart to wean from CPB successfully. This goal may be achieved by scanning for RV and LV wall motion in the midesophageal (four-chamber view at 0 degrees, two-chamber view at 90 degrees, aortic long-axis view at 120 to 150 degrees, RV inflow-outflow at 45 to 60 degrees) and transgastric views (LV and RV short-axis view at 0 degree). If evidence of poor contractility is visualized on TEE, initiation or titration of inotropic agents can begin at this time. As the pump flow is gradually reduced, the ability of the heart to fill and eject is continuously assessed, and drug therapy is titrated as needed. Once the heart has demonstrated the ability to maintain adequate hemodynamic status, separation from CPB is commenced. At this point, serial volume transfusions from the venous reservoir can be carefully titrated as needed, and the heart's response to volume can be monitored by TEE.[25] After each volume bolus, assessments of biventricular function and the end-diastolic and end-systolic areas of the right and ventricles are critical to prevent overdistention and unwanted wall tension. Reinstitution of CPB is warranted if the heart begins to distend or displays inadequate function.

Because the use of intraoperative and postoperative inotropic support may be associated with increased mortality rates, the decision to initiate pharmacologic therapy should be made with caution.[29] A prudent approach, using a slow and gradual weaning process from the pump and assessing cardiac filling and biventricular contractility in a stepwise manner, may help reduce unnecessary use of inotropic agents. As the heart is allowed to fill gradually, if significant chamber distention or depression of contractility is evident on TEE or by direct visual inspection, the safest approach is to prevent cardiac distention by resuming CPB. At this point, the heart may benefit from a resting

period of 10 to 20 minutes on CPB, and then the decision to start inotropes may be warranted before the patient is weaned from CPB.

Extreme depression of contractile function of the myocardium despite adequate pharmacologic therapy may require mechanical support with an intraaortic balloon pump (IABP), ventricular assist device, or extracorporeal membrane oxygenator (see later and Chapters 28, 33, and 38).

Afterload

Afterload is the tension developed within the ventricular muscle during contraction. An important component of afterload in patients is the SVR (see Chapters 6, 13, and 38).[39] During CPB at full flow (usually ≈2.2 L/m^2 per min), mean arterial pressure (MAP) is directly related to SVR and indicates whether the SVR is appropriate, too high, or too low. Low SVR after CPB can cause inadequate systemic arterial perfusion pressure, and high SVR can significantly impair cardiac performance, especially in patients with poor ventricular function. SVR during CPB can be approximated by using the following equation:

$$\text{SVR (dynes} \cdot \text{s} \cdot \text{cm}^{-5}) = \text{MAP} \times 80 / \text{pump flow}$$

If the SVR is less than normal, infusion of a vasopressor may be needed to increase the SVR before attempting to wean the patient from CPB. If the MAP is high during CPB, vasodilator therapy may be needed.

Final Considerations and Preparations

The state of coagulation and the potential requirement for blood transfusion or component therapy must be considered before separation from CPB. Review of data from prebypass studies such as hemoglobin, platelet count, thromboelastography, and coagulation panels may help in recognizing preexisting coagulopathy and predict transfusion requirements in the presence of post-CPB bleeding after protamine administration. Risk factors that may be associated with higher rates of transfusion include emergency or urgent surgical procedures, reoperation, cardiogenic shock, older age, female sex, low body weight, and preoperative anemia.[40] Preoperative use of antiplatelet agents, warfarin, and novel anticoagulants may also portend higher transfusion rates and warrant special attention. Assessing coagulation status and the need for transfusion is an important consideration before attempting to wean a patient from CPB.

The final preparations before discontinuing CPB include leveling the operating table, resetting the pressure transducers to zero, ensuring the proper function and location of all monitoring devices, confirming that the patient is receiving only intended drug infusions, ensuring the immediate availability of resuscitation drugs and appropriate fluid volume, and verifying that the lungs are being ventilated with 100% oxygen (Table 36.4).

The surgeon must confirm that he or she has completed the necessary preparations in the surgical field before CPB is discontinued. Macroscopic collections of air in the heart should be evacuated as described in detail earlier before starting to wean the patient from CPB. This is also an appropriate time to reassess the five major determinants of CO by using all available monitors and TEE. Major sites of bleeding should be controlled, cardiac vent suction should be off, all clamps on the heart and great vessels should be removed, coronary artery bypass grafts (CABGs) should be checked for kinks and bleeding, and tourniquets around the caval cannulas should be loosened or removed before starting to wean a patient from CPB.

TABLE 36.4 Final Preparations for Discontinuing Cardiopulmonary Bypass

Anesthesiologist's Preparations	*Surgeon's Preparations*
Level operating table	Remove macroscopic collections of air from the heart
Reset transducers to zero	Control major sites of bleeding
Activate monitors	Ensure CABG is lying nicely without kinks
Check drug infusions	Turn off or remove cardiac vents
Have resuscitation drugs and fluid volume at hand	Take clamps off the heart and great vessels
Reestablish TEE or PAC monitoring	Loosen tourniquets around caval cannulas

CABG, Coronary artery bypass graft; *PAC,* pulmonary artery catheter; *TEE,* transesophageal echocardiography.

Routine Weaning From Cardiopulmonary Bypass

The perfusionist, the surgeon, and the anesthesiologist should communicate closely and clearly while weaning a patient from CPB, and the surgeon or the anesthesiologist should be in charge of the process. The anesthesiologist should be positioned at the head of the table, able to see the CPB pump and perfusionist, the heart, the surgeon, and the anesthesia monitor display readily. The TEE display also should be easily in view. Weaning a patient from CPB is accomplished by diverting blood back into the patient's heart by occluding the venous drainage to the CPB pump. The arterial pump flow is decreased simultaneously as the pump reservoir volume empties into the patient, and the heart's contribution to systemic flow increases. This can be accomplished most abruptly by simply clamping the venous return cannula and transfusing blood from the pump until the heart fills and the preload appears to be adequate. Some patients tolerate this method of discontinuing CPB, but many do not, and a more gradual transfer from the pump to the heart usually is desirable. The worse the function of the heart is, the slower the transition from full CPB to off CPB needs to be.

Before beginning to wean the patient from CPB, the perfusionist should communicate to the physicians involved the following three important parameters: (1) the current flow rate of the pump, (2) the volume in the pump reservoir, and (3) the oxygen saturation of venous blood returning to the pump from the patient. The flow along with MAP can be used to gauge the SVR of the patient before weaning from CPB. The current flow rate of the pump indicates the stage of weaning as it is decreased. Weaning is just beginning at full flow, is well under way when down to 2 or 3 L/minute in adults, and is almost finished at less than 2 L/minute. The reservoir volume indicates how much blood is available for transfer to the patient to fill the heart and lungs as CPB is discontinued. If the volume is low (<400 to 500 mL in adults), more fluid may need to be added to the reservoir before weaning from CPB. The oxygen saturation of the venous return ($S\bar{v}O_2$) gives an indication of the adequacy of peripheral perfusion during CPB. If the $S\bar{v}O_2$ is greater than 60%, oxygen delivery during CPB is adequate; if it is less than 50%, oxygen delivery is inadequate, and measures to improve delivery (eg, increase pump flow or hematocrit) or decrease consumption (eg, give more anesthetic agents or neuromuscular blocking drugs) must be taken before CPB is discontinued. An $S\bar{v}O_2$ between 50% and 60% is marginal and must be followed closely. As the patient is weaned from CPB, an increasing $S\bar{v}O_2$ suggests that the net flow to the body is increasing and that the heart and lungs will support the circulation; a declining $S\bar{v}O_2$ indicates that tissue perfusion is decreasing and that further intervention to improve cardiac performance will be needed before CPB is discontinued.

The actual process of weaning from CPB begins with partially occluding the venous return cannula with a clamp (Fig. 36.1). This may be done in the field by the surgeon or at the pump by the perfusionist. This maneuver causes blood to flow into the right ventricle. As the right ventricle fills and begins to pump blood through the lungs, the left heart begins to fill. When this occurs, the left ventricle begins to eject, and the arterial waveform becomes pulsatile. Next, the perfusionist gradually decreases the pump flow rate. As more of the venous return goes through the heart and less to the pump reservoir, it becomes necessary to decrease the pump flow gradually to avoid emptying the pump reservoir.

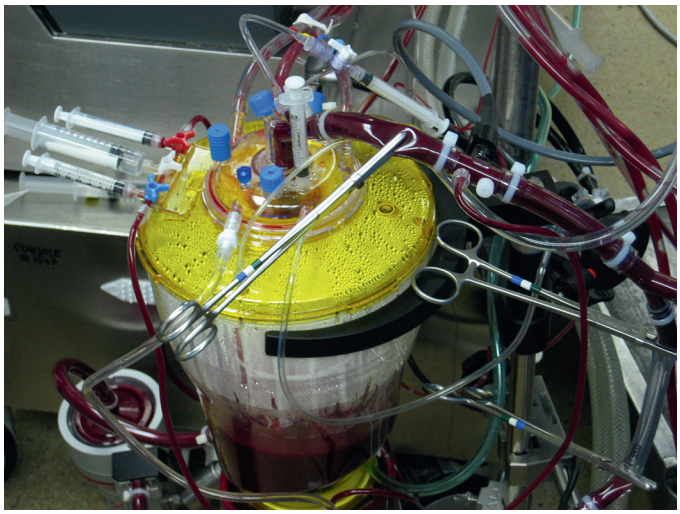


Fig. 36.1 The process of weaning from cardiopulmonary bypass is started by partially occluding the venous return cannula with a clamp.

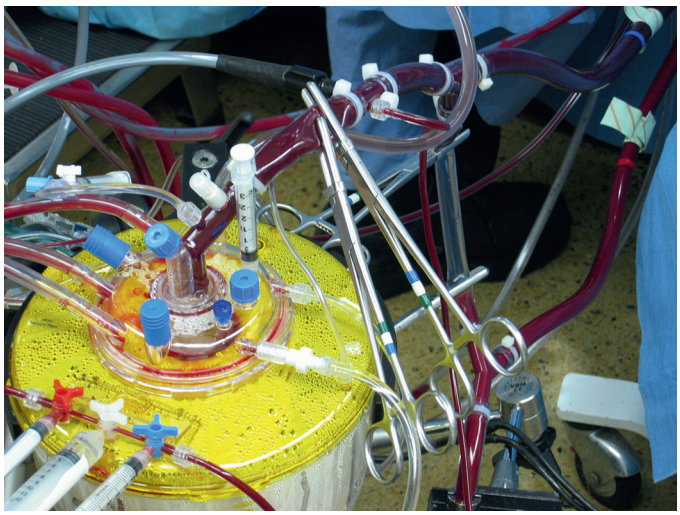


Fig. 36.2 When the venous return cannula is completely clamped, the patient is "off bypass."

One approach to weaning from CPB is to bring the filling pressure being monitored (eg, central venous pressure, pulmonary artery pressure, LAP) to a specific, predetermined level somewhat lower than may be necessary and then assess the hemodynamic status. Volume (preload) of the heart also may be judged by direct observation of its size or with TEE. Further filling is done in small increments (50–100 mL) while closely monitoring the preload until the hemodynamic status appears satisfactory as judged by the arterial pressure, the appearance of the heart, the trend of the $S\bar{v}O_2$, and CO measurements by TEE or pulmonary artery catheter. It typically is easy to see the right-sided heart volume and function directly in the surgical field and the left side of the heart with TEE; combining the two observations is a useful approach for weaning from CPB. Overfilling and distention of the heart should be avoided because they may stretch the myofibrils beyond the most efficient length and dilate the annuli of the mitral and tricuspid valves, thus rendering them incompetent, which can be detected with TEE. If the patient has two venous cannulas, the smaller of the two may be removed when the pump flow is half of the full flow rate to improve movement of blood from the great veins into the right atrium. When the pump flow has been decreased to 1 L/minute or less in an adult and the hemodynamics findings are satisfactory, the venous cannula may be completely clamped and the pump flow turned off. At this point, the patient is "off bypass" (Fig. 36.2).

This is a critical juncture in the operation. The anesthesiologist should pause a moment to make a brief scan of the patient and monitors to confirm that the lungs are being ventilated with oxygen, the hemodynamic status is acceptable and stable, the electrocardiogram shows no new signs of ischemia, the heart does not appear to be distending, and the drug infusions are functioning as desired. Further fine-tuning of the preload is accomplished by transfusing 50- to 100-mL boluses from the pump reservoir through the arterial cannula and observing the effect on hemodynamics. If acute failure of the circulation occurs, as evidenced by an unstable rhythm, falling arterial and rising filling pressures, or visible distention of the heart, the patient is put back on CPB by unclamping the venous return cannula and turning on the arterial pump flow. Once CPB has resumed, an assessment of the cause of failure to wean is made, and appropriate interventions are undertaken before attempting to wean the patient from CPB again. When the hemodynamic status appears to be stable and adequate, the surgeon may remove the venous cannula from the heart.

The next step in discontinuing CPB is to transfuse as much of the blood remaining in the pump reservoir as possible into the patient before removal of the arterial cannula. This technique is usually easier and quicker than transfusing through the intravenous infusions after decannulation. The blood in the venous cannula and tubing (usually ≈500 mL) may be drained into the reservoir for transfusion. The patient's venous capacitance can be increased by raising the head of the bed (ie, reverse Trendelenburg position) and/or giving NTG; more cautions is required with these maneuvers in patients with impaired cardiac function. Filling the vascular space with the patient's head up and while infusing NTG increases the ability to cope with volume loss after decannulation by allowing rapid augmentation of the central vascular volume by leveling the bed and decreasing the NTG infusion rate.

After discontinuing CPB, the anticoagulation by heparin is reversed with protamine. Depending on institutional preference, protamine may be administered before or after removal of the arterial cannula. Giving protamine before removal allows for continued transfusion from the pump and easier return to CPB if the patient has a severe protamine reaction (see Chapter 35). Giving protamine after removal of the arterial cannula may decrease the risk for thrombus formation and systemic embolization. After the infusion of protamine is started, pump suction return to the reservoir should be stopped to keep protamine out of the pump circuit in case subsequent return to CPB becomes necessary. Titrated dosing of protamine may be more effective in reducing postoperative bleeding compared with a standard protamine administration protocol.[41] Titrated dosing involves adjusting the protamine concentration to reflect measured circulating heparin levels. Protamine should be given slowly through a peripheral intravenous catheter over 5 to 15 minutes while the clinician watches for systemic hypotension and pulmonary hypertension, which may indicate that an untoward (allergic) reaction to protamine is occurring.[42–44] Technically flawed CABGs may thrombose after protamine administration, thus causing acute ischemia mimicking a protamine reaction.

When transfusion of the pump reservoir blood is completed, a thorough assessment of the patient's condition should be made before the arterial cannula is removed because after this is done, returning to CPB becomes much more difficult. The cardiac rhythm should be stable. Cardiac function and hemodynamic status, as assessed by arterial and venous filling pressures, CO, and TEE, should be satisfactory and stable. A more detailed and comprehensive TEE examination can be performed as time permits. RV free wall motion to assess RV function qualitatively can be obtained in the midesophageal four-chamber view (0 degrees) and midesophageal RV inflow-outflow view (45–60 degrees). In the midesophageal four-four-chamber view, RV function can also be quantified by measuring tricuspid annular systolic plane excursion (TAPSE) and comparing it with prebypass assessments.

Findings of interatrial septal bowing into the left atrium may indicate volume or pressure overload of the right atrium. Interventricular septal motion after CPB should be interpreted with caution because abnormal septal movement may be caused by several factors including epicardial pacing, stunned myocardium, volume or pressure overload,

and ischemia. The midesophageal four-chamber view at 0 degrees and the RV inflow-outflow view at 45 to 60 degrees may be used to assess for new or worsening tricuspid regurgitation, thereby indicating the possibility of RV dysfunction. Advancing the probe to the transgastric level allows for further evaluation of RV function in the short-axis view. After examining the right-sided chambers, all segments of the left side of the heart should be reviewed. This examination can be performed by using all sector planes in the midesophageal views (four-chamber view at 0 degrees, two-chamber at 90 degrees, and aortic long-axis view at 120–150 degrees) and transgastric views.

Special attention should be given to new regional wall motion abnormalities, systolic thickening, and excursion of all segments of the left ventricle, evidence of LVOT obstruction from systolic anterior motion of the mitral valve, new valvular abnormalities, and overall end-diastolic and systolic chamber dimensions. New regional wall motion abnormalities may signify a technically flawed CABG or intracoronary air. LVOT obstruction from systolic anterior motion may indicate the presence of inadequate chamber filling from hypovolemia and tachycardia or a hyperdynamic state of contractility. New valvular abnormalities may represent iatrogenic damage to the valvular apparatus, myocardial ischemia, volume overload, or ventricular dysfunction. It is also important to scan the aorta to rule out a new aortic dissection after aortic decannulation. As time permits, TEE can also be used to calculate SV and CO by Doppler interrogation of the LVOT and aortic outflow tract. Diastolic filling profiles of the left ventricle and left atrium may be obtained using transmitral and pulmonary venous inflow, respectively. Serial measurements of LA and LV inflow may allow for estimating filling pressures and chamber compliance.

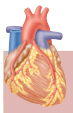
Adequate oxygenation and ventilation should be confirmed by arterial blood gas or pulse oximetry and capnography. Bleeding from the heart should be at a manageable level before removal of the arterial cannula. The perfusionist should not have to transfuse significant amounts of blood through the arterial cannula before removing it because keeping up with the blood loss through intravenous infusions alone may be difficult. Bleeding sites behind the heart may have to be repaired on CPB if the patient cannot tolerate lifting of the heart to expose the problem area. At the time of arterial decannulation, the systolic pressure should be lowered to between 85 and 100 mm Hg to minimize the risk for dissection or tearing of the aorta.[45] The head of the bed may be raised, or small boluses of a short-acting vasodilator may be given to lower the systemic blood pressure as necessary. Tight control of the arterial blood pressure may be needed for a few minutes until the cannulation site is secure. The routine process of discontinuing bypass is completed when removal of all cannulas is successful and full reversal of the anticoagulation is achieved.

Pharmacologic Management of Ventricular Dysfunction

Perioperative ventricular dysfunction usually is a transient state of contractile impairment that may require temporary support with positive inotropic agents. In a subset of patients, contractility may be significantly depressed such that combination therapy with positive inotropes and vasodilator agents is needed to improve CO and tissue perfusion effectively. The use of mechanical assist devices is reserved for conditions of overt or evolving cardiogenic shock.

Severe ventricular dysfunction, specifically the LCOS, occurring after CPB and cardiac operations differs from chronic congestive HF (CHF) (Box 36.2). Patients emerging from CPB have hemodilution, moderate hypocalcemia, hypomagnesemia, and altered K^+ levels. Depending on temperature and depth of anesthesia, these patients may demonstrate low, normal, or high SVR. Increasing age, female sex, decreased LV ejection fraction (LVEF), diastolic dysfunction, prolonged aortic cross-clamp time, and increased duration of CPB are associated with a greater likelihood that inotropic support will be needed after CABG procedures (see Table 36.3).[30,32,37,46]

Contractile dysfunction during or after cardiac operations can result from preexisting impairment in contractility or may be a new-onset condition. Abnormal contraction, especially in the setting of coronary artery disease (CAD), usually is caused by myocardial injury resulting in ischemia or infarction. The magnitude of contractile dysfunction corresponds to the extent and duration of injury. Brief periods of myocardial oxygen deprivation (<10 minutes) produce regional contractile dysfunction, which can be rapidly reversed by reperfusion. Extension of the ischemia to 15 to 20 minutes also is associated with restoration of cardiac function with reperfusion; however, this process is very slow and can take hours to days. This condition of postischemic reversible myocardial dysfunction in the presence of normal flow is referred to as *myocardial stunning*.[47–50] Irreversible cell injury occurs with longer periods of ischemia and produces myocardial infarction characterized by release of intracellular enzymes, disruption of cell membranes, influx of Ca^{2+}, persistent contractile dysfunction, and eventual cellular swelling and necrosis.[51]



BOX 36.2 RISK FACTORS FOR THE LOW CARDIAC OUTPUT SYNDROME AFTER CARDIOPULMONARY BYPASS

- Preoperative ventricular dysfunction
- Myocardial ischemia
- Poor myocardial preservation
- Reperfusion injury
- Inadequate cardiac surgical repair or revascularization

In addition to the previously described factors, RV dysfunction and RV failure are potential sources of morbidity and death after cardiac operations.[52–54] Numerous factors may predispose patients to the development of perioperative RV dysfunction, including CAD, RV hypertrophy, previous cardiac operation, and operative considerations such as inadequate revascularization or hypothermic protection. Technical and operative difficulties are associated with various cardiac surgical procedures (eg, right ventriculotomy), RV trauma, rhythm and conduction abnormalities, injury to the right ventricle during cessation of CPB, or protamine reaction.

The following discussion provides an overview of the pharmacologic approach to management of perioperative ventricular dysfunction in the setting of cardiac surgery. Management goals are described in Table 36.5. These are extensions of the routine preparations made for discontinuing CPB shown in Table 36.2.

Sympathomimetic Amines

Sympathomimetic drugs (ie, catecholamines) are pharmacologic agents capable of providing inotropic and vasoactive effects (Box 36.3). Catecholamines exert positive inotropic action by stimulation of the β_1- and β_2-receptors.[55–57] The predominant hemodynamic effect of a specific catecholamine depends on the degree to which the various α, β, and dopaminergic receptors are stimulated (Tables 36.6 and 36.7).

The physiologic effect of an adrenergic agonist is determined by the sum of its actions on α, β, and dopaminergic receptors. The effectiveness of any adrenergic agent is influenced by the availability and responsiveness of adrenergic receptors. Chronically increased levels of plasma catecholamines (eg, chronic CHF and long CPB time) cause downregulation of the number and sensitivity of β-receptors.[58] Acute depression of β-adrenergic receptor signaling has been reported following CPB.[59] Maintenance of normal acid-base status, normothermia, and electrolytes also improve the responsiveness to adrenergic-receptor stimulation.

The selection of a drug to treat ventricular dysfunction is influenced by pathophysiologic abnormalities, as well as by the physician's experience and preference. If LV performance is decreased primarily as a result of diminished contractility, the drug chosen should increase contractility. Although β-agonists improve contractility and tissue perfusion, their effects may increase myocardial oxygen consumption

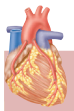
TABLE 36.5 Goals and Management of Cardiac Dysfunction

Variable	*Physiologic Management*
Heart rate and rhythm	Maintain normal sinus rhythm, avoid tachycardia; for tachycardia or bradycardia, consider pacing or chronotropic agents (atropine, isoproterenol, epinephrine), correct acid-base, electrolytes, and review current medications
Contractility	Assess hemodynamics, perform TEE to assess cardiac function, inspect for RWMA, rule out ischemia or infarction, inspect for dynamic outflow obstruction, consider inotropes; consider combination therapy with inotropes and/or vasodilators, and evaluate need for assist devices (IABP/LVAD/RVAD)
Preload	Assess end-diastolic volumes and chamber dimensions on TEE, rule out ischemia, significant valvular lesions, tamponade, and intracardiac shunts; reduce increased preload with diuretics or venodilators (nitroglycerin); monitor CVP, PCWP, and SV; consider using inotropes, IABP, or both
Afterload	Avoid increased afterload (increased wall tension), use vasodilators; avoid hypotension; maintain coronary perfusion pressure; consider IABP, inotropes devoid of α_1-adrenergic effects (dobutamine or milrinone), or both IABP and inotropes
Oxygen delivery	Increase Fio_2 and CO; check ABGs and chest radiograph; confirm adequate ventilation and oxygenation; correct acid-base disturbances

ABG, Arterial blood gas; *CO,* cardiac output; *CVP,* central venous pressure; *Fio_2,* fraction of inspired oxygen concentration; *IABP,* intraaortic balloon pump; *LVAD,* left ventricular assist device; *PCWP,* pulmonary capillary wedge pressure; *RVAD,* right ventricular assist device; *RWMA,* regional wall motion abnormality; *SV,* stroke volume; *TEE,* transesophageal echocardiography.

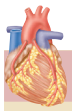
TABLE 36.6 Sympathomimetic Agents

	Dosage		Site of Action		
Drug	*Intravenous Bolus*	*Infusion*	*α*	*β*	*Mechanism of Action*
Dobutamine	—	2–20 μg/kg per min	+	++++	Direct
Dopamine	—	1–10 μg/kg per min	++	+++	Direct and indirect
Epinephrine	2–16 μg	2–10 μg/min Or 0.01–0.4 μg/kg per min	+++	+++	Direct
Ephedrine	5–25 mg	—	+	++	Direct and indirect
Isoproterenol	1–4 μg	0.5–10 μg/min Or 0.01–0.10 μg/kg per min		++++	Direct
Norepinephrine	—	2–16 μg/min Or 0.01–0.3 μg/kg per min	++++	+++	Direct



BOX 36.3 PHARMACOLOGIC APPROACHES TO VENTRICULAR DYSFUNCTION

- Inotropic drugs
- Phosphodiesterase inhibitors
- Calcium sensitizer
- Vasodilators
- Vasopressors
- Metabolic supplements



BOX 36.4 INOTROPIC DRUGS

- Epinephrine
- Norepinephrine
- Dopamine
- Dobutamine
- Isoproterenol

($M\dot{V}o_2$) and reduce coronary perfusion pressure (CPP). However, if the factor most responsible for decreased cardiac function is hypotension with concomitantly reduced CPP, infusion of α-adrenergic agonists can increase blood pressure and improve diastolic coronary perfusion.

Catecholamines also are effective for treating primary RV contractile dysfunction, and all the β_1-adrenergic agonists augment RV contractility. Studies have documented the efficacy of epinephrine, norepinephrine, dobutamine, isoproterenol, dopamine, levosimendan, and phosphodiesterase fraction III (PDE III) inhibitors in managing RV contractile dysfunction. When decreased RV contractility is combined with increased afterload, agents that exert vasodilator and positive inotropic effects may be used, including epinephrine, isoproterenol, dobutamine, levosimendan, PDE III inhibitors, and inhaled nitric oxide or prostaglandins.[60–66]

Epinephrine

Epinephrine is an endogenous catecholamine that stimulates both α- and β-adrenergic receptors in a dose-dependent fashion.[56,57] The β-selective pharmacology of epinephrine is characterized by a higher binding affinity for the β-receptor at lower doses and a stronger preference for the α-receptor at higher doses. This provides the clinical basis for the biphasic response observed for epinephrine, in which at lower doses the hemodynamic effects are predominated by increased inotropy and chronotropy of the heart (β-effect), and at higher doses a vasopressor effect (α-effect) is primarily observed.[56,57]

Epinephrine is often used to facilitate the separation from CPB (Box 36.4). In the earliest studies, epinephrine infusion at 0.03 μg/kg per minute following CPB resulted in an increase in cardiac index (CI), MAP, and HR by 30%, 27%, and 11%, respectively, compared with baseline.[67]

In another study, epinephrine infusion at dosages of 0.01, 0.02, and 0.04 μg /kg per minute was shown to increase SV by 2%, 12%, and 22%, respectively, corresponding to an increased CI of 0.1, 0.7, and 1.2 L/m^2 per minute.[68] In the lower dose range (0.01–0.04 μg/kg per min), the effect on the HR was less pronounced, with a maximum increase of 10 beats/minute in this study. Lobato and colleagues[69] similarly demonstrated, during CABG procedures, an increase in CO with a negligible increase in HR following CPB in response to an infusion of epinephrine at a dose of 0.03 μg/kg per minute. In a study comprising patients receiving preoperative β-blockers, epinephrine at a higher dose of 0.1 μg/kg per minute produced significant increases in CI and HR of 24.1% and 14.1%, respectively, compared with placebo.[70]

TABLE 36.7 Hemodynamic Effects of Inotropes

Drug	*CO*	*dP/dt*	*HR*	*SVR*	*PVR*	*PCWP*	*$M\dot{v}o_2$*
Dobutamine							
2–20 μg/kg per min[a]	↑↑↑	↑	↑↑	↓	↓	↓ or ↔	↑
Dopamine							
0–3 μg/kg per min	↑	↑	↑	↓	↓	↑	↑
3–10 μg/kg per min	↑↑	↑	↑	↓	↓	↑	↑
>10 μg/kg per min	↑↑	↑	↑↑	↑	(↑)	↑ or	↑↑
Isoproterenol							
0.5–10 μg/min	↑↑	↑↑	↑↑	↓↓	↓	↓	↑↑
Epinephrine							
0.01–0.4 μg/kg per min	↑↑	↑	↑	↑ (↓)	(↑)	↑ or ↔	↑↑
Norepinephrine							
0.01–0.3 μg/kg per min	↑	↑	↔ (↑↓)	↑↑	↔	↔	↑
Phosphodiesterase Inhibitors[b]	↑↑	↑	↑	↓↓	↓↓	↓↓	↓
Levosimendan[c]	↑↑↑	↑↑	↑	↓↓	↓↓	↓↓	↓ or ↔

[a]The indicated dosages represent the most common dosage ranges. For the individual patient, a deviation from these recommended doses may be indicated.
[b]Phosphodiesterase inhibitors are usually given as a loading dose followed by a continuous infusion: amrinone: 0.5 to 1.5 mg/kg loading dose, 5 to 10 μg/kg per minute continuous infusion; milrinone: 50 μg/kg loading dose, 0.375 to 0.75 μg/kg per minute continuous infusion.
[c]Levosimendan is usually administered as a loading dose followed by an infusion for 24 hours: 8 to 24 μg/kg loading dose, 0.1 to 0.2 μg/kg per minute (Toller W, Heringlake M, Guarracino F, et al. Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion. *Int J Cardiol.* 2015;184:323–336.)
CO, Cardiac output; *dP/dt,* myocardial contractility; *HR,* heart rate; *$M\dot{v}o_2$*, myocardial oxygen consumption; *PCWP,* pulmonary capillary wedge pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance; ↑, mild increase; ↑↑, moderate increase; ↑↑↑, major increase; ↔, no change; ↓, mild decrease; ↓↓, moderate decrease.
Modified from Lehmann A, Boldt J. New pharmacologic approaches for the perioperative treatment of ischemic cardiogenic shock. *J Cardiothorac Vasc Anesth.* 2005;19:97–108.

The results of these studies suggest that elevations in HR may be an effect observed at higher doses. Moreover, epinephrine is also used frequently after cardiac operations to support the function of the "stunned" reperfused heart following CPB. During emergence from CPB, Butterworth and associates[71] showed that epinephrine (0.03 μg/kg per min) increased CI and SV by 14% without increasing HR. In summary, epinephrine (0.01–0.04 μg/kg per min) at certain doses effectively increases CO with minimal increases in HR following CPB (see Table 36.7).[67–69,71] (see Chapters 11 and 38).

Dobutamine

Dobutamine is a synthetic catecholamine that displays a strong affinity for the β-receptor and results in dose-dependent increases in CO and HR, as well as reductions in diastolic filling pressures.[61] Administration of dobutamine in cardiac surgical patients produced a marked increase in CI and HR in several studies.[61,67,71,72] In patients with the LCOS, dobutamine resulted in an increase in HR in excess of 25% and a significant concomitant decrease in SVR.[61,72] The effects of epinephrine (0.03 μg/kg per min) were compared with those of dobutamine (5 μg/kg per min) in 52 patients recovering from CABG procedures.[71] Both drugs significantly and similarly increased SV index (SVI), but epinephrine increased the HR by only 2 beats/minute, whereas dobutamine increased the HR by 16 beats/minute. In an observational study of 100 cardiac surgical patients, HR increased by an average of 1.45 beats/minute per μg/kg per minute of dobutamine.[73] In the randomized multicenter trial comparing dobutamine and milrinone in patients with low CI (<2.0 L/m^2 per min), CI increased by 55% versus 36% after 1 hour in the dobutamine-treated group compared with the milrinone-treated group.[61] The hemodynamic effects of dobutamine were also characterized by a 35% increase in HR (vs 10% with milrinone) and a 31% increase in MAP (vs 7% with milrinone). Dobutamine was also associated with significantly higher incidences of hypertension and new atrial fibrillation (18% vs 5%; $P < .04$).[61]

In addition to increasing contractility, dobutamine may have favorable metabolic effects on ischemic myocardium. Intravenous and intracoronary injections of dobutamine increased coronary blood flow in animal studies.[74] In paced cardiac surgical patients, dopamine increased oxygen demand without increasing oxygen supply, whereas dobutamine increased myocardial oxygen uptake and coronary blood flow. However, because increases in HR are a major determinant of $M\dot{v}o_2$, these favorable effects of dobutamine could be lost if dobutamine induces tachycardia. During dobutamine stress echocardiography, segmental wall motion abnormalities suggestive of myocardial ischemia can result from tachycardia and increases in $M\dot{v}o_2$ (see Chapters 1 and 2).[75]

Dopamine

Dopamine is an endogenous catecholamine and an immediate precursor of norepinephrine and epinephrine. Its actions are mediated by stimulation of adrenergic receptors and specific postjunctional dopaminergic receptors (D_1 receptors) in the renal, mesenteric, and coronary arterial beds.[56,57,76] Dopamine is unique in comparison with other endogenous catecholamines because of its effects on the kidneys. It has been shown to increase renal artery blood flow by 20% to 40% by causing direct vasodilation of the afferent arteries and indirect vasoconstriction of the efferent arteries.[77] This action results in increases in glomerular filtration rate and in oxygen delivery to the juxtamedullary nephrons. In low doses (0.5–3.0 μg/kg per minute), dopamine predominantly stimulates the dopaminergic receptors; at doses ranging from 3 to 10 μg/kg per minute, it activates most adrenergic receptors in a nonselective fashion; and at higher doses (>10 μg/kg per min), dopamine behaves as a vasoconstrictor. The dose-dependent effects of dopamine are not very specific and can be influenced by multiple factors such as receptor regulation, concomitant drug use, and interindividual and intraindividual variability.[56,57,67]

In patients undergoing cardiac surgical procedures, dopamine in the dose range of 2.5 and 5.0 μg/kg per minute was observed to produce significant increases in CI and HR.[72,78] Doses greater than 5 μg/kg per minute may result in significant increases in MAP and pulmonary vascular resistance (PVR) without increasing CO.[78] In patients with the LCOS following cardiac operations, dopamine produced a 57.9% increase in CI compared with baseline and a simultaneous increase in HR by 25.5% in one study.[79] Tarr and colleagues[72] compared the efficacies of dopamine, dobutamine, and enoximone for weaning from CPB in a randomized trial of 75 patients. Nine of the 25 patients randomly assigned to dopamine displayed a poor and inadequate hemodynamic response. The remaining 16 patients recorded an increase in CI of 25.7% and elevations in HR of 44.3%, with minimal increase in SVI after receiving dopamine. The CI in the dopamine-treated group was significantly lower than in patients treated with dobutamine.[72] In the early study by Steen and associates,[67] dopamine caused more frequent and less predictable degrees of tachycardia than dobutamine or epinephrine at doses that produced comparable improvement in contractile function. These studies suggest that the hemodynamic

effects of dopamine at lower doses are predominately characterized by marked elevations in HR and moderate increases in CI. At higher doses, increases in MAP and PVR predominate without an increase in CO. The propensity of dopamine to increase HR and induce tachyarrhythmias may limit its utility in the cardiac surgical patient emerging from CPB.

Norepinephrine

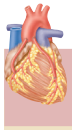
Norepinephrine is an endogenous catecholamine exhibiting potent α-adrenergic activity with a mild-to-modest effect on the β-adrenergic receptor.[56,57] The higher affinity for norepinephrine for the α-adrenergic receptor provides the basis for its powerful vasoconstrictor effect and less potent inotropic and chronotropic properties. The overall hemodynamic effects of norepinephrine are characterized by an increase in systolic, diastolic, and pulse pressure, with minimal net impact on CO and HR. In this regard, norepinephrine is used primarily to manage low SVR secondary to vasodilation after CPB. In this setting, norepinephrine has been used to increase MAP in patients receiving inotropic support. Norepinephrine has been used in combination with milrinone, dobutamine, or levosimendan to counteract systemic vasodilation and hypotension in patients following CPB.[80,81] Norepinephrine has also been reported in the management of sepsis. Meadows and associates[82] treated 10 patients with severe sepsis and hypotension unresponsive to volume expansion, dopamine, and dobutamine. Norepinephrine infusion (0.03–0.89 μg/kg per min) alone improved arterial blood pressure, LV stroke work index, urine output, and, in most cases, CI. Desjars and colleagues[83] studied the renal effects of prolonged norepinephrine infusion in hypotensive patients with sepsis. Norepinephrine (0.5–1.0 μg/kg per min) in combination with low-dose dopamine improved urine flow and renal function compared with dopamine alone.[83] Norepinephrine may be effective in restoring MAP in patients with a low SVR after CPB (ie, vasoplegia syndrome).[84] When cardiac dysfunction is primarily a result of decreased CPP, vasoconstrictors may be used to optimize performance.

Isoproterenol

Isoproterenol is a potent, nonselective β-adrenergic agonist, devoid of α-adrenergic agonist activity. Isoproterenol dilates skeletal, renal, and mesenteric vascular beds and decreases diastolic blood pressure.[56] The potent chronotropic action of isoproterenol, combined with its propensity to decrease CPP, limits its usefulness in patients with CAD. Applications include treatment of bradycardia (especially after orthotopic heart transplantation), pulmonary hypertension, and HF after surgical treatment of congenital cardiac disease.[85] Isoproterenol remains the inotrope of choice for stimulation of cardiac pacemaker cells in the management of acute bradyarrhythmias or atrioventricular heart block. Its use for this purpose during cardiac surgery is limited because artificial pacing is usually easily accomplished in this setting. This drug reduces refractoriness to conduction and increases automaticity in myocardial tissues. The tachycardia seen with isoproterenol is a result of direct effects of the drug on the sinoatrial and atrioventricular nodes and reflex effects caused by peripheral vasodilation. Isoproterenol is routinely used in the setting of cardiac transplantation for increasing automaticity and inotropy, as well as for its vasodilatory effect on the pulmonary arteries.

Phosphodiesterase Inhibitors

The PDE III inhibitors milrinone and amrinone (inamrinone), are bipyridine derivatives that increase cyclic adenosine monophosphate (cAMP), Ca^{2+} flux, and Ca^{2+} sensitivity of contractile proteins.[56,57] PDE III inhibitors increase the level of cAMP by inhibiting its breakdown within the cell; this action leads to increased myocardial contractility. These drugs have a unique site of action in that they do not bind and activate the adrenergic receptor. Their positive effects on inotropy are mediated primarily through an inhibition of the PDE enzyme and not through β-receptor stimulation. As a result, the effectiveness of the PDE III inhibitors is not altered by previous β-blockade, nor is it reduced in patients who may experience β-receptor downregulation.[58] In addition to their positive inotropic effects, these agents produce systemic and pulmonary vasodilation and improve diastolic relaxation (lusitropy). For these reasons, the term *inodilator* has been used to describe this class of drugs (Box 36.5).



BOX 36.5 INODILATOR DRUGS AND OTHER AGENTS

- Inamrinone
- Milrinone
- Dobutamine
- Epinephrine plus nitroprusside ("epipride")
- Levosimendan
- Nesiritide

Milrinone has been shown to increase CO without increasing overall $M\dot{v}o_2$. Monrad and colleagues[86] administered milrinone to patients with CHF; CI increased by 45%, but overall $M\dot{v}o_2$ did not change.[86] Several studies also suggested that milrinone may improve myocardial diastolic relaxation and compliance (ie, positive "lusitropic" effect) while augmenting coronary perfusion.[30,69,87,88] The proposed mechanism for this effect on diastolic performance is that by decreasing LV wall tension, ventricular filling is enhanced, and myocardial blood flow and oxygen delivery are optimized (see Table 36.7). The ability of short-term administration of milrinone to augment ventricular performance in patients undergoing cardiac surgical procedures was shown in the results from the European Milrinone Multicentre Trial Group.[89] In this prospective study, intravenous milrinone was studied in patients after CPB. All patients received a bolus infusion of milrinone at 50 μg/kg over 10 minutes, followed by a maintenance infusion of 0.375, 0.5, or 0.75 μg/kg per minute for 12 hours. Significant increases in SV and CI were observed. In addition, significant decreases in pulmonary capillary wedge pressure, central venous pressure, pulmonary artery pressure, MAP, and SVR were seen. Eighteen patients (14%) had arrhythmias, most of which occurred in the group receiving 0.75 μg/kg per minute. Two arrhythmic events were deemed serious; both were bouts of rapid atrial fibrillation occurring with the larger dose.

In another study, Bailey and associates[90] also showed that after CPB, a loading dose of milrinone at 50 μg/kg, followed by a continuous infusion of 0.5 μg/kg per minute, resulted in a significant increase in CO. Moreover, in a dose-escalation study, Butterworth and colleagues[91] investigated the pharmacokinetics and pharmacodynamics of milrinone in adult patients undergoing cardiac operations; milrinone (bolus doses of 25, 50, or 75 μg/kg) was given if the CI was less than 3.0 L/m^2 per minute after separation from CPB. All three bolus doses of milrinone significantly increased CI. The 50 and 75 μg/kg doses produced significantly greater increases in CI than did the 25 μg/kg dose. The 75 μg/kg dose produced increases in CI comparable to those observed with the 50 μg/kg dose, but the higher dose was associated with more hypotension, despite administration of intravenous fluid, blood, and a phenylephrine infusion. The initial redistribution half-lives were 4.6, 4.3, and 6.9 minutes, and the terminal elimination half-lives were 63, 82, and 99 minutes for the 25, 50, and 75 μg/kg doses, respectively. The results of these investigations suggest that for optimizing hemodynamic performance (while minimizing potential for arrhythmias), the middle dose range (ie, loading dose of 50 μg/kg) of milrinone may be most efficacious, with a continuous infusion of 0.5 μg/kg per minute, leading to a plasma concentration of more than 100 ng/mL. In patients with poor LV function, the loading dose should be given during CPB to avoid a decrease in MAP and to minimize the need for other inotropes on discontinuing CPB.[91–93]

Amrinone represents the first-generation PDE III inhibitor used to wean from CPB. Compared with dobutamine, amrinone was found to be more effective for separation from CPB, with observed increases

in SV and CO and decreases in SVR and PVR.[94,95] Gage and colleagues[96] reported that when amrinone was used in combination with dobutamine, CO was significantly increased compared with therapy with dobutamine alone. Thrombocytopenia has been a potential clinical concern with the administration of PDE III inhibitors. Currently, amrinone has been implicated in causing dose-dependent thrombocytopenia, thus limiting its utility in cardiac surgical procedures.[97,98] By contrast, the potential negative effects of PDE III inhibitors on platelets were not demonstrated with milrinone. George and associates[99] were unable to demonstrate any significant reduction in platelet count after 48 hours of milrinone infusion in cardiac surgical patients. Similarly, Kikura and colleagues[100] found that milrinone administration did not cause significant changes in platelet number or function in patients undergoing cardiac operations with CPB compared with controls.

In summary, the PDE III class of inodilators has a unique mechanism of action independent of the β-receptor. These agents combine increases in contractility with reductions in SVR and PVR. In addition, the properties that govern relaxation and compliance of the heart are enhanced with PDE III inhibitors and allow these drugs to improve diastolic filling. These unique properties render PDE III inhibitors particularly useful in patients with β-receptor downregulation, right-sided heart dysfunction, pulmonary hypertension, diastolic dysfunction, and the LCOS.[57]

Calcium Sensitizers

Levosimendan is a positive inotropic drug belonging to the unique class of Ca^{2+} sensitizers.[56,57] Levosimendan binds three distinct sites of action, and this property characterizes its unique tripartite mechanism of action and pharmacologic effects.[101] In the myocardium, levosimendan selectively binds troponin C through a Ca^{2+}-dependent binding site stabilizing the cross-bridging mechanism and resulting in positive inotropy. Levosimendan also specifically binds to the ATP-dependent K^+ channel (K^+/ATP) in cardiac mitochondria, governing its protective effects against ischemia and reperfusion injury. By regulating Ca^{2+} influx in the mitochondria, opening of the K^+/ATP channel attenuates infarct size as a result of ischemia-reperfusion injury.[102] The third site of action is at the level of the smooth muscle in the vasculature. At this site, levosimendan binds and opens K^+/ATP channels and thus leads to decreases in SVR and cardiac preload and afterload. The vasodilatory effect on the vasculature has been shown to increase coronary and renal blood flow. Levosimendan is unique in that it confers positive inotropy without an increase in cardiac bioenergetics.[103] The salutary effects on the myocardium are achieved through an observed decrease in overall cardiac workload, cardioprotective effects, lusitropy, and a net increase in myocardial oxygen supply.[101,103,104]

The pharmacokinetics and pharmacodynamics of levosimendan are unique in that an active metabolite is formed with potency and efficacy similar to those of the parent compound.[105,106] Following a loading dose, steady-state levels are reached at approximately 4 hours after drug infusion. However, an active metabolite known as OR-1986 peaks at 48 hours and remains active for more than 300 hours (12–14 days after the end of infusion). The active metabolite, OR-1986, is primarily responsible for the sustained increase in SVI, decrease in cardiac workload, and improved coronary and renal blood flow in patients with the LCOS following cardiac surgical procedures. The formation of an intermediate- or long-acting metabolite may allow for earlier pharmacologic weaning without fear of losing the beneficial inotropic and hemodynamic effects as a result of drug discontinuation. Moreover, because the mechanism of action is independent of the β-receptor, concomitant administration of β-blocker therapy and levosimendan is not antagonistic.[107] This property allows for earlier reinstitution of β-blocker therapy for prevention or management of postoperative tachyarrhythmias.[108]

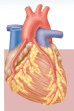
The effective perioperative use of levosimendan has been described in cardiac surgical patients with low LVEF.[109–112] In summary, levosimendan improved myocardial performance with an observed increase in SVI and coronary blood flow, as well as a decrease in SVR while minimizing oxygen consumption.[112] Levin and associates[113] demonstrated the superiority of levosimendan versus dobutamine in a randomized trial comprising 137 patients with the LCOS after CABG procedures. The postoperative 30-day mortality rate was lower in the levosimendan group compared with dobutamine (8.7% vs 25%; $P < .05$), as was the need for vasopressors, second or third inotropes, and IABP use.

In another study comparing the combined effects of levosimendan and dobutamine versus milrinone and dobutamine, patients receiving levosimendan and dobutamine demonstrated a sustained increase in SVI several hours after discontinuation of dual drug therapy compared with a dobutamine-milrinone combination.[114] Patients in the dobutamine-levosimendan arm of the trial also required less vasopressor support compared with the dobutamine-milrinone group. In a meta-analysis of clinical trials, Harrison and colleagues[115] evaluated the effects of levosimendan in cardiac surgical patients with and without preoperative systolic dysfunction. These investigators showed that death and other adverse outcomes, such as postoperative renal failure requiring dialysis, postoperative atrial fibrillation, and myocardial injury, were reduced with levosimendan treatment. These benefits were greatest for the patients with diminished LVEF. In the randomized, double-blind study by Eriksson and colleagues, levosimendan facilitated weaning from CPB and reduced the need for additional inotropic or mechanical circulatory support in patients with impaired LVEF (≤50%) who were undergoing CABG.[116] Sixty patients received either levosimendan as a 12 μg/kg bolus followed by 0.2 μg/kg per minute infusion, or placebo, immediately after the induction of anesthesia. Levosimendan significantly facilitated primary weaning from CPB as compared with placebo ($P = .002$). In four patients in the placebo group, the second weaning attempt failed, and these patients had to be supported by IABP, as compared with none in the levosimendan group (P = NS).

Currently, levosimendan is recommended by the European Society of Cardiology for treatment of acute worsening of HF and for acute HF after myocardial infarction.[112,117] It also has been found to enhance contractile function of stunned myocardium in patients with acute coronary syndromes.[118] It is available clinically in Europe and is now undergoing phase III trials in the United States.[112] The use of levosimendan has been reported in cardiac surgical patients with high perioperative risk, compromised LV function, difficulties in weaning from CPB, and severe RV failure after mitral valve replacement.[112,119–124] The drug has been used preoperatively, during emergence from CPB, and in the postoperative period for up to 28 days. The potential for levosimendan to produce increased contractility, decreased resistance, minimal metabolic cost, and minimal arrhythmias makes it a potentially useful addition to the treatments for patients with the LCOS or RV failure.

Vasodilators

The indications for using vasodilators such as NTG, sodium nitroprusside (SNP), nicardipine, and clevidipine in cardiac surgery include management of perioperative systemic or pulmonary hypertension, myocardial ischemia, and ventricular dysfunction complicated by excessive pressure or volume overload (Box 36.6).[125–128] In most conditions, NTG, SNP, or clevidipine may be used because of their shared features such as rapid onset, ultrashort half-lives, and easy titratability. Nevertheless, important pharmacologic differences exist among these vasodilators. In the setting of CAD or ischemia, NTG is preferred because it selectively vasodilates coronary arteries without producing coronary "steal." Similarly, in the management of ventricular volume overload or RV pressure overload, NTG may offer some advantage over SNP. NTG has a predominant influence on the venous bed such that preload can be reduced without significantly compromising systemic arterial pressure. The benefits of NTG are improvement in SV, reduction in wall tension and $M\dot{V}o_2$, increased perfusion to the subendocardium as a result of a lower LVEDP, and maintenance of CPP. SNP is a more potent arterial vasodilator and may potentiate myocardial



BOX 36.6 VASODILATOR MECHANISMS HELPFUL IN DISCONTINUING CARDIOPULMONARY BYPASS

- Decreased right and left ventricular wall stress (afterload)
- Decreased venous return (preload)
- Improved lusitropy
- Improved coronary blood flow

ischemia because of a coronary steal phenomenon or a reduction in CPP. Its greater potency, however, makes SNP a more rational choice for management of perioperative hypertensive disorders and for afterload reduction during or after operations for regurgitant valvular lesions.[125]

Although NTG and SNP have been used for the management of hypertension during cardiac surgical procedures, they both have notable limitations. NTG use as a primary antihypertensive agent is limited by its weak effect on arterial vasodilation. SNP is a potent arterial dilator, but its use is associated with reflex tachycardia, tachyphylaxis, inhibition of hypoxic pulmonary vasoconstriction, increase in intracranial pressure, and reduced renal blood flow.[128] The potential for cyanide toxicity is also an important consideration when administering SNP. This drug also may be difficult to titrate and often causes hypotension related to overshoot. In light of these limitations, the Ca^{2+} channel blocker class of antihypertensive agents such as clevidipine and nicardipine may prove to be valuable alternatives.

Clevidipine is an ultrafast-acting, dihydropyridine L-type Ca^{2+} channel blocker with a direct action on arteriolar resistance vessels and limited effects on venous capacitance vessels.[128–130] The fast onset and offset of approximately 1 minute make clevidipine especially suited for intraoperative management of acute hypertension.[131] Nicardipine is also a dihydropyridine Ca^{2+} channel blocker with a selective arterial vasodilator mode of action.[125,132,133] Nicardipine has a beneficial hemodynamic profile in that the drug reduces systemic and coronary artery resistance while increasing coronary blood flow. However, its use may be limited to the postoperative setting because of its longer half-life and slower offset of action compared with clevidipine.[134,135] In the ECLIPSE (Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events) trial, clevidipine was compared with NTG, SNP, and nicardipine in the perioperative treatment of hypertension during cardiac surgical procedures.[128] In an analysis of the individual treatment cohorts, clevidipine was significantly more effective at achieving blood pressure targets within the prespecified range compared with NTG or SNP in the perioperative period. In the postoperative period, the efficacy of clevidipine was similar to that of nicardipine in achieving blood pressure control after cardiac operations. With respect to safety profile, no differences in the incidences of myocardial infarction, stroke, or renal dysfunction were observed among the treatment groups. Mortality rates were similar between the clevidipine-treated versus NTG-treated groups and the clevidipine versus nicardipine-treated groups, whereas mortality rates appeared to be higher in the SNP-treated group compared with the clevidipine-treated group ($P = .04$ in a univariate analysis). The incidence of atrial fibrillation and sinus tachycardia were similar between clevidipine and all comparators.[128]

Despite the benefits of vasodilator therapy in the management of CHF, these drugs can be difficult to use in treatment of perioperative ventricular dysfunction. This is most evident in cases of the LCOS when impaired pump function is complicated by inadequate perfusion pressure. In these situations, multidrug therapy with vasoactive and cardioactive agents is warranted (ie, NTG or SNP in combination with epinephrine or milrinone and norepinephrine). Combination therapy enables greater selectivity of effect. The unwanted side effects of one drug can be avoided while supplementing the desired effects with another agent.[136,137] To maximize the desired effects of any particular combination of agents, frequent assessment of cardiac performance with a pulmonary artery catheter and TEE is needed. This approach allows the Starling curve and the pressure-volume loops to be visualized as they are shifted up and to the left with therapy (see Chapters 6, 13, and 38).

Vasoplegic Syndrome and Cardiopulmonary Bypass

The concept of the vasoplegic syndrome, characterized by hypotension associated with profound vasodilation unresponsive to conventional catecholamines or vasopressors, was introduced in association with CPB in the late 1990s.[138] It has been linked with preoperative use of vasodilators and shown to be a risk factor for increased morbidity and death after cardiac surgical procedures.[139] Two pharmacologic agents have been reported to be used to treat vasoplegic syndrome after CPB: vasopressin and methylene blue (MB).

Vasopressin

Arginine vasopressin (antidiuretic hormone) is a peptide hormone normally produced in the posterior pituitary that plays a crucial role in water homeostasis by controlling water resorption in the renal collecting ducts.[140] Administered as an intravenous infusion, vasopressin was initially used as a potent vasoconstrictor for vasodilatory shock associated with sepsis[141] and ventricular assist device implantation.[142] Because its vasopressor effect is mediated through a different mechanism (VP1 receptors) from that of the catecholamines, vasopressin can be infused at a constant rate as a strategy to decrease high doses of catecholamines such as norepinephrine and has been used in this way to treat vasodilation occurring after CPB.[143] The vasoconstricting effects of vasopressin may spare the pulmonary vasculature, thus making it an attractive choice to treat hypotension associated with RV dysfunction, but this effect has not been clearly demonstrated in intact humans.[144,145] Reported infusion doses vary widely from 0.01 to 0.6 IU/minute.[146] Use of vasopressin has been associated with necrotic lesions of the skin, and this agent should be used with caution and in the lowest possible effective dose.[147]

Methylene Blue

MB, a substance commonly used intravenously during surgical procedures for its ability to dye certain tissues, inhibits guanylate cyclase and hence the production of cyclic guanosine monophosphate, which is known to increase vascular smooth muscle relaxation.[148] MB has been used as a rescue treatment for profound vasodilatory shock in several settings, including cardiac surgery.[149–151] At a dose of 3 mg/kg given during CPB, MB was shown to increase SVR and MAP without adverse effects in a randomized trial of patients taking angiotensin-converting enzyme inhibitors, as well as decrease pressor requirements and serum lactate levels after CPB.[152] In another randomized trial, MB, 2 mg/kg, was given 1 hour preoperatively to patients at risk for CPB-associated vasoplegic syndrome. None of the treatment group developed vasoplegic syndrome, whereas 26% of the control group did.[153] MB causes transient discoloration of the urine and the skin and interferes with pulse oximetry measurements of arterial oxygen saturation. In a retrospective analysis of 57 patients with vasoplegia during cardiac surgical procedures and CPB, use of MB as treatment for vasoplegia was independently associated with poor outcomes.[154] The use of MB has also been implicated in causing serotonin syndrome through its inhibition of monoamine oxidase-A enzyme.[155] In another case report, MB was causally linked to the development of methemoglobinemia during CPB.[156] These reports highlight the need for more studies on the safety and possible poor outcomes associated with MB. Although more studies are warranted, it may be prudent to reserve MB for rescue therapy, as opposed to using it as a preventive agent.[154]

Additional Pharmacologic Therapy

Following the steps outlined in Tables 36.2 and 36.5, most patients can be weaned from CPB. However, a small percentage will be difficult to remove safely from CPB because of their chronic end-stage CHF or an acute insult during cardiac operation that produced cardiogenic shock. These patients probably will require mechanical circulatory support

(eg, IABP, ventricular assist device), as discussed later and in Chapter 28. However, while instituting these further steps, some clinicians may try additional pharmacologic therapy.

Controversial Older Treatments

Some studies suggest that a reduction in plasma thyroid hormone concentration may cause decreased myocardial function after CPB.[157,158] Multiple investigators have documented declines in the circulating triiodothyronine (T_3) concentration during and after CPB, and the most dramatic decreases in T_3 are seen at the end of CPB and during the first few hours after CPB.[157] Thyroid hormone in the form of an intravenous T_3 infusion (2 µg/h to a total dose of 0.5 µg/kg) has been used during cardiac surgical procedures and has resulted in increases in the MAP and HR, as well as reductions in LAP and central venous pressure, in patients who initially could not be weaned from CPB. Moreover, the administration of glucose-insulin-K^+ (GIK) or just glucose and insulin has been found to be useful for metabolic support of the heart after CPB. Insulin therapy may improve glucose use and energy metabolism during cardiac operations, thereby improving myocardial function.[159–163]

Emerging Intravenous Drugs for Heart Failure and Cardiogenic Shock

Natriuretic Peptide

The activation of several neuroendocrine pathways as a result of CPB may contribute to the pathophysiology of postbypass ventricular dysfunction, especially in patients with preoperative LCOS. Release of plasma epinephrine, norepinephrine, and arginine vasopressin has been observed in patients undergoing cardiac surgical procedures with CPB.[164] The overall effects of neuroendocrine activation are the promotion of Na^+ and volume retention and a concomitant increase in SVR, which may contribute to cardiac and renal dysfunction and increased mortality rates.[165,166] The identification of the humoral mediators of neuroendocrine activation has facilitated the development of therapeutic targets aimed at blocking specific neuroendocrine pathways.

The cardiac natriuretic peptides and brain natriuretic peptide (BNP) and their precursors may represent important targets for the modulation or attenuation of the neuroendocrine activation cascade observed in patients with postbypass cardiac dysfunction.[167,168] The recombinant human BNP, nesiritide, possesses both vasodilatory and diuretic effects. This 30–amino acid peptide may also play a role in inhibiting the activation of the renin-angiotensin axis and the release of plasma catecholamines.[169] In patients with HF, intravenous nesiritide acts as a vasodilator and reduces preload and SVR, and CI subsequently increases.[170–172] The drug has no positive inotropic effects. Compared with NTG and dobutamine, nesiritide had a greater effect on decreasing preload than NTG, and it did not cause as many arrhythmias as dobutamine.[173,174] In the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial, patients with LVEF of less than 40% randomized to receive nesiritide during CABG benefited with improved postoperative renal function and enhanced intermediate survival after 180 days.[175] Chen and colleagues[176] studied the renal effects of low-dose nesiritide in patients with preexisting renal dysfunction undergoing cardiac surgical procedures. These investigators demonstrated that 24 hours of a low-dose infusion of nesiritide at 0.005 µg/kg per minute resulted in the preservation of renal function in the nesiritide-treated group at 48 and 72 hours in patients with preexisting renal insufficiency. The results of these two trials suggest that nesiritide may play a future role in preserving renal function in patients undergoing cardiac operations.

Human atrial natriuretic peptide (ANP) is a 28–amino acid peptide produced primarily by the atria in response to an increased intravascular volume.[177] A low-dose infusion of carperitide (Table 36.8), a recombinant form of ANP, in patients with poor LV function during CABG proved effective in improving renal function marked by lower serum creatinine levels and increased glomerular filtration rate in the treatment group.[178,179] In another randomized controlled study of 303 patients with chronic kidney disease who were undergoing CABG, carperitide infusion conferred a cardioprotective effect, as suggested by reduced rates of cardiac events and cardiac-related deaths in the treatment group compared with placebo.[180] Neurohormonal levels of angiotensin II and aldosterone were also reduced 1 week postoperatively in the treatment group. Sezai and associates[179] later investigated the efficacy of carperitide in patients undergoing CABG in a randomized controlled trial of 367 high-risk patients (European System for Cardiac Operative Risk Evaluation [EuroSCORE] >6). This investigation demonstrated that the rates of major adverse cardiac and cerebrovascular events were significantly lower in the carperitide-treated group compared with placebo ($P < .0001$). The rate of dialysis was also significantly lower in the carperitide-treated group ($P = .0147$) compared with the control group. These investigators concluded that in the early postoperative period, carperitide infusion may confer protection against postoperative major adverse cardiac and cerebrovascular events and hemodialysis in high-risk patients undergoing CABG.

In summary, the administration of low-dose carperitide during CABG improved renal and cardiac outcomes, possibly through a combination of vasodilatory and natriuretic effects and modulation of the neurohormonal response during cardiac surgical procedures with CPB. This drug may provide another option in the management of cardiac and renal dysfunction in patients undergoing cardiac operations with CPB.

TABLE 36.8 Emerging Intravenous Drugs for Heart Failure and Cardiogenic Shock

*Drug**	*Molecular Target and Mechanism of Action*	*Phase of Development*
Istaroxime	Inhibition of Na^+/K^+-ATPase and increased SERCA2a ATPase activity	Phase II
Carperitide	Recombinant atrial natriuretic peptide	Phase II
Levosimendan[a]	Calcium sensitizer-troponin C/K^+-ATP channel	Phase II
Nesiritide	Brain natriuretic peptide	Approved
Omecantiv mecarbil	Cardiac myosin ATPase activator	Phase II

[a]Levosimendan is currently approved in Europe and is undergoing phase III trials in the United States.

ATP, Adenosine triphosphate; *ATPase,* adenosine triphosphatase; *K^+,* potassium; *Na^+,* sodium; *SERCA2a,* sarcoplasmic reticulum calcium adenosine triphosphatase isoform 2a pump.

Modified from George M, Rajaram M, Shanmugam E, et al. Novel drug targets in clinical development for heart failure. *Eur J Clin Pharmacol.* 2014;70:765–774.

Istaroxime

Istaroxime is a first in class intravenous steroid derivative that activates the sarcoplasmic reticulum Ca^{2+} ATPase isoform 2a pump (SERCA2a; see Table 36.8). It also possesses a key inhibitory effect on the membrane Na^+/K^+-ATPase.[169,181] Regulating intracellular Ca^{2+} fluxes is a key mechanism in controlling the relaxation and contractile forces of the myocardium. Diminished activity of SERCA2a contributes to poor contractility and relaxation. Istaroxime has shown great promise in the treatment of HF in clinical trials.[182–184] It exerts its action during both the relaxation and contraction phases of the cardiac cycle.[169,183] This action is accomplished by inhibition of the membrane Na^+/K^+ ATPase, thus leading to an overall increase in cytosolic Ca^{2+} available for contraction.[185,186] During diastole, istaroxime enhances Ca^{2+} sequestration into the sarcoplasmic reticulum by increasing SERCA2a pump activity, which ultimately leads to more effective myocardial relaxation. In the phase II randomized, placebo-controlled, double-blind Hemodynamic Effects of Istaroxime in Patients with Worsening Heart Failure and Reduced LV Systolic Function (HORIZON-HF) trial, istaroxime reduced LVEDP and pulmonary capillary wedge pressures while increasing CI and systolic blood pressures in patients with a history of HF and an LVEF of up to 35%.[184] Escalating doses of 0.5, 1, and 1.5 µg/kg per minute were used to study the efficacy of istaroxime in 3 separate cohorts comprising 40 patients in each respective arm.

The investigators noted an increase in systolic blood pressure without a significant change in diastolic blood pressure. A transient increase in CI with the highest dose and a decrease in HR and diastolic and systolic volumes were observed without a change in ejection fraction. Improvement in diastolic filling parameters was also observed on echocardiography in the istaroxime-treated group.[183,184] Istaroxime has not been investigated in patients undergoing cardiac surgical procedures. Nevertheless, the unique properties of this agent make for a promising candidate for the treatment of the LCOS with separation from CPB.

Omecamtiv Mecarbil

Omecamtiv mecarbil is a first in class intravenous myosin activator (see Table 36.8).[169,187] The tight binding of myosin to actin leads to the contraction mechanism. Increasing the tight binding of myosin to actin proportionally enhances the force and the time of contraction. Omecamtiv mecarbil increases the rate of myosin binding onto actin and leads to both improved contractility and increased systolic ejection time.[169,188] This inotrope is unique in that it improves contractile forces at the level of the sarcomere, downstream from the activation of Ca^{2+}-dependent pathways that may be energetically deleterious.[187] In the phase II double-blind, placebo-controlled Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) study, patients receiving omecamtiv mecarbil exhibited a dose-dependent increase in blood pressure and systolic ejection time and a concomitant decrease in HR.[189] Although the primary end point of improvement in dyspnea was not observed, omecamtiv mecarbil may potentially prove to be a valuable drug because of its lack of chronotropic effects. This new drug is currently in phase II clinical trials and awaits further studies to examine its potential role in cardiac surgery.

Pharmacogenetics and Genotyping: the Rational Basis for Individualized Therapy

Variability in gene expression may play a pivotal role in how an individual patient responds to drug therapy.[190,191] Polymorphisms have been implicated in the differential effects of β-blockers, antiplatelet agents, anticoagulant agents, and antiarrhythmic agents in certain patients.[192–194] Similarly, individual differences in the degree of adrenergic receptor downregulation may mediate variable sensitivity to β-agonists.[192,195] Moreover, genotypic polymorphisms of the mediators of the β-adrenergic signaling pathway may be linked to poor outcome resulting from an increased incidence of major adverse cardiac events after cardiac surgical procedures.[192,196] For instance, specific haplotypes of the downstream effector protein, $G_{\alpha s}$, which is coupled to the adrenergic receptor, may be associated with altered cardiac contractility and hemodynamics.[59,197,198] In addition, inflammatory gene polymorphisms have been associated with increased risk of postoperative myocardial infarction.[199] These examples highlight the importance of molecular genotyping in the clinical management and risk stratification of cardiac surgical patients. The study of pharmacogenetics may lay the foundation for personalizing clinical management based on individual genotyping.[196,200] In the future, it may be conceivable to obtain a molecular "fingerprint" of a patient before a cardiac operation and modify prebypass and postbypass management based on the genotype data (see Chapter 8).

Intraaortic Balloon Pump Counterpulsation

The IABP is a device that is designed to augment myocardial perfusion by increasing coronary blood flow during diastole and unloading the left ventricle during systole (see Chapter 28). This is accomplished by mass displacement of a volume of blood (usually 30–50 mL) by alternately inflating and deflating a balloon positioned in the proximal segment of the descending aorta. The gas used for this purpose is carbon dioxide (because of its great solubility in blood) or helium (because of its inertial properties and rapid diffusion coefficients). Inflation and deflation are synchronized to the cardiac cycle by the electronics of the balloon console by producing counterpulsations. The results of effective use of the IABP are often quite dramatic. Improvements in CO, LVEF, coronary blood flow, and MAP frequently are seen, as well as decreases in aortic and ventricular systolic pressures, LVEDP, pulmonary capillary wedge pressure, LAP, HR, frequency of premature ventricular contractions, and suppression of atrial arrhythmias.

TABLE 36.9 Intraaortic Balloon Pump Counterpulsation Indications and Contraindications

Indications	*Contraindications*
1. Cardiogenic shock a. Myocardial infarction b. Myocarditis c. Cardiomyopathy 2. Failure to separate from CPB 3. Stabilization of preoperative patient a. Ventricular septal defect b. Mitral regurgitation 4. Stabilization of noncardiac surgical patient 5. Procedural support during coronary angiography 6. Bridge to transplantation	1. Aortic valvular insufficiency 2. Aortic disease a. Aortic dissection b. Aortic aneurysm 3. Severe peripheral vascular disease 4. Severe noncardiac systemic disease 5. Massive trauma 6. Patients with "do not resuscitate" instructions 7. Mitral SAM with dynamic outflow tract obstruction

CPB, Cardiopulmonary bypass; *SAM,* systolic anterior motion.

Indications and Contraindications

Since the introduction of the IABP, the indications for its use have grown (Table 36.9). The most common use of the IABP is for treatment of cardiogenic shock. This may occur after CPB or after cardiac operations in patients with preoperative shock, patients with acute postinfarction ventricular septal defects or mitral regurgitation, those who require preoperative stabilization, or patients who decompensate hemodynamically during cardiac catheterization. Patients with myocardial ischemia refractory to coronary vasodilation and afterload reduction are stabilized with an IABP before cardiac catheterization, and some patients with severe CAD prophylactically have an IABP inserted before undergoing CABG or off-pump CABG procedures.[201–205]

Contraindications to IABP use are relatively few (see Table 36.9). The presence of severe aortic regurgitation or aortic dissection is an absolute contraindication for the IABP, although successful reports of its use in patients with aortic insufficiency or acute trauma to the descending thoracic aorta have appeared. Other relative contraindications are listed; use of the IABP in these instances is at the discretion of the physician. Because the hemodynamic changes caused by an IABP theoretically would tend to worsen dynamic outflow tract obstruction caused by systolic anterior motion of the mitral valve, the device should be used with caution, if at all, in these patients.

Insertion Techniques

In the initial development of the IABP, insertion was by surgical access to the femoral vessels. In the late 1970s, refinements in IABP design allowed the development of percutaneous insertion techniques. Now the technique most commonly used, percutaneous IABP insertion, is performed rapidly with commercially available kits.

The femoral artery with the greater pulse is sought by careful palpation. The length of the balloon to be inserted is estimated by laying the balloon tip on the patient's chest at the Louis angle and appropriately marking the distal point corresponding to the femoral artery. Care must be taken when removing the balloon from its package to follow the manufacturer's procedures exactly, to avoid perforating the balloon before insertion. Available balloons come wrapped and need only be appropriately deflated before removal from the package. The femoral artery is entered with the supplied needle, a J-tipped guidewire is inserted to the level of the aortic arch, and the needle is removed.

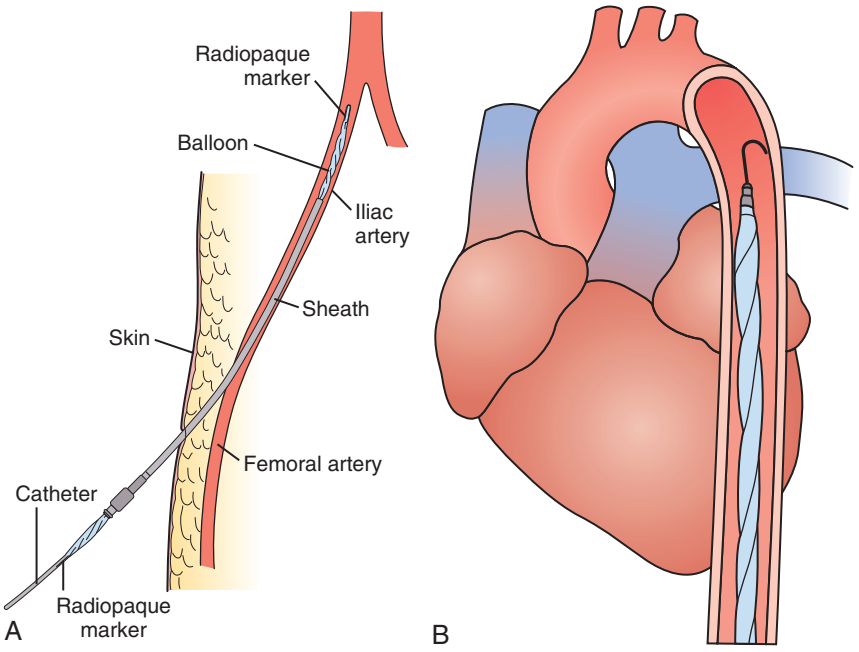


Fig. 36.3 Intraaortic balloon pump insertion. (A) Cannulation and insertion of the balloon through the femoral artery. Notice the tightly wrapped balloon as it traverses the sheath. A guidewire is not visible in this drawing. (B) Correct positioning of balloon in proximal descending aorta. The J-tipped guidewire is seen exiting from the balloon's central lumen. *(A, Courtesy Datascope Corporation, Fairfield, NJ; B, Courtesy Kontron, Inc., Augsburg, Germany.)*

The arterial puncture site is enlarged with the successive placement of an 8-Fr dilator and then a 10.5- or 12-Fr dilator and sheath combination (Fig. 36.3). In the adult-sized (30- to 50-mL) balloons, only the dilator needs to be removed, leaving the sheath and guidewire in the artery. The balloon is threaded over the guidewire into the central aorta and into the previously estimated correct position in the proximal segment of the descending aorta. The sheath is gently pulled back to connect with the leakproof cuff on the balloon hub, ideally so that the entire sheath is out of the arterial lumen to minimize risk for ischemic complications to the distal extremity. Alternatively, the sheath may be stripped off the balloon shaft much like a peel-away pacemaker lead introducer, thereby entirely removing the sheath from the insertion site. At least one manufacturer offers a "sheathless" balloon for insertion.

If fluoroscopy is available during the procedure, correct placement is verified before fixing the balloon securely to the skin. Position also may be checked by radiography or TEE after insertion. If an indwelling left radial arterial catheter is functioning at the time of insertion, a reasonable estimate of position may be made by watching balloon-mediated alteration of the arterial pulse waveform (Fig. 36.4). After appropriate positioning and timing of the balloon, 1:1 counterpulsation may be initiated. The entire external balloon assembly should be covered in sterile dressings.

Removal of a percutaneously inserted IABP may be by the open (surgical removal) or closed technique. If a closed technique is chosen, the artery should be allowed to bleed for several seconds while pressure is maintained on the distal artery after balloon removal to flush any accumulated clot from the central lumen. This maneuver helps prevent distal embolization of clot. Pressure is then applied for 20 to 30 minutes on the puncture site for hemostasis. If surgical removal is chosen, embolectomy catheters may be passed in antegrade and retrograde fashion before suture closure of the artery.

Alternate routes of IABP insertion exist. The balloon may be placed surgically through the femoral artery. This is now performed without the use of an end-to-side vascular conduit, although this placement still requires a second surgical procedure for removal. In patients with extreme peripheral vascular disease or in pediatric patients whose peripheral vasculature is too small, the ascending aorta or aortic arch may be entered for balloon insertion. These approaches necessitate median sternotomy for insertion and usually require reexploration for removal. Other routes of access include the abdominal aorta and the subclavian, axillary, and iliac arteries. The iliac approach may be especially useful for pediatric cases.

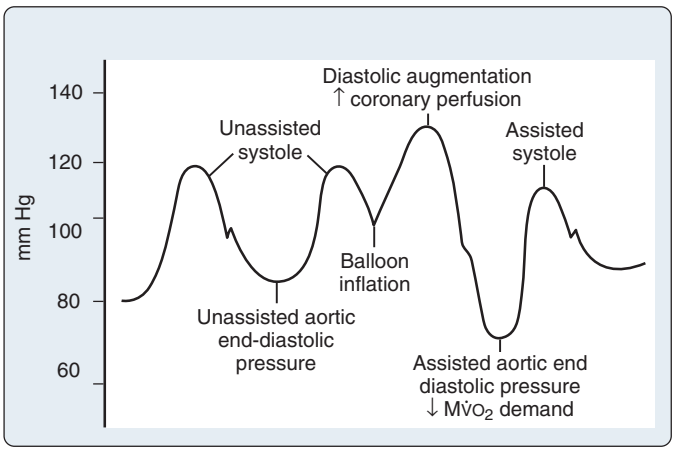


Fig. 36.4 Arterial waveforms seen during intraaortic balloon pump assist. The first two waveforms are unassisted, and the last is assisted. Notice the decreased end-systolic and end-diastolic pressures and augmented diastolic pressures caused by balloon pump augmentation and the (correct) point at which balloon inflation occurs. These are waveforms generated by a correctly positioned and timed balloon. $M\dot{V}O_2$, Myocardial oxygen consumption. *(Courtesy Datascope Corporation, Fairfield, NJ.)*

Timing and Weaning

IABP systems are commercially available from several different manufacturers. The basic console design includes electrocardiographic and

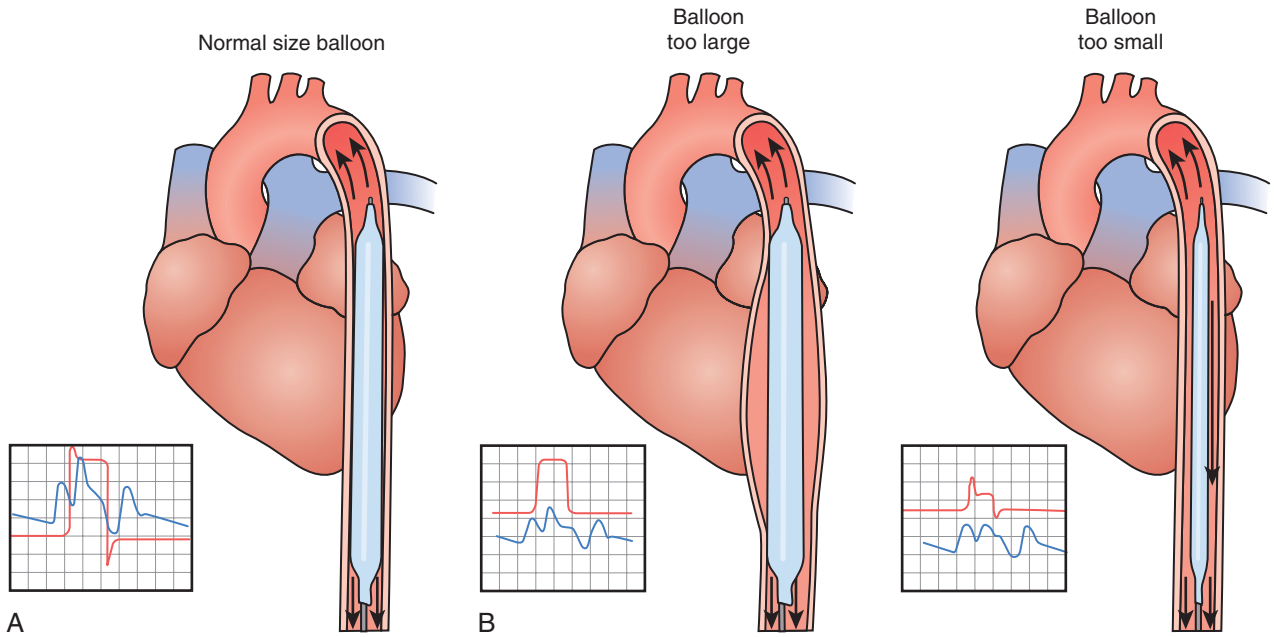


Fig. 36.5 Variations in waveform caused by incorrect balloon size. (A) The balloon is correctly positioned and appropriately sized for the aorta. Notice the arterial waveform diagram in the *lower left corner.* (B) Examples of too large *(left)* or too small *(right)* balloon sizes with their correspondingly altered arterial waveforms. A similar effect can result from overinflation and underinflation of the balloon. Compare the waveforms in B with the ideal waveform in A.

arterial blood pressure waveform monitoring and printing, balloon volume monitoring, triggering selection switches, adjustments for inflation and deflation timing, battery backup power sources, and gas reservoir. Some of these systems have become quite sophisticated, with advanced computer microprocessor circuits allowing triggering based on pacemaker signals or detection of and compensation for aberrant rhythms such as atrial fibrillation. Portable models exist for transportation of patients by ground, helicopter, or air ambulances.

For optimal effect of the IABP, inflation and deflation must be correctly timed to the cardiac cycle. Although certain variables, including positioning of the balloon within the aorta, balloon volume (Fig. 36.5), and the patient's cardiac rhythm, can affect the performance of the IABP, basic principles regarding the function of the balloon must be followed. Balloon inflation should be timed to coincide with aortic valve closure, or aortic insufficiency and LV strain will result. Similarly, late inflation results in a diminished perfusion pressure to the coronary arteries. Early deflation causes inappropriate loss of afterload reduction, and late deflation increases LV work by causing increased afterload, if only transiently. These errors and correct timing diagrams are shown in Figs. 36.4 and 36.6.

As the patient's cardiac performance improves, the IABP support must be removed in stages rather than abruptly. Judicious application and dosing of vasodilator and inotropic medications can assist this procedure. The balloon augmentation may be reduced in steps from 1:1 counterpulsation to 1:2 and then to 1:4, with appropriate intervals at each stage to assess hemodynamic and neurologic stability, CO, and $S\bar{v}O_2$ changes. After appropriate observation at 1:4 or 1:8 counterpulsation, balloon assistance can be safely discontinued, and the device can be removed by one of the methods discussed. If percutaneous removal is chosen, an appropriate interval for reversal of anticoagulation (if used) before removal of the balloon should be allowed.

Complications

Several complications have been associated with IABP use (Table 36.10). The most frequently seen complications are vascular injuries, balloon malfunction, and infection.[201–205] Treatment of these respective problems is straightforward. Flaps, dissections, perforations, embolic events, and pseudoaneurysms should be managed directly by surgical intervention and repair. Steal syndromes or ischemia, if not severe, may be managed with expectantly, but if severe extremity compromise is observed, the balloon should be moved to another site. An alternative means of treatment is a femoral-to-femoral crossover graft placed surgically to help alleviate the affected extremity.

Problems associated with the balloon are managed directly by removal or replacement or, if necessary, repositioning. Gas embolization, although rare, has been successfully treated with hyperbaric oxygen.

Infections usually require removal or replacement of the balloon in an alternate site. Appropriate antibiotic coverage should be instituted and adjusted as culture results become available. Prosthetic materials

TABLE 36.10 Intraaortic Balloon Pump Counterpulsation Complications

Vascular	*Miscellaneous*	*Balloon*
Arterial injury (perforation, dissection)	Hemolysis	Perforation (preinsertion)
Aortic perforation	Thrombocytopenia	Tear (during insertion)
Aortic dissection	Infection	Incorrect positioning
Femoral artery thrombosis	Claudication (postremoval)	Gas embolization
Peripheral embolization	Hemorrhage	Inadvertent removal
Femoral vein cannulation	Paraplegia	—
Pseudoaneurysm of femoral vessels	Entrapment	—
Lower extremity ischemia	Spinal cord necrosis	—
Compartment syndrome	Left internal mammary artery occlusion	—
Visceral ischemia	Aggravation of dynamic outflow tract obstruction	—

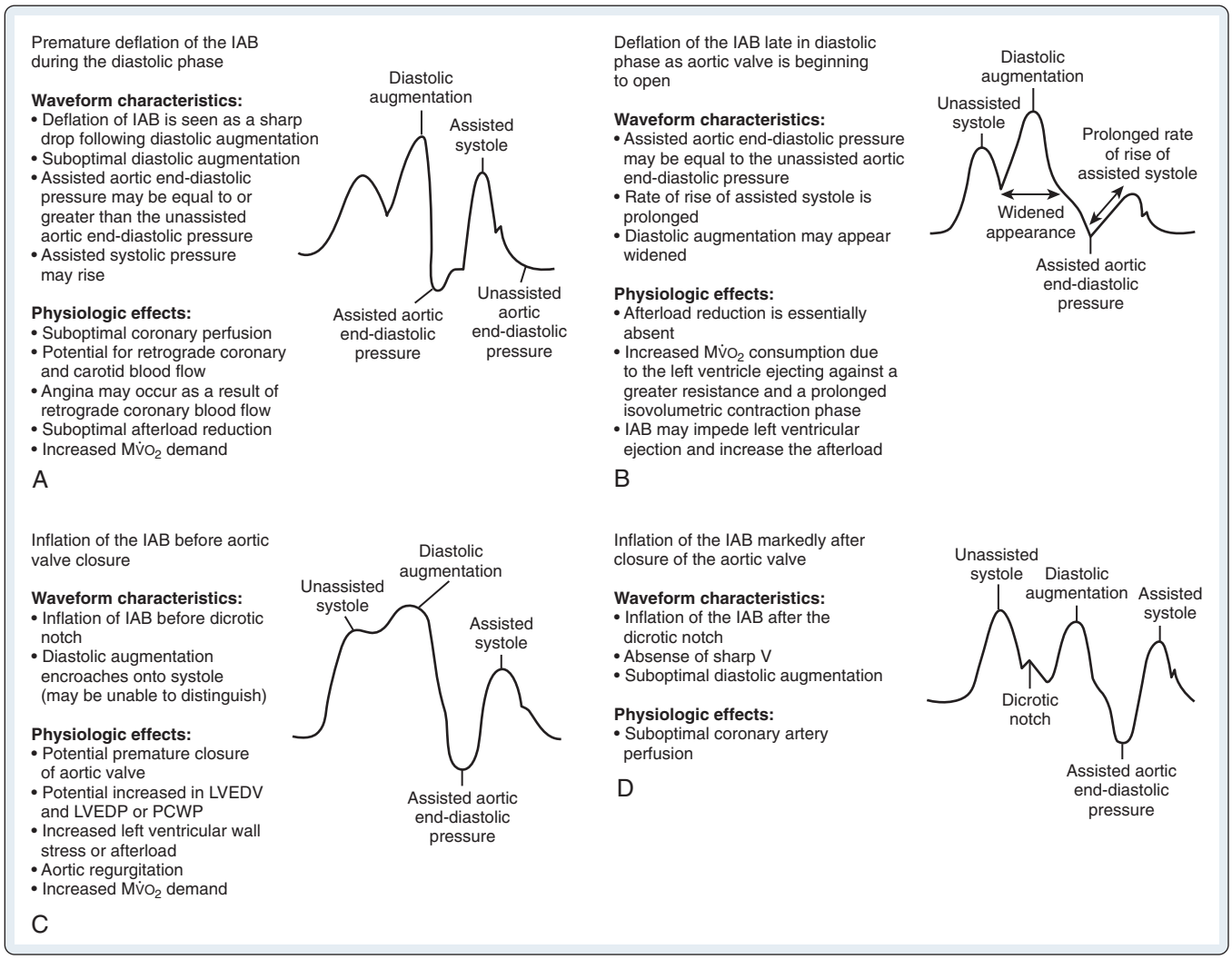


Fig. 36.6 Alterations in arterial waveform tracings caused by errors in timing of intraaortic balloon *(IAB)* pump. (A) The balloon was deflated too early. (B) The balloon was deflated too late. (C) The balloon was inflated too early. (D) The balloon was inflated too late. *LVEDP,* Left ventricular end-diastolic pressure; *LVEDV,* left ventricular end-diastolic volume; *MV̇O$_2$,* myocardial oxygen consumption. *PCWP,* pulmonary capillary wedge pressure. *(Courtesy Datascope Corporation, Fairfield, NJ.)*

should be removed if present, and débridement of the insertion site should be performed as necessary. Septicemia can occur and have detrimental effects if not aggressively treated.

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