Index

Disorders of Circulatory Flow

Chapter 12

HEMORRHAGE AND HYPOVOLEMIA

The dominant concern in the bleeding patient is the intolerance of the circulatory system to acute blood loss. The circulatory system operates with a small volume and a volume-responsive pump. This seems to be an energy efficient design, but the system falters when blood volume is not maintained. While most internal organs can lose more than 50% of their functional mass before organ failure is apparent, loss of only 30 to 40% of the blood volume can result in life-threatening circulatory failure. This intolerance of the circulatory system to blood loss means that time is the enemy of the bleeding patient. This chapter describes the evaluation and early management of acute blood loss (1,2), and the next chapter describes the variety and use of asanguinous resuscitation fluids. These two chapters will introduce you to the fluids you will live with in the ICU, including body fluids (blood and plasma), transfusion fluids (whole blood and erythrocyte concentrates), and infusion fluids (colloids and crystalloids).

BODY FLUIDS AND BLOOD LOSS

Fluids account for at least half of the body weight in healthy adults. The volume of total body fluid (in liters) is equivalent to 60% of lean body weight (in kilograms) in males, and 50% of lean body weight in females. In Table 12.1, these volumes are shown as 600 mL/kg for males and 500 mL/kg for females. A healthy adult male who weighs 80 kg (1761bs) will then have 0.6 X 80 = 48 liters of total body fluid, and a healthy adult female who weighs 60 kg (132 lbs) will have 0.5 X 60 = 30 liters of total body fluid. Table 12.1 also contains weight-based estimates for blood volume (3): 66 mL/kg for males and 60 mL/kg for females. An 80 kg adult male will then have 0.066 X 80 = 5.3 liters of blood, and a 60 kg

TABLE 12.1 Body Fluid and Blood Volumes

Fluid	Men	Women
Total body fluid	600 m L/kg	500 mL/kg
Whole blood	66 m L/kg	60 m L/kg
Plasma	40 m L/kg	36 m L/kg
Erythrocytes	26 m L/kg	24 m L/kg

Values expressed for lean body

adult female will have 0.06 X 60 = 3.6 liters of blood. According to these estimates, blood represents about 11 to 12% of the total body fluid.
The graduated beakers in Figure 12.1 show a comparison of the volumes of total body fluid, blood, and the components of blood (plasma and red blood cells) for an 80 kg adult male. The beakers are drawn to scale (i.e., the small, 5 mL beakers are one-tenth the size of the large, 50 mL beaker) to help demonstrate that only a small portion of the total body fluid is in the vascular compartment (the small beaker). The limited volume in the bloodstream is a disadvantage during hemorrhage because loss of seemingly small volumes of blood can represent loss of a significant fraction of the blood volume.

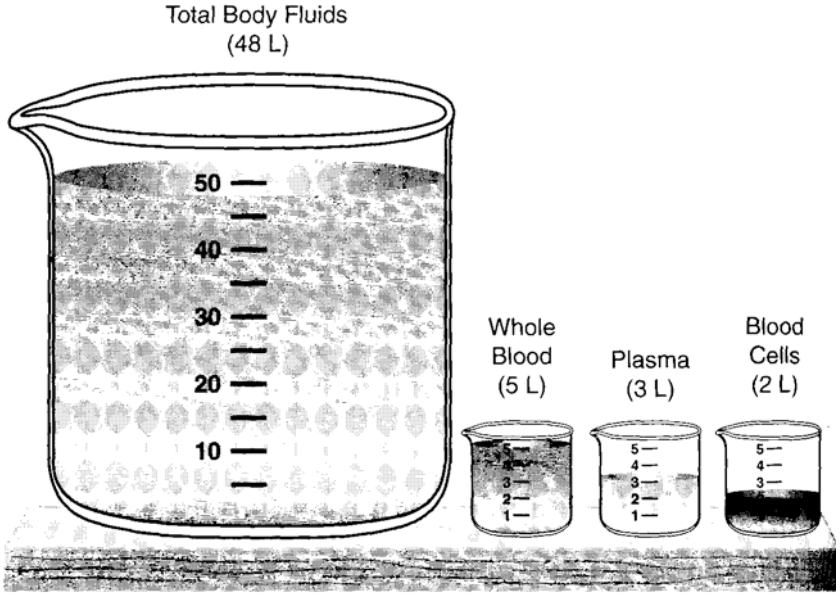

FIGURE 12.1 Scaled drawing comparing the volume of total body fluids and the volume of whole blood and its components in an adult male weighing 80 kg. The small beakers are one-tenth the size of the large beaker.

Compensatory Responses

The loss of blood triggers certain compensatory responses that help to maintain blood volume and tissue perfusion (4). The earliest response involves movement of interstitial fluid into the capillaries. This *transcapillary refill* can replenish about 15% of the blood volume, but it leaves an interstitial fluid deficit.

Acute blood loss also leads to activation of the renin-angiotensin-aldosterone system, resulting in sodium conservation by the kidneys. The retained sodium distributes uniformly in the extracellular fluid. Because interstitial fluid makes up about 2/3 of the extracellular fluid, the retained sodium helps to replenish the interstitial fluid deficit created by trans capillary refill. The ability of sodium to replace interstitial fluid deficits, not blood volume deficits, is the reason that crystalloid fluids containing sodium chloride (saline fluids) gained early popularity as resuscitation fluids for acute blood loss (5).

Within a few hours after the onset of hemorrhage, the bone marrow begins to increase production of red blood cells. This response develops slowly, and complete replacement of lost erythrocytes can take up to 2 months (4). These compensatory responses can maintain an adequate blood volume in cases of mild blood loss (i.e., loss of <15% of the blood volume). When blood loss exceeds 15% of blood volume, volume replacement is usually necessary.

Progressive Blood Loss

The American College of Surgeons identifies four categories of acute blood loss based on the percent loss of blood volume (6).

Class I. Loss. of 15% or less of the total blood volume. This degree of blood loss is usually fully compensated by transcapillary refill. Because blood volume is maintained, clinical findings are minimalar absent.

Class II. Loss of 15 to 30% of the blood volume. The clinical findings at this stage may include orthostatic changes in heart rate and blood pressure. However, these clinical findings are inconsistent (see later). Sympathetic vasoconstriction maintains blood pressure and perfusion of vital organs (7), but urine output can fall to 20 or 30 mL/hr, and splanchnic flow may also be compromised (8). Splanchnic hypoperfusion is a particular concern because it can lead to breakdown of the intestinal barrier and translocation of microbes and inflammatory cytokines, setting the stage for systemic inflammation and multiple organ failure (8). (See ehapters 4 and 40 for more information on this topic.)

Class III. Loss of 30 to 40% of the blood volume. This marks the onset of decompensated hypovolemic shock, where the vasoconstrictor response to hemorrhage is no longer able to sustain blood pressure and organ perfusion. The clinical consequences include hypotension and reduced urine output (usually 5 to 15 mL/hr).

Systemic vasoconstriction may be attenuated or lost at this stage (7), resulting in exaggerated hypotension.

Class IV. Loss of more than 40% of blood volume. Hypotension and oliguria are profound at this stage (urine output may be <5 mL/hr), and these changes may be irreversible.

CLINICAL EVALUATION

The clinical evaluation of the bleeding (or otherwise hypovolemic) patient is aimed at determining the magnitude of the blood volume deficit and the impact of this deficit on circulatory flow and organ viability. A variety of bedside, laboratory, and invasive techniques are available for this evaluation, and these are described briefly in this section.

Vital Signs

Resting tachycardia (>90 beats per minute) is often assumed to be a common occurrence in the hypovolemic patient, but tachycardia in the supine position is absent in a majority of patients with moderate-tosevere blood loss (see Table 12.2) (9). In fact, bradycardia may be more prevalent in acute blood loss (9). Hypotension (systolic blood pressure <90 mm Hg) in the supine position is also an insensitive marker of blood loss. This is shown in Table 12.2 (i.e., the sensitivity of supine hypotension is 50% or less in patients with either moderate or severe blood loss) (9). Hypotension usually appears in the advanced stages of hypovolemia, when the loss of blood exceeds 30% of the blood volume (6). The method used to measure blood pressure is an important consideration in the bleeding patient because, in low flow states, noninvasive measures of blood pressure often yield spuriously low values (see ehapter 8,

TABLE 12.2 Accuracy of Vital Signs in the Detection of Acute Blood Loss

	Range of Reported Sensitivities	
Parameter	Moderate Blood Loss (450-630 mL)	Severe Blood Loss (630-1150 mL)
Supine tachycardia	0-42%	5-24%
Supine hypotension	0-50%	21-47%
Postural pulse increment' or postural dizziness	6-48%	91-100%
Postural hypotension t		
Age < 65 yrs	6-12%	Not known
Age > =65 yrs	14-40%	Not known

'Increase in pulse rate 2: 30 beats/min on standing.

tDecrease in systolic pressure> 20 mm Hg on standing.

Table 8.2). As a result, direct intraarterial recordings are recommended for monitoring blood pressure in the bleeding patient.

Orthostatic Vital Signs

Moving from the supine to the standing position causes a shift of 7 to 8 mL/kg of blood to the lower extremities (9). In healthy subjects, this change in body position is associated with a small increase in heart rate (about 10 beats/min) and a small decrease in systolic blood pressure (about 3 to 4 mm Hg) (9). These changes can be exaggerated in the hypovolemic patient, but this is not a consistent finding.

When recording postural changes in pulse rate and blood pressure, the patient should move from the supine to standing position (sitting instead of standing reduces the magnitude of change and the sensitivity of the test) and at least one minute should elapse in the standing position before the measurements are obtained (9). A significant postural (orthostatic) change is defined as any of the following: an increase in pulse rate of at least 30 beats/minute, a decrease in systolic pressure > 20 mm Hg, or dizziness on standing. The sensitivity of these postural changes for detecting hypovolemia is shown in Table 12.2. The only tests with a sensitivity high enough to be of any value are postural dizziness and postural increments in heart rate in severe blood loss (defined in Table 12.1 as loss of 630 to 1,150 mL of blood). The information in Table 12.1 indicates that orthostatic vital signs have limited value in the evaluation of hypovolemia.

The Hematocrit

The use of the hematocrit (and hemoglobin concentration in blood) to determine the extent of acute blood loss is both common and inappropriate. The following statement from the Advanced Trauma Life Support eourse deserves emphasis. "Use of the hematocrit to estimate acute blood loss is unreliable and inappropriate" (6). ehanges in hematocrit show a poor correlation with blood volume deficits and erythrocyte deficits in acute hemorrhage (10), and the reason for this discrepancy is demonstrated in Figure 12.2. Acute blood loss involves the loss of whole blood, with proportional decreases in the volume of plasma and erythrocytes. As a result, the hematocrit will not change significantly in the early period after acute blood loss. In the absence of volume resuscitation, the hematocrit will eventually decrease because hypovolemia activates the renin-angiotensin-aldosterone system, leading to renal conservation of sodium and water and expansion of the plasma volume. This process begins 8 to 12 hours after acute blood loss and can take a few days to become fully established.

Resuscitation Fluids &. *Hematocrit*

Decreases in hematocrit in the early hours after acute hemorrhage is usually the result of volume resuscitation rather than ongoing blood loss. The influence of different resuscitation fluids on the hematocrit is demonstrated in Figure 12.2. Infusion of saline (0.9% sodium chloride)

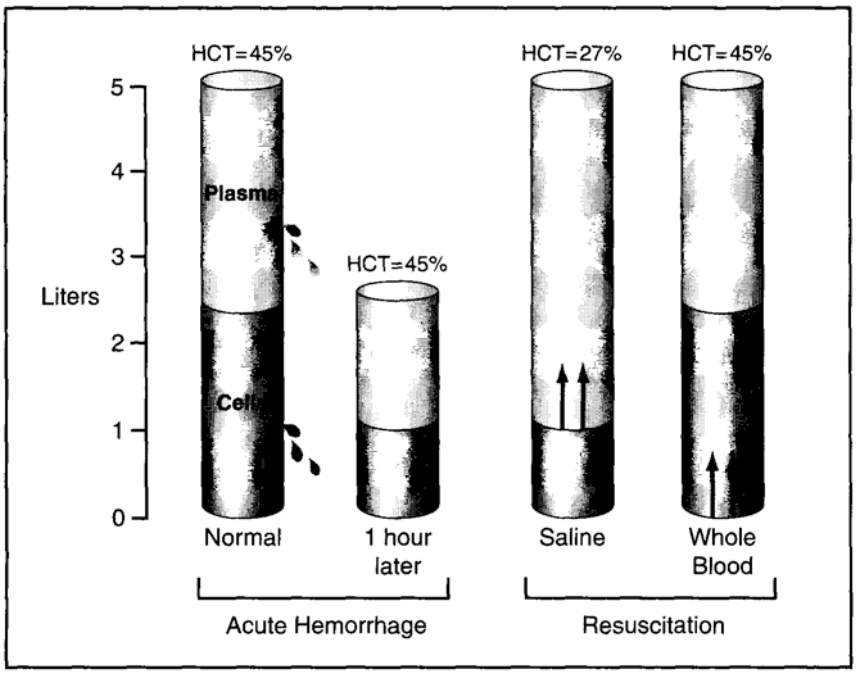

FIGURE 12.2 Influence of acute hemorrhage and type of resuscitation fluid on blood volume and hematocrit. Each vertical column shows the contribution of plasma and red blood cells to the blood volume, and the corresponding hematocrit is shown above the columns.

increases the plasma volume selectively and thereby decreases the hematocrit without affecting the volume of red blood cells. All cell-free resuscitation fluids have a similar dilutional effect on the hematocrit (11). Figure 12.2 also shows the effect of resuscitation with whole blood: in this case, the erythrocyte and plasma volumes are increased proportionately, without a change in hematocrit. Thus Figure 12.2 clearly shows that, in the early hours after acute hemorrhage, the hematocrit is a reflection of the resuscitation effort (the type of infusion fluid and the volume infused), not the severity of blood loss. The change in hematocrit produced by each type of resuscitation fluid is shown below.

Resuscitation fluid	*Expected Change in Hematocrit*
Asanguinous fluids	Decrease
Whole blood	No change
Packed red cells	Increase

Invasive Hemodynamic Measures

eentral venous catheters are inserted routinely in hypovolemic: patients, and these catheters allow the measurement of pressure in the superior vena cava, which is equivalent to the filling pressure of the right side of the heart. These catheters also permit the measurement of central venous

oxyhemoglobin saturation ($Scv0_2$), which can be used to evaluate global tissue oxygen balance (see Chapter 11).
Pulmonary artery catheters may be inserted to guide the management of hemodynamically unstable patients, and these catheters allow measurement of cardiac output and systemic oxygen transport. (The measurements provided by this catheter are described in Chapter 9.)
Cardiac Filling Pressures
The popular notion that cardiac filling pressures (the central venous pressure for the right heart, and the pulmonary artery occlusion [wedge] pressure for the left heart) provide an accurate representation of blood volume status is not supported by experimental studies (12-14). As described in chapter 10 and demonstrated in Figure 10.4, there is a poor correlation between ventricular filling pressures and ventricular volumes (13). This discrepancy is caused by the influence of ventricular distensibility (compliance) on cardiac filling pressures (i.e., a decrease in ventricular distensibility will result in higher cardiac filling pressures at any given ventricular volume). In fact, hypovolemia can be accompanied by a decrease in ventricular distensibility (presumably as a result of sympathetic activation) (15), which means that cardiac filling pressures will overestimate the intravascular volume status in hypovolemic patients.
The cardiac filling pressures can provide *qualitative* information about the general state of intravascular volume, but only when the measurements are very high (e.g., CVP > 15 mm Hg) or very low (e.g., CVP = 0-1 mm Hg). Intermediate-range measurements are not interpretable.

Oxygen Transport Parameters
Monitoring oxygen transport parameters permits identification of patients with hypovolemic shock. This is illustrated in Figure 12.3. Progressive hypovolemia causes a steady decline in systemic 02 delivery (002)' but in the early stages of hypovolemia, systemic 02 uptake ($V0_2$) remains unchanged. This condition (where $V0_2$ remains constant despite reductions in blood volume) is known as *compensated hypovolemia,* and it is characterized by an increase in 02 extraction from capillary blood to compensate for the decrease in 02 delivery. When 02 extraction reaches its maximum level of about 50% (which means that 50% of the hemoglobin molecules release their oxygen in the capillaries), V02, begins to decrease in response to decreases in D02. The point where the $V0_2$ (02 consumption) begins to decline is the onset of anaerobic metabolism and *hypovolemic shock.* (The 02 transport parameters are described in detail in ehapter 2.)
According to the relationships in Figure 12.3, compensated hypovolemia is identified by a normal $V0_2$ (> 100 mL/min/m2) and an 02 extraction that is less than 50%, while hypovolemic shock is identified by an abnormally low $V0_2$ (<100 mL/min/m2) and an 02 extraction that is 50%.

Acid-Base Parameters
Two measures of acid-base balance can provide information about the adequacy of tissue oxygenation: arterial base deficit and arterial lactate concentration. Both are used as markers of impaired tissue oxygenation.

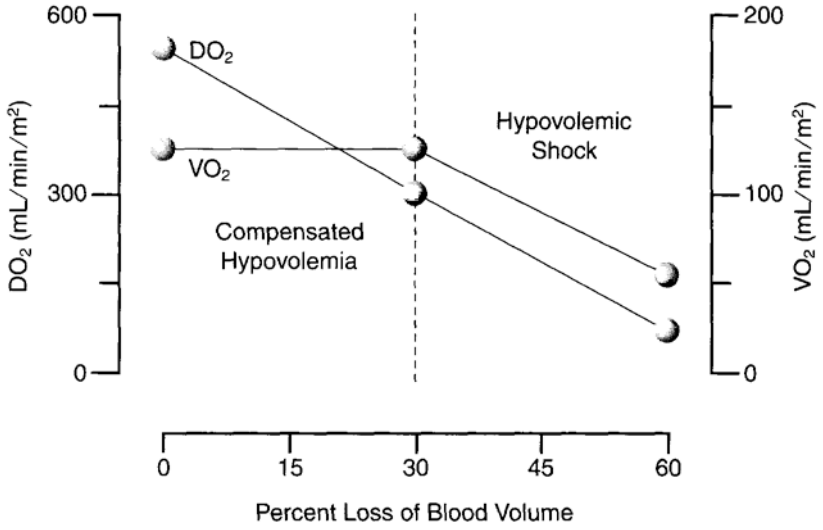

FIGURE 12.3 The effects of progressive hypovolemia on systemic oxygen delivery (DO_2) and oxygen uptake (VO_2). The point where O_2 uptake begins to decrease marks the onset of hypovolemic shock.

Arterial Base Deficit

The base deficit is the amount (in millimoles) of base needed to titrate one liter of whole blood to a pH of 7.40 (at temperature of 37° C and pCo_2 = 40 mm Hg). Because base deficit is measured when the pCo_2 is normal, it was introduced as a more specific marker of non-respiratory acid-base disturbances than serum bicarbonate (16). In the injured or bleeding patient, an elevated base deficit is a marker of global tissue acidosis from impaired oxygenation (17).

One advantage of the base deficit is its availability. Most blood gas analyzers determine the base deficit routinely using a $pC02/HC0_3$ nomogram, and the results are included in the blood gas report. The base deficit (BD) can also be calculated using the equation below (18), where BD is base deficit in mmol!L, Hb is the hemoglobin concentration in blood, and $HC0_3$ is the serum bicarbonate concentration.

$$BD = [(1 - 0.014\ Hb) \times HC0_3] - 24 + [(9.5 + 1.63\ Hb) \times (pH - 7.4)] \quad (12.1)$$

The normal range for base deficit is +2 to -2 mmol/L. Abnormal elevations in base deficit are classified as mild (-2 to -5 mmol!L), moderate (-6 to -14 mmol!L), and severe (<-15 mmol/L).

Clinical studies in trauma patients have shown a direct correlation between the magnitude of increase in base deficit at presentation and the extent of blood loss (19). eorrection of the base deficit within hours after volume replacement is associated with a favorable outcome

(19), while persistent elevations in base deficit are often a prelude to multiorgan failure.

Arterial Lactate Concentration

As described in ehapter 11, the lactate concentration in blood is a marker of impaired tissue oxygenation and a prognostic factor in circulatory shock (see Figure 11.5). Whole blood or serum lactate concentrations above 2 mEq/L are considered abnormal. When compared with the base deficit, blood lactate levels show a closer correlation with both the magnitude of blood loss (20) and the risk of death from hemorrhage (20,21). The predictive value of serum lactate is not confined to the time of initial assessment but also extends to the period of volume resuscitation. Persistent elevations in serum lactate despite volume resuscitation carry a poor prognosis (20,21).

BASICS OF VOLUME RESUSCITATION

The mortality in hypovolemic shock is directly related to the magnitude and duration of organ hypoperfusion (22), which means that prompt replacement of volume deficits is the hallmark of success for managing the hypovolemic patient. The following information will help to ensure prompt volume replacement and will also help to dispel some common misconceptions about volume resuscitation.

The Trendelenburg Position

Elevation of the pelvis above the horizontal plane in the supine position was introduced in the latter part of the 19th century as a method of facilitating surgical exposure of the pelvic organs. The originator was a surgeon named Friedrich Trendelenburg, who specialized in the surgical correction of vesicovaginal fistulas (23). The body position that now bears his name was later adopted during World War I as an antishock maneuver that presumably promotes venous return by shifting blood volume from the legs toward the heart. This maneuver continues to be popular today, despite evidence that it does not perform as expected (24-27).

Hemodynamic Effects

The hemodynamic effects of the Trendelenburg position (legs elevated and head below the horizontal plane) are shown in Table 12.3. The data in this table are from a study we performed on postoperative patients with indwelling pulmonary artery catheters who had evidence of severe hypovolemia (i.e., low cardiac filling pressures and hypotension) (24). The hemodynamic measurements were obtained in the supine position and then repeated after the patients were placed in a position with the legs elevated 45 degrees above the horizontal plane and the head placed 15 degrees below the horizontal plane. As shown in the table, the change in position was associated with significant increases in the mean arterial pressure, wedge (left-ventricular filling) pressure, and systemic vascular

TABLE 12.3 Hemodynamic Effects of the Trendelenburg Position in HypovolemicICU Patients

Parameter	Supine	Legs Up, Head Down	Change %	Change p	Change Effect
Mean arterial blood pressure (mm Hg)	64	71	11	<.001	+
Wedge pressure (mm Hg)	4.6	7.2	57	<.001	+
Cardiac index (Umin . m2)	2.1	1.9	9	NS	=
Systemic vascular resistance (dyne. sec/cm^5. m2)	2347	2905	24	<.001	+

Sing R et al. Ann Emerg Med

resistance, while the cardiac output remained the same. This lack of an effect on the cardiac output indicates that the Trendelenburg position does *not* promote venous return to the heart. The increase in the wedge pressure can be due to an increase in intrathoracic pressure (transmitted into the pulmonary capillaries) caused by cephalad displacement of the diaphragm during the body tilt. The increase in blood pressure during body tilt is likely due to systemic vasoconstriction (indicated by the rise in systemic vascular resistance). These observations are consistent with other studies in animals and humans (25-27).

Why the TrendelenburB Position Doesn't Work

The inability of the Trendelenburg position to augment cardiac output is likely explained by the high capacitance (distensibility) of the venous circulation. To augment cardiac output, the Trendelenburg position must increase the pressure gradient from peripheral to central veins, which would then increase venous blood flow. However, the venous system is a high-capacitance system designed to absorb pressure and act as a volume reservoir. When pressure is applied to a vein, the pressure is dissipated as the vein distends and increases its volume capacity. The distensibility of veins will thereby limit any increase in pressure gradient between peripheral and central veins. The venous system is more likely to transmit pressure when the veins are volume overloaded and less distensible. In other words, the Trendelenburg position is more likely to augment venous return during volume *overload,* not volume depletion.

In summary, the Trendelenburg position has (for a sound physiologic reason) not proven effective in promoting venous return or cardiac output in hypovolemia. As such, this maneuver should be abandoned for the management of hypovolemia. **It** remains axiomatic that the effective treatment for hypovolemia is volume replacement.

Central Versus Peripheral Vein Cannulation

There is a tendency to cannulate the large central veins for volume resuscitation because larger veins permit more rapid fluid infusions. However, the rate of volume infusion is determined by the dimensions

of the vascular catheter, not the size of the vein. The catheters used for central venous cannulation are 15 cm (about 6 inches) to 20 cm (about 8 inches) in length, whereas catheters used to cannulate peripheral veins are only 2 inches in length. The influence of catheter length on infusion rate is defined by the Hagen-Poiseuille equation, which is described in ehapters 1 and 6 (see Figure 1.6) and is shown below.

$$Q = \text{Delta } P(\pi r 4/8\mu L) \qquad (12.2)$$

According to this equation, steady flow (Q) through a catheter is directly related to the driving pressure (Delta P) for flow and the fourth power of the radius (r) of the catheter and is inversely related to the length (L) of the catheter and the viscosity (μ) of the infusate. This equation predicts that flow through longer central venous catheters will be much slower than flow through short peripheral venous catheters of equal diameter.

The influence of catheter length on infusion rate is demonstrated in Figure 12.4 (28). The fluid in this case is water, and the driving force for flow is the height of the fluid reservoir above the catheter. Using catheters of equal diameter (16 gauge), flow in the 2-inch catheter is about 30% higher than flow in the 5.5-inch catheter and is more than twice the flow rate in the 12-inch catheter. Therefore for rapid volume resuscitation, cannulation of peripheral veins with short catheters is preferred to cannulation of large central veins with long catheters.

Introducer Catheters

Volume resuscitation of trauma victims sometimes requires flow rates in excess of 5 L/min (29). Because flow increases with the fourth power

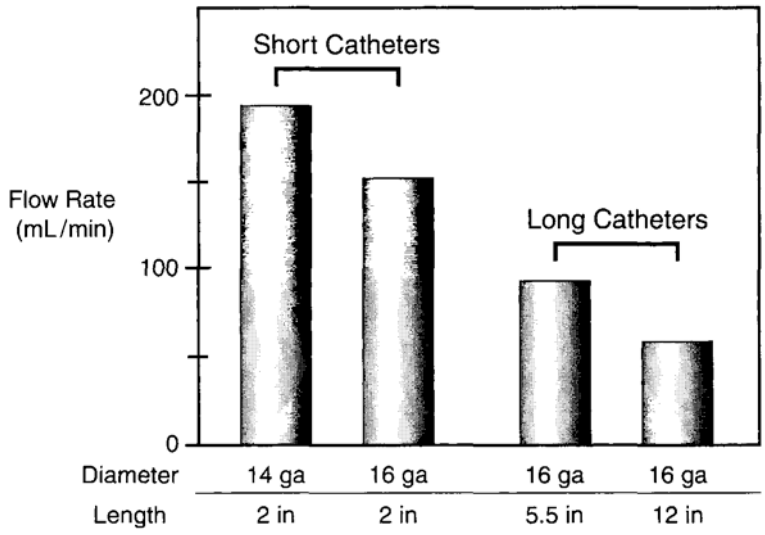

FIGURE 12.4 The influence of catheter dimensions on the gravity-driven infusion rate of water. Catheter dimensions are indicated below the horizontal axis of the graph. (From Mateer JR Thompson BM, Aprahamian C, et al. Rapid fluid resuscitation with central venous catheters. Ann Emerg Med 1983;12:149–152.)

of the radius of a catheter, very rapid flow rates are best achieved with large-bore catheters such as the *introducer catheters* described in ehapter 6 (see Figure 6.4). These catheters are 5 to 6 inches in length and are available in 8.5 French (2.7 mm outer diameter) and 9 French (3 mm outer diameter) sizes. They are normally inserted to facilitate placement and exchange of multilumen central venous catheters and pulmonary artery catheters, but they can be used as stand-alone infusion devices when rapid infusion rates are desirable.
Gravity-driven flow through introducer catheters can reach 15 mL/ sec (using low viscosity, cell-free fluids), which is only slightly less than the flow through standard (3 mm diameter) intravenous tubing (18 mL!sec) (30). There is an additional side infusion port on the hub of introducer catheters (see Figure 6.4), but the flow capacity is only 25% of that in the catheter (30). Therefore when introducer catheters are used for rapid infusion, the side infusion port should be bypassed.

Flow Properties of Resuscitation Fluids

There are three types of resuscitation fluids (see Table 12.4): fluids that contain red blood cells (whole blood and erythrocyte concentrates or "packed" cells), fluids that contain large molecules with limited movement out of the bloodstream (called *colloid* fluids), and fluids that contain only electrolytes (sodium and chloride) and small molecules that move freely out of the bloodstream (called *crystalloid* fluids). The flow capabilities of these fluids are determined by their viscosity, as described in the Hagen-Poiseuille equation (Equation 12.2).
The infusion rates of the resuscitation fluids in Figure 12.5 are explained by differences in viscosity (31). The erythrocyte-containing

TABLE 12.4 Types of Fluids Used for Volume Resuscitation

Type of Fluid	Products	Performance Characteristics
1. Fluids that contain red blood cells.	Whole blood, Packed cells	These fluids increase the oxygen-carrying capacity of blood. Their ability to flow and augment cardiac output are limited by the viscosity effects of the cells.
2. Fluids that contain large molecules with restricted egress from the vascular space. Called *colloids.*	Plasma, Albumin, Dextrans, Hetastarch	These fluids preferentially increase intravascular volume, and are the most effective fluids for increasing cardiac output.
3. Fluids that contain electrolyes and other small molecules that move freely in the extracellular. space. Called *crystalloids.*	Saline, Ringer's fluids, Normosol	These fluids distribute evenly in the extracellular space, and preferentially increase interstitial fluid volume.

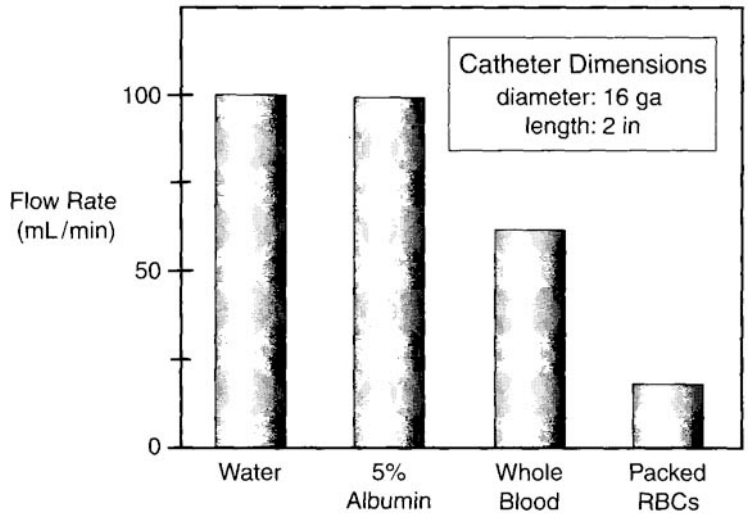

FIGURE 12.5 Comparative infusion rates of erythrocyte-containing and cell-free resuscitation fluids. Catheter size and driving pressure are the same for all fluids. (From Dula DJ, Muller A, Donovan JW, et al. Flow rate variance of commonly used IV infusion techniques. J Trauma 1981;21:480.)

fluids are the only resuscitation fluids with a viscosity greater than that of water, and the viscosity of these fluids is a function of the erythrocyte density or hematocrit (see Table 1.2 in ehapter 1). Therefore whole blood flows less rapidly than the cell-free fluids (water and 5% albumin), and densely packed erythrocytes (packed RBes) have the slowest infusion rates. The sluggish flow of packed RBes can be improved by increasing the driving pressure for flow with an inflatable cuff wrapped around the blood bag (which works like a blood pressure cuff). Adding saline to the infusion line (in equal volumes) will also improve infusion rates by decreasing the viscosity of the infusate.
A popular misconception is that colloid fluids, because of their large molecules, flow less rapidly than crystalloid fluids or water. However, viscosity is a function of cell density, so cell-free resuscitation fluids will have the same flow capabilities as water. This is demonstrated by the equivalent flow rates of water and 5% albumin in Figure 12.5.

RESUSCITATION STRATEGIES

The ultimate goal of volume replacement for acute blood loss is to maintain oxygen uptake (VO_z) into tissues and sustain aerobic metabolism (29). The strategies used to maintain VO_z are identified by the determinants of VO_z in Equation 12.3. (This equation is described in detail in Chapter 2.)

$$VO_z = Q \times Hb \times 13.4 \times (SaO_z - SvO_z) \qquad 02.3)$$

Acute blood loss affects two components of this equation: cardiac output (Q) and hemoglobin concentration in blood (Hb). Therefore promoting cardiac output and correcting hemoglobin deficits are the two goals of resuscitation for acute blood loss. Each of these goals involves a distinct strategy, as described next.

Promoting Cardiac Output

The consequences of a low cardiac output are far more threatening than the consequences of anemia, so the first priority in the bleeding patient is to support cardiac output.

Resuscitation Fluids and Cardiac Output

The ability of each type of resuscitation fluid to augment cardiac output is shown in Figure 12.6 (32). The graph in this figure shows the effects of a one-hour infusion of each fluid on the cardiac output. The infusion volume of whole blood (1 unit = 450 mL), packed cells (2 units = 500 mL), and dextran-40 (500 mL) is equivalent, while the infusion volume of lactated Ringer's (1 L) is twice that of the other fluids. The colloid fluid (dextran-40) is the most effective: on a volume-to-volume basis, the colloid fluid is about twice as effective as whole blood, six times more effective than packed cells, and eight times more effective than the crystalloid fluid (lactated Ringer's). The limited ability of blood (whole blood or

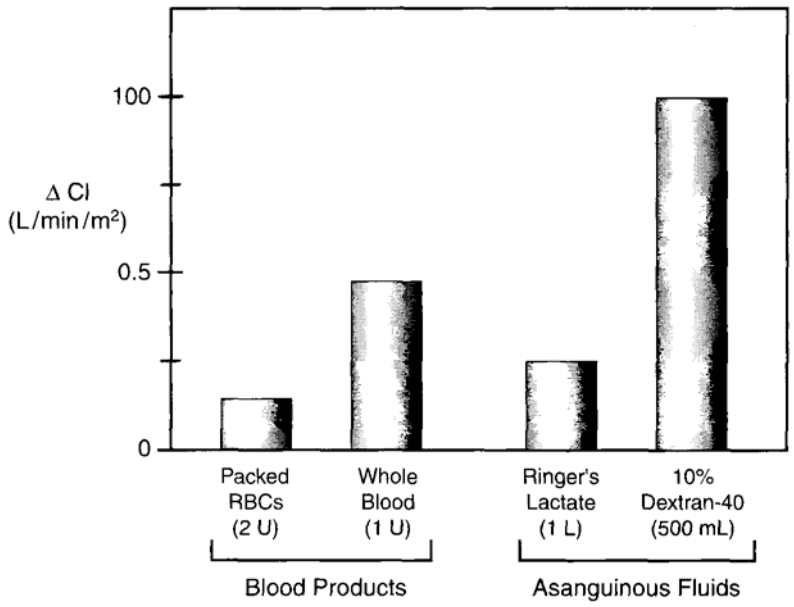

FIGURE 12.6 Effectiveness of different types of resuscitation fluids in augmenting cardiac output. (From Shoemaker WC. Relationship of oxygen transport patterns to the pathophysiology and therapy of shock states. Intensive Care Med 1987;13:230.)

packed cells) to augment cardiac output is due to the viscosity effects of erythrocytes.
If augmenting cardiac output is the first priority in the management of acute hemorrhage, then Figure 12.6 indicates that blood is not the fluid of choice for early volume resuscitation in acute blood loss. This is particularly the case with concentrated erythrocyte products (packed cells), which can actually *decrease* cardiac output (33).

Colloid and Crystalloid Fluids
The graph in Figure 12.6 shows a marked difference in the ability of colloid and crystalloid fluids to augment blood flow. This difference cannot be explained by viscosity, because both types of fluids are cell-free and have a viscosity equivalent to water. The difference is due to the differences in volume distribution. crystalloid fluids are primarily sodium chloride solutions, and because sodium is distributed evenly in the extracellular fluid, crystalloid fluids will also distribute evenly in the extracellular fluid. Because plasma represents only 20% of the extracellular fluid, only 20% of the infused volume of crystalloid fluids will remain in the vascular space and add to the plasma volume, while the remaining 80% will add to the interstitial fluid volume. colloid fluids, on the other hand, will add primarily to the plasma volume because the large molecules in colloid fluids do not readily escape from the vascular compartment. As much as 75 or 80% of the infused volume of colloid fluids will remain in the vascular space and add to the plasma volume, at least in the first few hours after infusion. The increase in plasma volume augments cardiac output not only by increasing ventricular preload (volume effect) but also by decreasing ventricular afterload (dilutional effect on blood viscosity).

Points to Remember
The following statements summarize the important points about resuscitation fluids that were included in this section (22,32,34-36).
Colloid fluids are more effective than whole blood, packed cells, and crystalloid fluids for increasing cardiac output.
Erythrocyte concentrates (packed cells) are relatively ineffective in promoting cardiac output, and thus they should never be used alone for volume resuscitation.
Colloid fluids primarily add to the plasma volume, while crystalloid fluids primarily add to the interstitial fluid volume.
To achieve equivalent effects on cardiac output, the volume of infused crystalloid fluid is at least three times greater than the volume of infused colloid fluid.
Despite the superiority of colloid fluids over crystalloid fluids for increasing plasma volume and promoting cardiac output, crystalloid fluids continue to be the more popular resuscitation fluid. This preference is due to the lack of documented survival benefit with colloid

TABLE 12.5 Estimating the Resuscitation Volume

Sequence of Determinations	Equations
1. Estimate normal blood volume (BV)	BV = 66 mUkg (males) = 60 mUkg (females)
2. Estimate % loss of blood volume	Class I: <15% Class II: 15-30% Class III: 30-40% Class IV: >40%
3. Calculate volume deficit (VD)	VD = BV x % loss BV
4. Determine resuscitation volume (RV)	RV = VD x 1.5 (colloids) = VD x 4 (crystalloids)

resuscitation (36). The next chapter (chapter 13) expands further on the benefits and shortcomings of colloid and crystalloid fluids.

Estimaton the Total Resuscitation Volume

The following stepwise approach is designed to obtain a rough estimate of the volume of each type of resuscitation fluid that is needed to fully restore cardiac output and organ perfusion. This approach is outlined in Table 12.5.

Estimate the normal blood volume using the weight-based estimates in Table 12.1 (60 mL/kg for females, 66 mL/kg for males). Remember to use lean body weight.

Estimate the percent loss of blood volume by assigning the patient to one of the four stages of progressive blood loss described earlier in the chapter. Then apply the following relationships: class I, <15% loss of blood volume; class 11, 15-30% loss of blood volume; class III, 30-40% loss of blood volume class IV, >40% loss of blood volume.

Calculate the volume deficit using the estimated normal blood volume and the percent volume loss. (Volume deficit = normal blood volume X % volume loss)

Determine the resuscitation volume for each type of fluid by assuming that the increase in blood volume is 100% of the infused volume of whole blood, 50 to 75% of the infused volume of colloid fluids, and 20 to 25% of the infused volume of crystalloid fluids (34). The resuscitation volume for each type of fluid is then determined as the volume deficit divided by the percent retention of the infused fluid. For example, if the volume deficit is 2 L and the resuscitation fluid is a colloid, which is 50 to 75% retained in the vascular space, then the resuscitation volume is 2/0.75 = 3 L to 2/0.5 = 41.

Once the total replacement volume is determined, the rapidity of volume replacement can be determined using the clinical condition of the patient.

End-Points of Resuscitation
The goal of resuscitation in hemorrhagic shock is to restore three parameters: blood flow, oxygen transport, and tissue oxygenation. The parameters are defined by the end-points shown below.

cardiac index = 3 L/min/m2
Systemic oxygen delivery (OO2) > 500 mL/min/m2
Systemic oxygen uptake (VO_2) > 100 mL/min/m^2
Arterial lactate < 2 mmol/L or base deficit> -2 mmol/L

Unfortunately, it is not always possible to reach these end-points despite aggressive volume replacement, and the ability to reach the desired end points is a principal determinant of survival (1,20,21,32,37-39). This is demonstrated in Figure 12.7. The graph in this figure shows the effects of controlled hemorrhage and resuscitation on oxygen uptake (VO_z) in an animal model of hemorrhagic shock (20). Note that in the survivors, the VO_z increases and returns to the baseline (pre-hemorrhage) level in response to resuscitation. In contrast, the VO_z in the non survivors shows no response to resuscitation and actually deteriorates further. Thus when hemorrhagic shock becomes refractory to volume resuscitation, the prognosis is bleak.

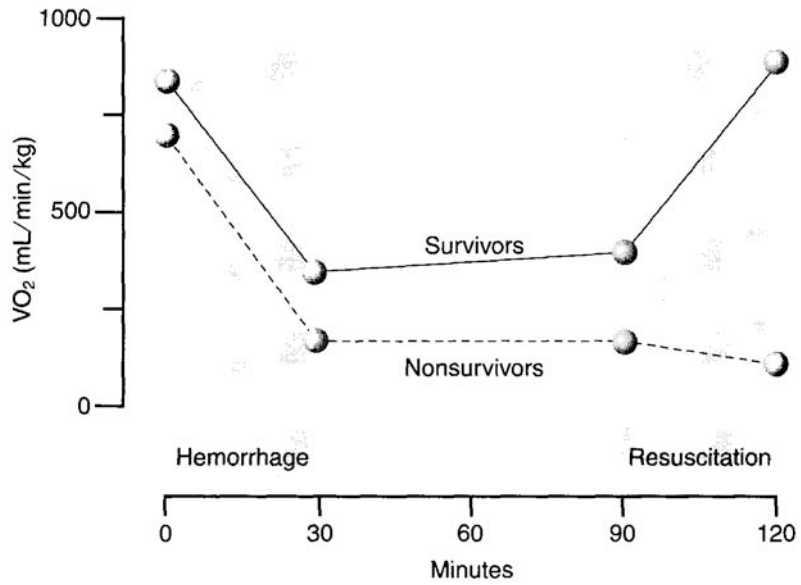

FIGURE 12.7 The effects of controlled hemorrhage and subsequent volume resuscitation on systemic oxygen uptake (VO_2) in an animal model of hemorrhagic shock. (From Moomey CB Jr, Melton SM, Croce MA, et al. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD_{50} model of penetrating trauma. Crit Care Med 1999;27:154.)

The time required to reach the desired end-points is another determinant of survival in hemorrhagic shock. One of the most predictive parameters in this regard is lactate clearance. In one study of trauma victims (39), there were no deaths when arterial lactate levels returned to normal within 24 hours, but when lactate levels remained elevated after 48 hours, 86% of the patients died. Rapid restoration of tissue perfusion is one of the most important goals in hemorrhagic shock because continued tissue hypo perfusion creates a time-dependent *oxygen debt,* and the greater the oxygen debt, the greater the risk of multiorgan failure and a fatal outcome.

Correcting Anemia

After volume deficits are replaced and cardiac output is restored, attention can be directed to correcting deficits in the oxygen carrying capacity of blood. The use of erythrocyte transfusions to correct normovolemic anemia is discussed in detail in ehapter 36. The presentation here will be limited to the most appropriate indication for blood transfusion (transfusion trigger) in normovolemic anemia.

Hematocrit: A Lousy Tranifusion Trigger

There is no rational basis for the use of hematocrit (or hemoglobin concentration) as an indicator for blood transfusion because the hematocrit is not an accurate representation of the total erythrocyte volume in blood, and it provides no information about the adequacy of tissue oxygenation. As described earlier (and demonstrated in Figure 12.2), the hematocrit and erythrocyte volume will change in opposite directions when there is a selective change in plasma volume (e.g., from diuresis or infusion of asanguinous fluids), and the hematocrit will remain unchanged despite a change in erythrocyte volume when there is a proportional change in plasma volume and erythrocyte volume (e.g., from acute blood loss or transfusion with whole blood). Because the hematocrit (and hemoglobin concentration) is not an accurate reflection of the erythrocyte volume in blood, it cannot be used as an indication for blood transfusion to increase the erythrocyte volume.

Abandoning the hemoglobin and hematocrit as transfusion triggers was suggested over a decade ago, when guidelines on red blood cell transfusions published by the American eo liege of Physicians included the following statement (40): "In the absence of patient risks, transfusion is not indicated, *independent of hemoglobin level"* (italics mine).

02 Extraction: A Better Transfusion Trigger

The ultimate goal of correcting anemia is to improve tissue oxygenation, so a measure of tissue oxygen balance could be used to determine the need for correcting anemia with erythrocyte transfusions. The oxygen extraction from systemic capillaries could be such a measure. As described earlier in the chapter, an increase in systemic 0, extraction to 50% represents the maximum compensation for a decrease In 02 delivery. Thus in the setting of anemia (which results in a decrease in systemic 02

delivery), an 02 extraction of 50% can be used as an indirect marker of tissue dysoxia or impending dysoxia (dysoxia is defined in Chapter 2 as a state of oxygen-limited metabolic energy production). Because the ultimate goal of ,erythrocyte transfusions is to correct or prevent tissue dysoxia, an 02 extraction of 50% can be used as an indication for transfusion of erythrocytes (i.e., a transfusion trigger). This approach has been used in patients with coronary artery disease (41).
An approximate measure of systemic 02 extraction can be obtained by measuring the oxyhemoglobin saturation in both arterial blood ($Sa0_2$) and central venous blood ($Scv0_2$).
02 Extraction (%) = $Sa0_2$ - $Scv0_2$
The $Sa0_2$ can be monitored continuously with a pulse oximeter, and the $Scv0_2$ is measured in a blood sample taken from an indwelling central venous catheter.

Refractory Shock

Prolonged periods of hemorrhagic shock can produce an irreversible condition with severe hypotension that is refractory to volume expansion and pressor agents. Vasopressin has shown some promise in this condition, as described next.

Vasopressin

Some cases of hemorrhagic hypotension that are unresponsive to conventional vasopressor therapy have shown a favorable response to vasopressin infusion at a rate of 1 to 4 mU/kg/min (42). The mechanism for this vasopressin effect is not clear. Circulating levels of vasopressin are reduced in the late stages of hemorrhagic shock (42), and it is possible that vasopressin deficiency plays a role in the refractory hypotension that accompanies severe or prolonged hemorrhagic shock. Vasopressin infusions can also raise blood pressure and reduce vasopressor requirements in patients with severe septic shock (43).

A FINAL WORD

The nonsurgical approach to hemorrhage and hypovolemia has not changed significantly in the past 20 years, which is unfortunate. The following are some of the persistent problems and practices that need to change.
The evaluation of intravascular volume is so flawed it has been called a "comedy of errors" (44).
The hemoglobin and hematocrit continue to be used inappropriately as transfusion triggers.
The Trendelenburg position continues to be as popular as it is ineffective.
There is still no satisfactory end-point for the resuscitation effort.

References

Chapter 13

COLLOID AND CRYSTALLOID RESUSCITATION

In 1861, Thomas Graham's investigations on diffusion led him to classify substances as crystalloids or colloids based on their ability to diffuse through a parchment membrane. Crystalloids passed readily through the membrane, whereas colloids (from the Greek word for glue) did not. Intravenous fluids are similarly classified based on their ability to pass from intravascular to extravascular (interstitial) fluid compartments (see Figure 13.1). This chapter describes the comparative features of crystalloid and colloid fluids, both individually and as a group. These fluids are used every day in the care of hospitalized patients, so you must become familiar with the material in this chapter.

CRYSTALLOID FLUIDS

Crystalloid fluids are electrolyte solutions with small molecules that can diffuse freely throughout the extracellular space. The principal component of crystalloid fluids is the inorganic salt sodium chloride (NaCl). Sodium is the most abundant solute in the extracellular fluid, where it is distributed uniformly. Because 75 to 80% of the extracellular fluid is located in the interstitial space, a similar proportion of the total body sodium is in the interstitial fluids. Intravenously administered sodium follows the same distribution, so 75 to 80% of the volume of infused sodium chloride (saline) solutions will be distributed in the interstitial space. This means that the predominant effect of volume resuscitation with crystalloid fluids is to expand the interstitial volume rather than the plasma volume.

Volume Effects

The effects of crystalloid fluid resuscitation on plasma volume and interstitial fluid volume are shown in Figure 13.2. Infusion of one liter of 0.9% sodium chloride (isotonic saline) adds 275 mL to the plasma volume

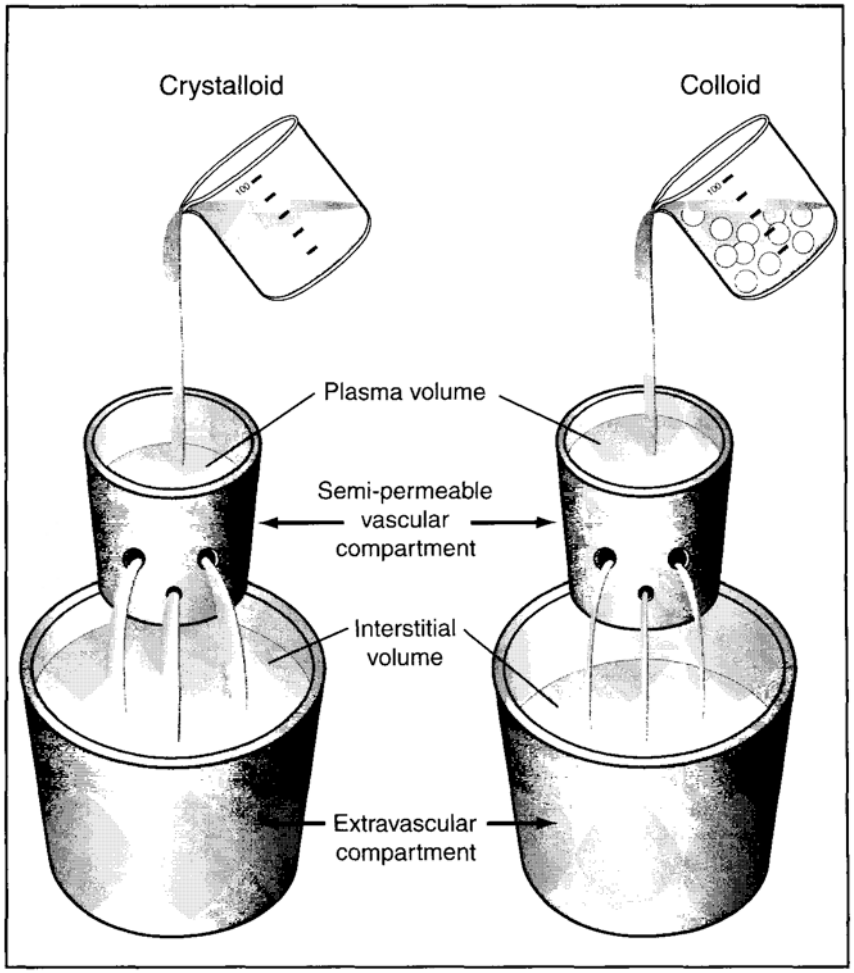

FIGURE 13.1 Illustration depicting the different tendencies of colloid and crystalloid fluids to flow out of the vascular space and into the interstitial space. The large spheres in the colloid fluid represent large molecules that do not pass readily through the semi-permeable barrier that separates the vascular and interstitial spaces. Note that the colloid fluid has a smaller stream flowing out of the vascular space.

and 825 mL to the interstitial volume (1). Note that the total volume expansion (1,100 mL) is slightly greater than the infused volume. This is the result of a fluid shift from intracellular to extracellular space, which occurs because 0.9% sodium chloride is slightly hypertonic to extracellular fluid. The comparative features of 0.9% sodium chloride and extracellular fluid (plasma) are shown in Table 13.1.

Isotonic Saline

The prototype crystalloid fluid is 0.9% sodium chloride (NaCl), also called isotonic saline or normal saline. The latter term is inappropriate

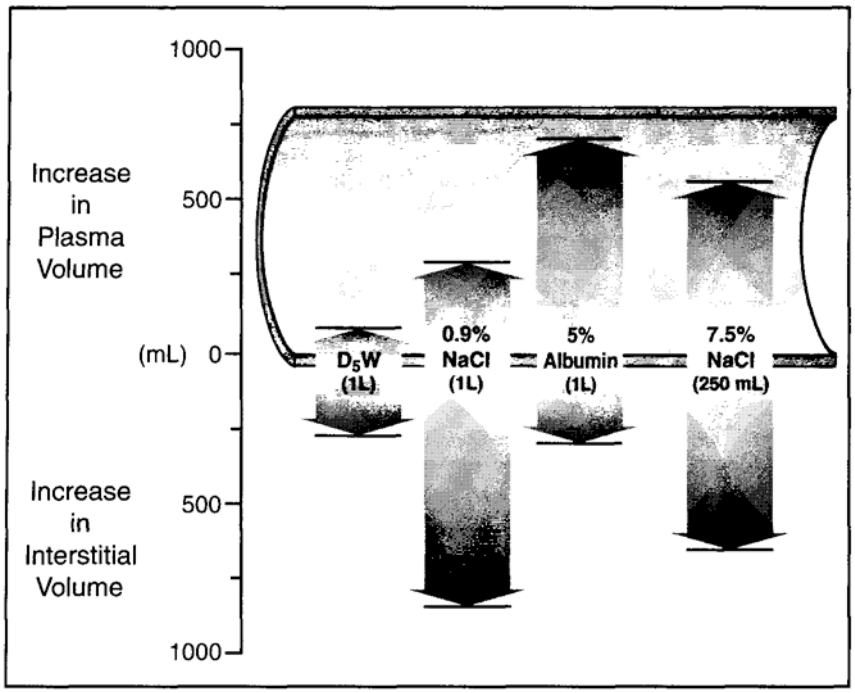

FIGURE 13.2 The effects of selected colloid and crystalloid fluids on the plasma volume and interstitial fluid volume. The volume of each fluid infused is shown in parentheses. (From Imm A, Carlson RW. Fluid resuscitation in circulatory shock. Crit Care Clin 1993;9:313.)

TABLE 13.1 Comparison of Plasma and Crystalloid Infusion Fluids

				mEq/L				Osmolality
Fluid	**Na**	**Cl**	K	**Ca**	**Mg**	**Buffers**	**pH**	**(mOsm/L)**
Plasma	140	103	4	5	2	Bicarb (25)	7.4	290
0.9% NaCl	154	154	–	–	–	–	5.7	308
7.5% NaCla	1,283	1,283	–	–	–	–	5.7	2,567
Lactated Ringer's Normosol }	130	109	4	3	–	Lactate (28)	6.4	273
Plasma-Lyte Isolyte[b]	140	98	5	–	3	Acetate (27) Gluconate (23)	7.4	295

Isolyte also contains phosphate 1mEq/L

because a one-normal (1 N) NaCl solution contains 58 grams NaCl per liter (the combined molecular weights of sodium and chloride), whereas isotonic (0.9%) NaCl contains only 9 grams NaCl per liter.

Features
A comparison of isotonic saline and plasma in Table 13.1 shows that isotonic saline has a higher sodium concentration (154 vs. 140 mEq/Ll, a much higher chloride concentration (154 vs. 103 mEq/L), a much lower pH (5.7 vs. 7.4), and a slightly higher osmolality (308 vs. 290 mOsm/L). The difference in chloride concentrations can create an acid-base imbalance, as described next.

Disadvantages
Infusion of large volumes of isotonic saline can produce a metabolic acidosis, as demonstrated in Figure 13.3. In this case, intraoperative infusion of isotonic saline at a rate of 30 mL/kg/h was accompanied by a drop in serum pH from 7.41 to 7.28 after two hours (2). This acidosis is a hyperchloremic acidosis produced by the high chloride concentration

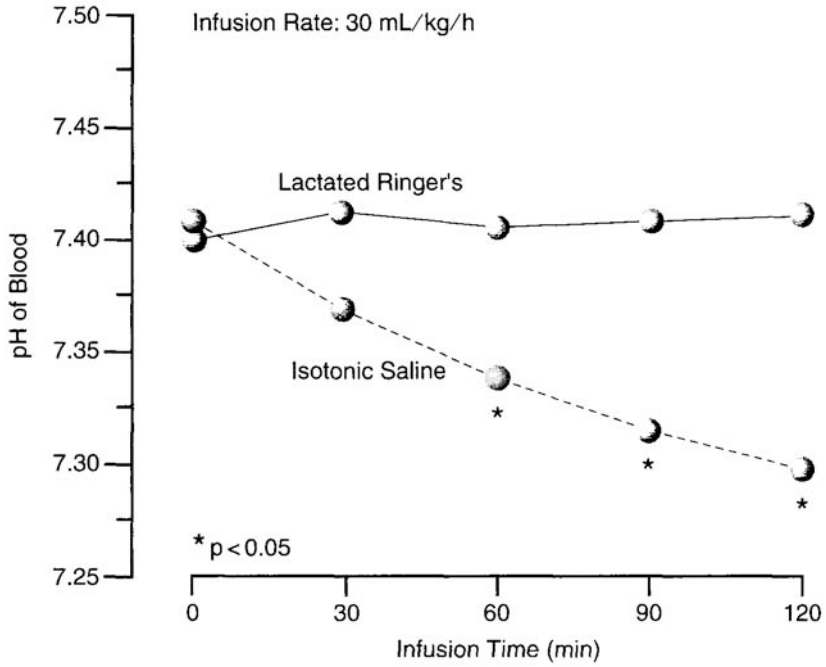

FIGURE 13.3 The effects of large-volume resuscitation with isotonic saline and lactated Ringer's solution on the pH of blood in patients undergoing elective surgery. Total volume infused after 2 hours was 5 to 6 liters for each fluid. (From Scheingraber S, Rehm M, Schmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265.)

in isotonic saline. Saline-induced acidosis occurs only after large volumes of isotonic saline are infused (e.g., during prolonged surgery), and it is usually has no adverse consequences (3). The major concern is differentiating this type of acidosis from lactic acidosis because the latter condition can be a marker of tissue ischemia (see Chapter 29 for the diagnostic approach to lactic acidosis).

Lactated Ringer's Solution

Sydney Ringer, a British physician who studied mechanisms of cardiac contraction, introduced a solution in 1880 that consisted of calcium and potassium in a sodium chloride diluent and was intended to promote the contraction of isolated frog hearts (4). This (Ringer's) solution slowly gained in popularity as an intravenous fluid, and, in the 1930s, an American pediatrician named Alexis Hartmann proposed the addition of sodium lactate to the solution to provide a buffer for the treatment of metabolic acidoses. This *lactated Ringer's solution,* also known as Hartmann's solution, eventually replaced the standard Ringer's solution for routine intravenous therapy. The composition of lactated Ringer's solution is shown in Table 13.1.

Features

Lactated Ringer's solution contains potassium and calcium in concentrations that approximate the free (ionized) concentrations in plasma. The addition of these cations requires a reduction in sodium concentration for electrical neutrality, so lactated Ringer's has a lower sodium concentration than either isotonic saline or plasma (see Table 13.1). The addition of lactate (28 mEq/L) similarly requires a reduction in chloride concentration, and the resultant chloride concentration in lactated Ringer's 009 mEq/L) is a close approximation of the plasma chloride concentration 003 mEq/L). This eliminates the risk of hyperchloremic metabolic acidosis with large-volume infusions of lactated Ringer's solution (see Figure 13.3).

Disadvantages

The calcium in Ringer's solutions can bind to certain drugs and reduce their effectiveness. Drugs that should not be infused with Ringer's solution for this reason include aminocaproic acid (Amicar), amphotericin, ampicillin, and thiopental (4).

The calcium in Ringer's can also bind to the citrated anticoagulant in blood products. This can inactivate the anticoagulant and promote the formation of clots in donor blood. For this reason, the American Association of Blood Banks has stated that lactated Ringer's solution is contraindicated as a diluent for red blood cell transfusions (5). However, clot formation in erythrocyte concentrates (packed RBCs) does not occur if the volume of Ringer's lactate does not exceed 50% of the volume of packed RBCs (6).

Serum Lactate Levels

The high concentration of lactate in lactated Ringer's solution (28 mEq/L) creates concern about the risk of spurious hyperlactatemia with largevolume infusions of the fluid. In healthy subjects, infusion of one liter of lactated Ringer's over one hour does not raise serum lactate levels (7). In critically **ill** patients, who may have impaired lactate clearance from circulatory shock or hepatic insufficiency, the effect of lactated Ringer's infusions on serum lactate levels is not known. However, if lactate clearance is zero, the addition of one liter of lactated Ringer's to a blood volume of 5 liters (which would require infusion of about 4 liters of fluid) would raise the serum lactate level by 4.6 mmol/L (7). Therefore because only 25% of crystalloid fluids remain in the vascular compartment, lactated Ringer's infusions are not expected to have a considerable impact on serum lactate levels, even in patients with impaired lactate clearance.

Blood samples obtained from intravenous catheters that are being used for lactated Ringer's infusions can yield spuriously high serum lactate determinations (8). Therefore in patients receiving lactated Ringer's infusions, blood samples for lactate measurements should be obtained from sites other than the infusion site.

Fluids with a Normal pH

Three crystalloid fluids contain both acetate and gluconate buffers to achieve a pH of 7.4 (see Table 13.1): Normosol (Abbott Labs), Isolyte (B. Braun Medical), and Plasma-Lyte (Baxter Healthcare). All three fluids contain potassium (5 mEq/L) and magnesium (3 mEq/L), while Isolyte also contains phosphate (1 mEq/L). These fluids are not commonly used as resuscitation fluids, but they may be preferred to saline for washing or diluting red blood cell preparations (9).

DEXTROSE SOLUTIONS

In the days before the introduction of enteral and parenteral nutrition, dextrose was added to intravenous fluids to provide calories. One gram of dextrose provides 3.4 kilocalories (kcal) when fully metabolized, so a 5% dextrose solution (50 grams dextrose per liter) provides 170 kcal per liter. Daily infusion of 3 liters of a 5% dextrose (D_s) solution will then provide about 500 kcal per day, which is enough nonprotein calories to limit the breakdown of endogenous proteins to meet daily caloric requirements. This *protein-sparing effect* is responsible for the early popularity of Ds infusion fluids. However, with the advent of effective enteral and parenteral nutrition regimens, the popularity of Ds infusion fluids is no longer justified.

Adverse Effects

Routine or aggressive use of dextrose-containing fluids can be harmful in a number of ways, as explained next.

Dextrose and Osmolality

The addition of dextrose to intravenous fluids increases osmolarity (50 g of dextrose adds 278 mOsm to an intravenous fluid). For a 5% dextrosein-water solution (DsW), the added dextrose brings the osmolality close to that of plasma. When dextrose is added to isotonic saline (D_s normal saline), the infusion fluid becomes hypertonic to plasma (560 mOsm/L), and, if glucose utilization is impaired (as is common in critically ill patients), the hypertonic infusion creates an undesirable osmotic force that can promote cell dehydration.

5% Dextrose in *Water (D5 W)*

As shown in Figure 13.2, 5% dextrose in water (DoW) is a relatively ineffective fluid for expanding the plasma volume.' Less than 10% of the infused volume of Ds W remains in the vascular compartment. The total increase in extracellular fluid volume (plasma plus interstitial fluid) is much less than the infused volume of DsW because 2/3 of the infused volume ends up inside cells. Therefore the predominant effect of DsW infusions is cellular swelling.

Enhanced Lactate Production

In healthy subjects, only 5% of an infused glucose load will result in lactate formation, but in critically ill patients with tissue hypoperfusion, as much as 85% of glucose metabolism is diverted to lactate production (0). This latter effect is demonstrated in Figure 13.4. In this case, tissue hypoperfusion was induced by aortic clamping during abdominal aortic aneurysm surgery (11). Patients received intraoperative fluids to maintain normal cardiac filling pressures using either a Ringer's solution or a 5% dextrose solution. When the dextrose-containing fluid was infused, the serum lactate levels began to rise after the aorta was cross-clamped, and the increase in circulating lactate levels persisted throughout the remainder of the surgery. These results indicate that, when circulatory flow is compromised, infusion of 5% dextrose solutions can result in metabolic acid production instead of metabolic energy production.

Adverse Effects lif Hyperglycemia

Hyperglycemia has several deleterious effects in critically ill patients, including immune suppression (2), increased risk of infection (3), aggravation of ischemic brain injury (4), and an increased mortality 03,15). The association between hyperglycemia and increased mortality is supported by studies showing that aggressive use of insulin to prevent hyperglycemia is associated with improved survival in ICU patients (13). The mechanism for the mortality-lowering effect of tight glycemic control is unclear at present.

About 20% of patients admitted to ICUs are diabetic (2), and as many as 90% of patients will develop hyperglycemia at some time during their ICU stay (3). Considering the high risk of hyperglycemia in ICU patients, and the numerous adverse consequences of hyperglycemia, infusion of dextrose-containing fluids should be avoided whenever

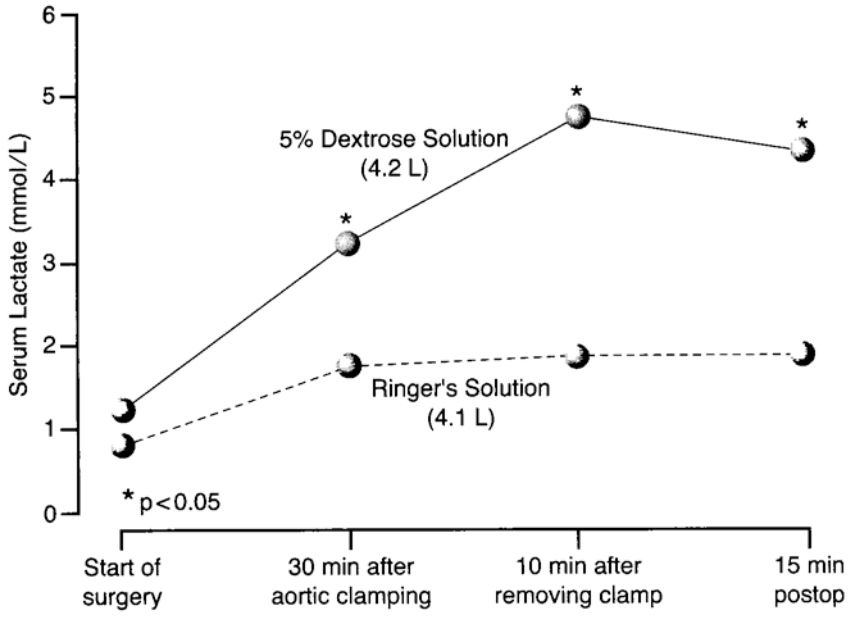

FIGURE 13.4 The effect of intravenous fluid therapy with and without dextrose on blood lactate levels in patients undergoing abdominal aortic aneurysm repair. Each point represents the mean lactate level in 10 study patients. The average infusion volume for each fluid is indicated in parentheses. (From Degoute CS, Ray MJ, Manchon M, et al. Intraoperative glucose infusion and blood lactate: endocrine metabolic relationships during abdominal aortic surgery. Anesthesiology 1989;17:355.)

possible. In fact, considering the overall potential for harm with dextrose infusions, it seems that the routine use of 5% dextrose solutions should be abandoned in critically ill patients.

COLLOID FLUIDS

Colloid fluids are more effective than crystalloid fluids for expanding the plasma volume because they contain large, poorly diffusible, solute molecules that create an osmotic pressure to keep water in the vascular space. A description of osmotic pressure and its influence on capillary fluid exchange is included next for those who need a brief review of the topic. This information will help to understand the behavior of colloid fluids.

Colloid Osmotic Pressure

The movement of water from one fluid compartment to another requires a difference in the concentration of solutes in the two compartments, and this requires a solute that does not diffuse readily through the barrier

separating the two compartments. When there is a solute concentration gradient between two fluid compartments, water moves into the compartment with the higher solute concentration. (The water is actually moving down its own concentration gradient because the compartment with the higher solute concentration also has the lower concentration of free water). The movement of water into the compartment with the higher solute concentration creates an increase in pressure in the compartment, and this pressure increment is equivalent to the *osmotic pressure* in the compartment. Therefore osmotic pressure can be defined as the driving force for the movement of water into a fluid compartment.

Osmotic Pressure oj Plasma

Plasma contains large proteins that do not diffuse readily across capillary walls, and these proteins (mostly albumin) create an osmotic pressure called the *colloid osmotic pressure* or oncotic pressure. In healthy subjects, the colloid osmotic pressure of plasma is 25 mm Hg in the upright position and 20 mm Hg in the supine position. The positional change in oncotic pressure is explained by changes in plasma volume. A change in body position from supine to standing can result in a 5 to 25% decrease in plasma volume (6) (presumably as a result of fluid losses from capillary blood in the lower extremities in response to gravitational increases in capillary hydrostatic pressure), and this can raise on co tic pressure by increasing plasma protein concentrations (hemoconcentration effect).

Capillary Fluid Exchanne

The direction and rate of fluid exchange (Q) between capillary blood and interstitial fluid is determined, in part, by the balance between the hydrostatic pressure in the capillaries *(Pc)'* which promotes the movement of fluid out of capillaries, and the colloid osmotic pressure of plasma (Posm)' which promotes the movement of fluid into capillaries.

Q - (Pc - Posm)

The direction of fluid flow is determined by which of the two pressures is highest. If *Pc* is greater than Posm' fluid will flow from capillaries into the interstitial fluid, and if Posm is greater than *Pc'* fluid will move from the interstitial fluid into the capillaries (in this condition, Q has a negative value). The rate of fluid flow is then determined by the magnitude of the difference between the two pressures. These relationships were identified over a century ago by the prolific British physiologist Ernest Starling, and the pressures *Pc* and Posm are often referred to as the *Starling forces.* These forces will be used to explain the behavior of colloid fluids as plasma volume expanders.

Volume Effects

The effect of volume resuscitation with a colloid fluid is demonstrated in Figure 13.2. The colloid fluid in this case is a 5% albumin solution. Infusion of one liter of this solution results in a 700 mL increment in the

TABLE 13.2 Comparative Features of Colloid Fluids

Fluid	Average Molecular Wt (kilodaltons)	Oncotic Pressure (mm Hg)	aPlasma Volume Infusate Volume	Duration of Effect
25% Albumin	69	70	4.0-5.0	16 hr
1 0% Dextran-40	26	40	1.0-1.5	6 hr
6% Hetastarch	450	30	1.0-1.3	10 hr
5% Albumin	69	20	0.7-1.3	16 hr

Data from References 17-20 and

plasma volume and a 300 mL increment in the interstitial fluid volume. Thus 70% of the infused volume of this colloid fluid remains in the vascular space and adds to the plasma volume. Figure 13.2 also shows that infusion of an equivalent volume (one liter) of a crystalloid fluid (0.9% sodium chloride) results in a 250 mL increase in plasma volume and a 750 mL increase in interstitial fluid volume. Comparing the effects of the colloid and crystalloid fluid on the increment in plasma volume indicates that colloid fluids are about three times more effective than crystalloid fluids for increasing plasma volume (17-20).

Colloid Comparisons

Individual colloid fluids differ in their ability to augment the plasma volume, and this difference is a function of the colloid osmotic pressure of each fluid. This is demonstrated in Table 13.2. This table includes the commonly used colloid fluids in this country and shows the colloid osmotic pressure of each fluid (in mm Hg) and the increment in plasma volume produced by a given volume of each fluid. Note that fluids with higher colloid osmotic pressures produce greater increments in plasma volume. Note also that if a fluid has a colloid osmotic pressure greater than that of plasma (greater than 25 mm Hg), the increment in plasma volume can exceed the infusion volume of the fluid. This is most apparent with 25% albumin, which has a colloid osmotic pressure of 70 mm Hg (about 3 to 4 times greater than plasma), and produces an increment in plasma volume that is 3 to 4 times greater than the volume infused.

Albumin Solutions

Albumin is a versatile and abundant protein that is synthesized almost continuously by the liver (an average of 10 grams is produced daily). The average-sized adult has about 120 grams of albumin in plasma and another 160 grams in the interstitial fluid (21). Thus albumin is located primarily in the interstitial fluid, which is perplexing in light of the important role played by albumin in the plasma. Albumin is the principal transport protein in blood (see Table 13.3) and is also responsible for 75% of the colloid osmotic pressure in plasma (17,20,21). It also acts as a buffer (see Chapter 2), has significant antioxidant activity (22), and helps maintain

TABLE 13.3 **Substances that are Transported by Albumin**

Drugs	Others
Benzodiazepines	Adrenal hormones
Cephalosporins	Estrogen
Furosemide	Progesterone
NSAIDs	Testosterone
Phenytoin	Bilirubin
Quinidine	Fatty acids
Salicylates	Inflammatory mediators
Sulfonamides	Prostaglandins
Valproic acid	Metals
Warfarin	Copper
	Nickel
	Zinc

blood fluidity by inhibiting platelet aggregation (21). What it does outside the bloodstream, where most of the albumin resides, is unknown.

Features

Albumin solutions are heat-treated preparations of human serum albumin that are available as a 5% solution (50 giL) and a 25% solution (250 giL) in an isotonic saline diluent. The 5% albumin solution has an albumin concentration of 5 *gl* dL and a colloid osmotic pressure of 20 mm Hg, both equivalent to plasma. Infusion of 5% albumin is performed using aliquots of 250 mL. About 70% of the infusate volume remains in the plasma for the first few hours post-infusion, but the increment in plasma volume dissipates rapidly thereafter, and the effect can be lost after just 12 hours (17,20).

The 25% albumin solution is a non-physiologic, hyperoncotic fluid that is given in aliquots of 50 mL or 100 mL. Following acute infusions of 25% albumin, plasma volume increases by 3 to 4 times the infusate volume. The effect is produced by fluid shifts from the interstitial space, so interstitial fluid volume is expected to decrease by equivalent amounts. Because the small volumes of 5% albumin solutions do not represent a significant sodium load, this solution is sometimes referred to as "saltpoor albumin."

It is important to emphasize that infusion of 25% albumin does not provide replacement of lost volume but merely shifts body fluid from one fluid compartment to another. Therefore 25% albumin should not be used as volume replacement therapy for patients with acute blood loss or dehydration. This fluid should be reserved for the occasional patient with hypovolemia resulting from fluid shift into the interstitial space, which is usually the result of severe hypoalbuminemia.

Safety of Albumin Solutions

Albumin's reputation was sullied in 1998 when a clinical review was published claiming that one of every 17 patients who receive albumin infusions dies as a result of the fluid (23). This began a prolonged and passionate debate between albumin lovers and haters that continues to this day. However, the original claim that albumin is a lethal poison has not been corroborated in subsequent clinical reviews (24,25) or in a very large prospective, multicenter study of albumin and saline infusions that involved close to 7,000 patients (26). Thus the bulk of evidence indicates that albumin solutions are no more dangerous than any other colloid or crystalloid fluid. In fact, if adverse events are evaluated instead of deaths, the evidence indicates that albumin solutions are safer to use than crystalloid fluids (27). The influence of colloid and crystalloid fluids on clinical outcomes is discussed again later in the chapter.

Hetastarch

Hydroxyethyl starch (hetastarch) is a chemically modified starch polymer that is available as a 6% solution in isotonic saline. There are three types of hetastarch solution based on the average molecular weight (MW) of the starch molecules (28): high MW (450,000 daltons), medium MW (200,000 daltons), and low MW (70,000 daltons). High MW hetastarch is used exclusively in the United States, while in other countries, medium MW hetastarch is the popular fluid. High MW solutions have the greatest oncotic activity but also have the highest risk of certain adverse effects (see later).

Hetastarch elimination is a two-step process. First, circulating starch molecules undergo hydrolysis by amylase enzymes in blood. When the starch molecules are cleaved into small fragments (MW < 50,000 daltons), they are cleared by the kidney. Clearance of hetastarch can take several weeks, but the oncotic activity is lost after one day.

Volume Effects

The performance of 6% hetastarch as a plasma volume expander is very similar to 5% albumin. The oncotic pressure (30 mm Hg) is higher than 5% albumin (20 mm Hg), and the increment in plasma volume can be slightly higher as well (see Table 13.2). The effect on plasma volume usually is lost by 24 hours (16,27).

Overall, 6% hetastarch is equivalent to 5% albumin as a plasma volume expander. The major difference between these two fluids is cost (hetastarch is less costly) and the risk of altered hemostasis (which is greater with hetastarch).

Altered Hemostasis

The most celebrated side effect of hetastarch is a bleeding tendency caused by inhibition of factor VII and von Willebrand factor and impaired platelet adhesiveness (28,29). This effect is seen predominantly with high MW hetastarch, is less pronounced with medium MW hetastarch, and is absent with low MW hetastarch (29). The coagulation defects become

pronounced whi:m more than 1,500 mL hetastarch is infused within a 24 hr period (28). Overt bleeding is inconsistent, but it may be more frequent when hetastarch is used during cardiopulmonary bypass surgery. Despite lack of convincing evidence of harm, the Food and Drug Administration has issued a warning label to alert users of the bleeding risk from hetastarch in cardiopulmonary bypass surgery (30).

Troublesome bleeding from hetastarch can be minimized by limiting the infusion volume to less than 1,500 mL in 24 hours and by avoiding the use of hetastarch in patients with an underlying coagulopathy, particularly von Willebrand's disease. The use of hetastarch in cardiopulmonary bypass surgery should be left to the discretion of those who perform or are otherwise involved in bypass surgery on a daily basis.

Other Concerns

As mentioned earlier, hetastarch molecules are hydrolyzed by circulating amylases before they are cleared by the kidneys. The amylase enzymes attach to the hetastarch molecules, and this reduces amylase clearance by the kidneys. The result is an increase in serum amylase levels (2 to 3 times above normal) that'represents macroamylasemia (28). Amylase levels return to normal within one week after the hetastarch is discontinued (29). The hyperamylqsemia from hetastarch is not a deleterious side effect. The only adverse risk is misinterpretation of the elevated levels as a sign of acute pancreatitis, which could prompt unnecessary diagnostic and therapeutic interventions. Lipase levels are not elevated by hetastarch infusions (31), and this is an important consideration to avoid a misdiagnosis of acute pancreatitis.

Anaphylactic reactions to hetastarch are rare, occurring in 0.006% of infusions (28). Chronic administration of hetastarch can produce a troublesome pruritis that is difficult to treat. This is not an allergic reaction and is caused by extravascular starch deposits (27).

Hextend

Hextend is a 6% hetastarch solution with a buffered, multielectrolyte solution as a diluent instead of isotonic saline. This solution contains sodium (143 *mEq/L),* chloride (125 mEq/L), potassium (3 mEq/L), calcium (5 mEq/L), magnesium (0.9 mEq/L), lactate (28 mEq/L), and glucose (5 *mM/L).* Hextend has the same molecular weight and starch concentration as 6% hetastarch, so it is no surprise that it is equivalent to 6% hetastarch as a plasma volume expander.

Although the clinical experience is limited, Hextend offers no documented benefit over the other colloid resuscitation fluids. There is one study showing that Hextend infusions in an average volume of 1.6 liters had no detectable effect on blood coagulation during major surgery (32), but it is not possible to draw any conclusions based on this single study.

The Dextrans

The dextrans are glucose polymers produced by a bacterium *(Leuconostoc)* incubated in a sucrose medium. First introduced in the 1940s, these colloids are not popular (at least in the United States) because of the

perceived risk of adverse reactions. The two most common dextran preparations are 10% dextran-40 and 6% dextran-70, each having a different average molecular weight (see Table 13.2). Both preparations use an isotonic saline diluent.

Features

Both dextran preparations have a colloid osmotic pressure of 40 mm Hg and cause a greater increase in plasma volume than either 5% albumin or 6% hetastarch (see Table 13.2). Dextran-70 may be preferred because the duration of action (12 hours) is longer than that of dextran-40 (6 hours) (17).

Disadvantages

Dextrans produce a dose-related bleeding tendency tha t involves impaired platelet aggregation, decreased levels of factor VIII and von Willebrand factor, and enhanced fi!:lrinolysis (29,31). The hemostatic defects are minimized by limiting the daily dextran dose to 20 mLlkg.

Dextrans coat the surface of red blood cells and can interfere with the ability to cross-match blood. Red cell preparations must be washed to eliminate this problem. Dextrans also increase the erythrocyte sedimentation rate as a result of their interactions with red blood cells (31).

Dextrans have been implicated as a cause of acute renal failure (31,33). The proposed mechanism is a hyperoncotic state with reduced filtration pressure. However, this mechanism is unproven, and renal failure occurs only rarely in association with dextran infusions. Anaphylactic reactions, once common with dextrans, are now reported in only .032% of infusions (31).

THE COLLOID-CRYSTALLOID WARS

There is a long standing (and possibly eternal) debate concerning the type of fluid (crystalloid or colloid) that is most appropriate for volume resuscitation. Each fluid has its army of loyalists who passionately defend the merits of their fluid. The following are the issues involved in this debate.

Early Focus on Crystalloids

Early studies of acute blood loss in the 1960s produced two observations that led to the popularity of crystalloid fluids for volume resuscitation. The first observation was a human study showing that acute blood loss is accompanied by a shift of interstitial fluid into the bloodstream (transcapillary refill), leaving an *interstitial fluid deficit* (34). The second observation was an animal study showing that survival in hemorrhagic shock is improved if crystalloid fluid is added to reinfusion of the shed blood (35). The interpretation of these two observations, at that time, was that a major consequence of acute blood loss was an interstitial fluid deficit

and that replenishing this deficit with a crystalloid fluid will reduce mortality. Thus crystalloid fluids were popularized for volume resuscitation because of their ability to add volume to the interstitial fluids. Later studies using more sensitive measures of interstitial fluid revealed that the interstitial fluid deficit in acute blood loss is small and is unlikely to play a major role in determining the outcome from acute hemorrhage. This refuted the importance of filling the interstitial fluid compartment with crystalloids, yet the popularity of crystalloid fluids for volume resuscitation did not wane.

The Goal of Volume Resuscitation

The most convincing argument in favor of colloids for volume resuscitation is their superiority over crystalloid fluids for expanding the plasma volume. Colloid fluids will achieve a given increment in plasma volume with only one-quarter to one-third the volume required of crystalloid fluids. This is an important consideration in patients with brisk bleeding or severe hypovolemia, where rapid volume resuscitation is desirable.

The proponents of crystalloid resuscitation claim that crystalloids can achieve the same increment in plasma volume as colloids. This is certainly the case, but three to four times more volume is required with crystalloids than colloids to achieve this goal. This adds fluid to the interstitial space and can produce unwanted edema. In fact, as mentioned earlier (and demonstrated in Figure 13.2), the principal effect of crystalloid infusions is to expand the interstitial fluid volume, not the plasma volume. Since the goal of volume resuscitation is to support the intravascular volume, colloid fluids are the logical choice over crystalloid fluids.

Filling the Bucket

The following example illustrates the problem with using crystalloids to expand the plasma volume. Assume that you have two buckets, each representing the intravascular compartment, and each bucket is connected by a clamped hose to an overhanging reservoir that contains fluid. One reservoir contains a colloid fluid in the same volume as the bucket, and the other reservoir contains a crystalloid fluid in a volume that is three to four times greater than the colloid volume. Now release the clamp on each hose and empty the reservoirs: both buckets will fill with fluid, but most of the crystalloid fluid will spill over onto the floor. Now ask yourself which method is better suited for filling buckets: the colloid method, with the right amount of fluid and no spillage, or the crystalloid method, with too much fluid, most of which spills onto the floor.

Clinical Outcome

As mentioned earlier (see section on Safety of Albumin Solutions), the bulk of available evidence indicates that neither type of resuscitation

fluid provides a survival benefit (24-26), while colloid (albumincontaining) fluids may cause fewer adverse events (27).

The Problem with Mortality Studies

There are two problems with the studies comparing mortality rates associated with colloid and crystalloid fluids. The first problem is that most studies included a diverse group of patients who could have died from a variety of illnesses, and there is no way of determining if an intravenous fluid was directly related to the cause of death. For example, a resuscitation fluid could restore a normal plasma volume, but the patient dies of pneumonia: in this case, the fluid should not be blamed for the death. The second problem is the assumption that an intervention must save lives to be considered beneficial. It seems that an intervention should be judged by whether it achieves its intended goal (e.g., a resuscitation fluid should be judged by how well it restores plasma volume); determining if that goal influences mortality is a separate question.

Expense

The biggest disadvantage of colloid resuscitation is the higher cost of colloid fluids. Table 13.4 shows a cost comparison for colloid and crystalloid fluids. Using equivalent volumes of 250 mL for colloid fluids and 1,000 mL for crystalloid fluids, the cost of colloid resuscitation is nine times higher (if hetastarch is used) to twenty-one times higher (if albumin is used) than volume resuscitation with crystalloid fluids.

A Suggestion

Most studies comparing colloid and crystalloid fluids have attempted to determine if one type of resuscitation fluid is better than the other for all critically ill patients. This seems unreasonable, considering the multitude

TABLE 13.4 Relative Cost of Intravenous Fluids

Fluid	Manufacturer	Unit size	AWp·
Crystalloid fluids			
Isotonic saline	Hospira	1,000 ml	$1.46
Lactated Ringer's	Hospira	1,000 ml	$1.48
Colloidal fluids			
5% Albumin	Bayer	250 ml	$30.63
25% Albumin	Bayer	50ml	$30.63
6% Hetastarch	Abbott	500 ml	$27.63
6% Dextran-70	Hospira	500 ml	$14.96

"Average wholesale price listed in *2005 Redbook.* Montvale, NJ: Thomson

of clinical problems encountered in ICU patients. A more reasonable approach would be to determine if one type of fluid is more appropriate than the other for a given clinical condition (36). For example, patients with hypovolemia secondary to dehydration (where there is a uniform loss of extracellular fluid) might benefit more from a crystalloid fluid (which is expected to fill the extracellular space uniformly) than a colloid fluid, and patients with hypovolemia secondary to hypoalbuminemia (where there are fluid shifts from the intravascular to extravascular space) might benefit more from a colloid fluid (particularly 25% albumin) than a crystalloid fluid. Tailoring the type of resuscitation fluid to the specific clinical condition seems a more logical approach than using the same type of fluid without exception for all ICU patients.

HYPERTONIC RESUSCITATION

Volume resuscitation with hypertonic saline (7.5% NaCl) has received much attention as a method of small-volume resuscitation. A 7.5%

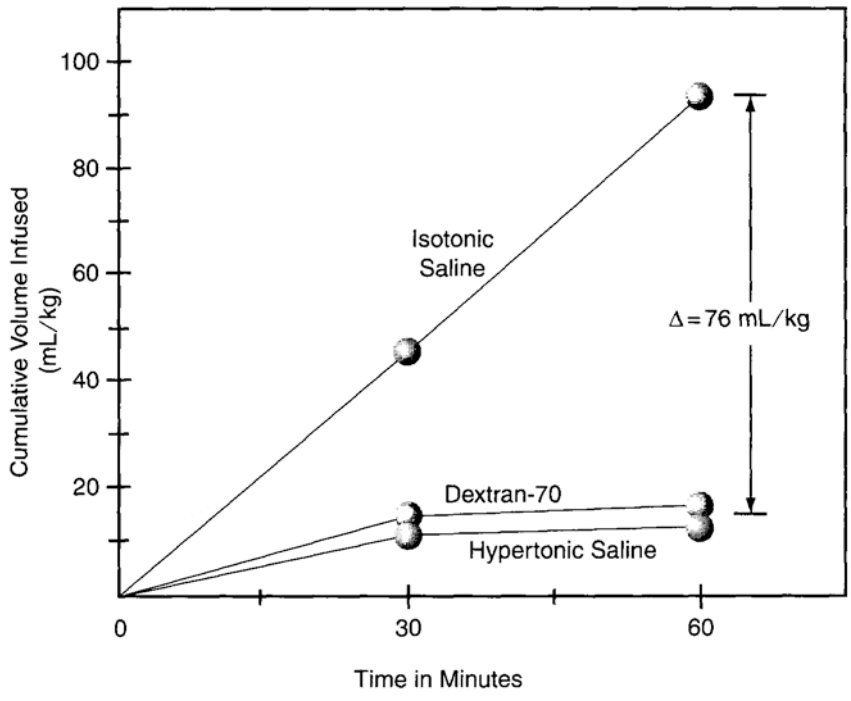

FIGURE 13.5 A comparison of the volume of three intravenous fluids needed to maintain a normal rate of aortic blood flow in an animal model of hemorrhagic shock. (From Chiara O, Pelosi P, Brazzi L, et al. Resuscitation from hemorrhagic shock: experimental model comparing normal saline, dextran, and hypertonic saline solutions. Crit Care Med 2003;31:1915.)

sodium chloride solution has an osmolality that is about 8.5 times greater than plasma (see Table 13.1). Figure 13.2 demonstrates that infusion of 250 mL of 7.5% NaCl will increase plasma volume by about twice the infused volume, indicating that hypertonic saline allows for volume resuscitation with relatively small volumes. Also note in Figure 13.2 that the total increase in extracellular fluid volume (1,235 mL) produced by 7.5% NaCl is about 5 times greater than the infused volume (250 mL). The additional volume comes from intracellular fluid that moves out of cells and into the extracellular space. This demonstrates one of the feared complications of hypertonic saline resuscitation: cell dehydration.

What Role?
The small volumes required with hypertonic saline resuscitation have been proposed as a possible benefit in the resuscitation of trauma victims with head injuries (to limit the severity of cerebral edema). However, the effective resuscitation volumes with hypertonic saline are similar to colloid resuscitation, as shown in Figure 13.5 (37), and a recent clinical study documented no advantage with hypertonic saline in the prehospital resuscitation of patients with traumatic head injury (38). At the present time, hypertonic saline is a resuscitation fluid without a clear indication.

A FINAL WORD
There is too much chatter about which type of resuscitation fluid (colloid or crystalloid) is most appropriate in critically ill patients because it is unlikely that one type of fluid is best for all patients. A more logical approach is to select the type of fluid that is best designed to correct a specific problem with fluid balance. For example, crystalloid fluids are designed to fill the extracellular space (interstitial space plus intravascular space) and would be appropriate for use in patients with dehydration (where there is a loss of interstitial fluid and intravascular fluid). Colloid fluids are designed to expand the plasma volume and are appropriate for patients with hypovolemia due to blood loss, while albumin-containing colloid fluids are appropriate for patients with hypovolemia associated with hypoalbuminemia. Tailoring fluid therapy to specific problems of fluid imbalance is the best approach to volume resuscitation in the ICU.
REFERENCES

Chapter 14

ACUTE HEART FAILURE SYNDROMES
There's no doubt that the proper functioning of *our pipes and pumps does have an immediate urgency well beyond that of almost any* of *our other bits and pieces.*
Steven Vogel (Vital Circuits, 1992)

Acute or decompensated heart failure is responsible for about 1 million hospital admissions each year in the United States 0), and it is the leading cause of hospital admissions for adults over the age of 65 (2). Heart failure is not a single entity but can be classified according to the side of the heart that is involved (right-sided vs. left-sided failure) or the portion of the cardiac cycle that is affected (diastolic vs. systolic failure). This chapter describes the diagnostic and therapeutic approach to each of these four heart failure syndromes using the principles of cardiac performance described in Chapter 1 (2-6). The approach to heart failure in this chapter is designed for the ICU: it is based on invasive hemodynamic measurements, rather than clinical symptoms and signs, and focuses on the mechanical

problems of heart failure rather than the responsible diseases. The usual causes of heart failure are shown in Figure 14.1.

HEMODYNAMIC ALTERATIONS

The hemodynamic consequences of progressive left-sided heart failure are shown in Figure 14.2. (The measurements in this graph were obtained from a patient who had just undergone cardiopulmonary bypass surgery). The hemodynamic changes progress through three stages (the numbers below correspond to the circled numbers in Figure 14.2);

The earliest sign of ventricular dysfunction is an increase in cardiac filling pressures. The stroke volume is maintained, but at the expense of the elevated filling pressure.

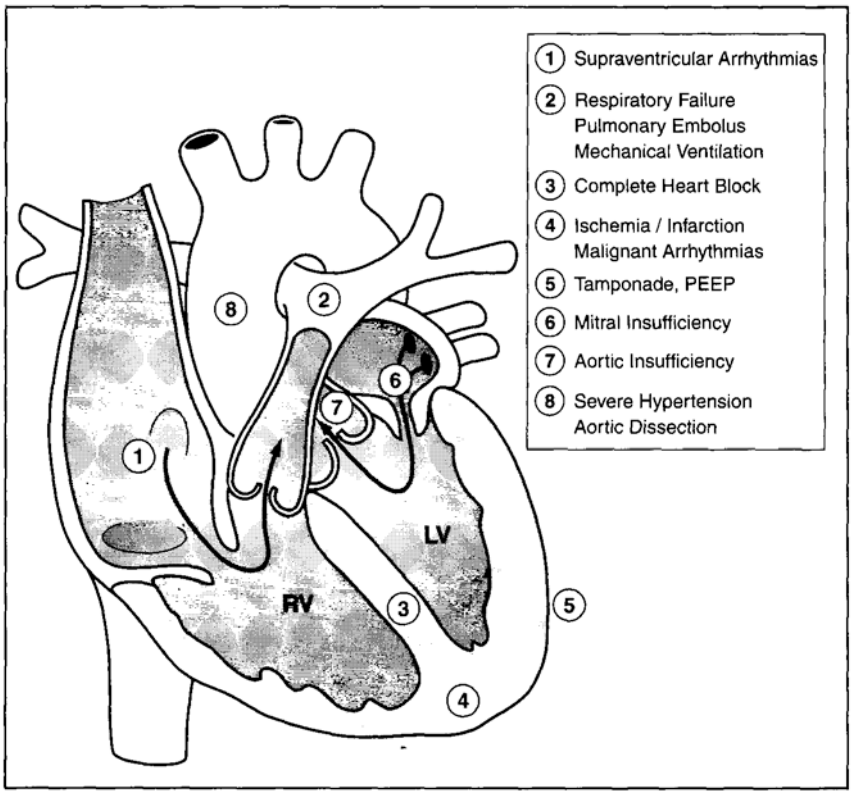

FIGURE 14.1 Common causes of acute heart failure, listed according to the anatomic region involved. *RV* = right ventricle; *LV* = left ventricle.

The next stage is marked by a decrease in stroke volume and an increase in heart rate. The tachycardia offsets the reduction in stroke volume, so the cardiac output remains unchanged.
The final stage is characterized by a decrease in cardiac output.
The point at which the cardiac output begins to decline marks the transition from compensated to decompensated heart failure.
The serial hemodynamic changes shown in Figure 14.2 demonstrate that cardiac output is impaired only in the more advanced stages of heart failure; therefore a normal cardiac output is not necessarily a normal cardiac pump.
Cardiac pump function should be evaluated using the relationship between ventricular filling pressure and stroke volume. This relationship is the basis for ventricular function curves, which are described in Chapter 1 (see Figure 1.2).

Systolic Versus Diastolic Failure
Heart failure is not synonymous with contractile failure because systolic function is normal in 40 to 50% of newly-diagnosed cases of heart

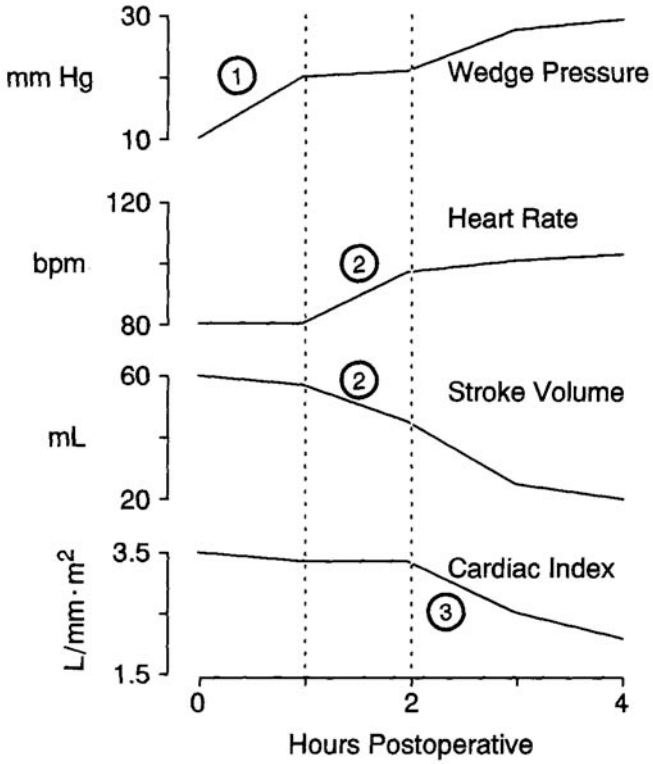

FIGURE 14.2 Hemodynamic effects of progressive left-sided heart failure in a postoperative patient.

failure (2). The problem in this condition is a combination of impaired ventricular relaxation and a decrease in passive ventricular distensibility, a disorder known as *diastolic heart failure* (6,7). In this type of heart failure, the decrease in cardiac output is due to inadequate ventricular filling, not impaired systolic contraction. Common causes of diastolic heart failure in ICD patients include ventricular hypertrophy, myocardial ischemia (stunned myocardium), and positive-pressure mechanical ventilation.

Diagnostic Difficulties

The usual method of evaluating cardiac pump function (by the relationship between ventricular filling pressure and stroke volume) will not distinguish between diastolic and systolic heart failure (7,8). This is illustrated in Figure 14.3. The curves in this figure are similar to the pressure-volume curves shown in Figures 1.2 and 1.3. The upper curves in the figure are ventricular function curves relating ventricular enddiastolic pressure and stroke volume. These curves indicate that heart failure is associated with an increase in end-diastolic pressure and a decrease in stroke volume. It is not possible, however, to determine if

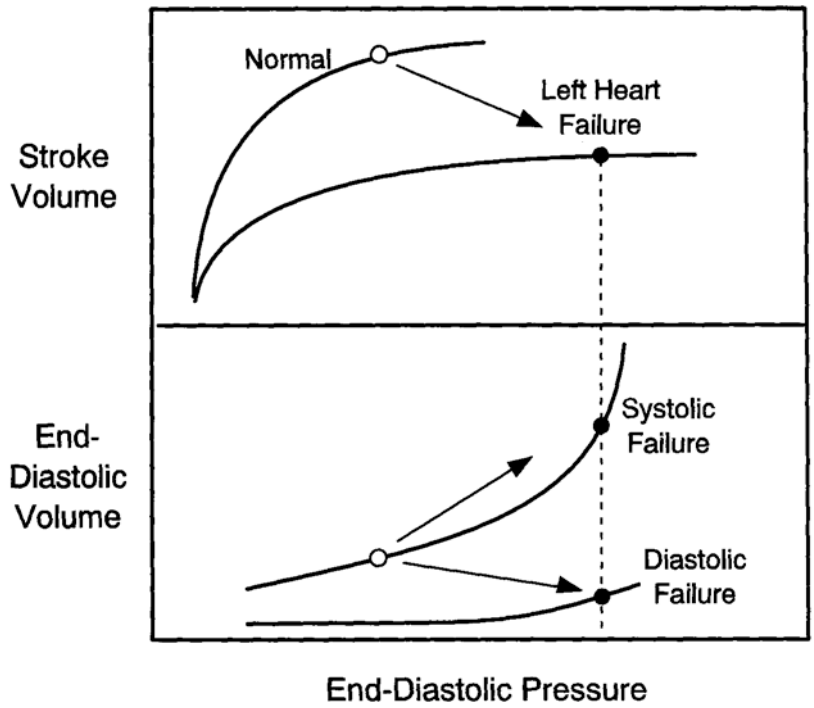

FIGURE 14.3 Graphs showing diastolic pressure volume curves in systolic and diastolic heart failure (lower curves) and ventricular function curves in heart failure (upper curves). The ventricular function curves, which are used to evaluate cardiac function in the clinical setting, are unable to distinguish between diastolic and systolic failure.

the heart failure is systolic or diastolic based on these measurements. The lower set of curves shows the pressure-volume relationships during diastole in the two types of heart failure. The end-diastolic pressure is increased in both types of heart failure, but the end-diastolic volume changes in different directions: it is increased in systolic heart failure and decreased in diastolic heart failure. Thus the end-diastolic volume, not the end-diastolic pressure, is the hemodynamic measure that will distinguish diastolic from systolic heart failure. There is a specialized pulmonary artery catheter that measures the end-diastolic volume of the right ventricle (see later), but otherwise this measurement is not readily available.

Ventricular Ejection Fraction

The measurement that is most often used to distinguish between diastolic and systolic heart failure is the ventricular *ejection fraction* (EF), which is a measure of the strength of ventricular contraction. The EF expresses the stroke volume (SV) as a fraction of the end-diastolic volume (EDV)

$$EF = SV / EDV$$

The normal EF of the right ventricle is 0.50 to 0.55, and the normal EF of the left ventricle is 0.40 to 0.50. The EF is normal in patients with diastolic heart failure and is reduced in patients with systolic heart failure.
Cardiac ultrasound can be used to measure ventricular EF at the bedside. Transthoracic ultrasound can be used to measure the EF of the left ventricle (6,7), and transesophageal ultrasound can be used to measure the EF of the right ventricle (8). A specialized pulmonary artery catheter is also available for measuring the EF of the right ventricle, as described in the next section.

Right Versus Left Heart Failure

Right heart failure (which is predominantly systolic heart failure) is more prevalent than suspected in ICU patients (9), and it may be particularly prominent in ventilator-dependent patients. The following measurements can prove useful in identifying right heart failure.

Cardiac Filling Pressures

The relationship between the central venous pressure (CVP) and the pulmonary capillary wedge pressure (PCWP) can sometimes be useful for identifying right heart failure. The following criteria have been proposed for right heart failure : CVP> 15 mm Hg and CVP = PCWP or CVP > PCWP. Unfortunately, at least one-third of patients with acute right heart failure do not satisfy these criteria. One problem is the insensitivity of the CVP; an increase in the CVP is seen only in the later stages of right heart failure. Contractile failure of the right ventricle results in an increase in end-diastolic volume, and only when the increase in volume of the right heart is impeded by the pericardium does the end-diastolic pressure (CVP) rise (9).
Another problem with the CVP-PCWP relationship for identifying right heart failure is the interaction between the right and left sides of the heart. This is shown in Figure 14.4. Both ventricles share the same septum, so enlargement of the right ventricle pushes the septum to the left and compromises the left-ventricular chamber. This interaction between right and left ventricles is called *interventricular interdependence,* and it can confuse the interpretation of ventricular filling pressures. In fact, as indicated by the diastolic pressures in Figure 14.4, the hemodynamic changes in right heart failure can look much like the hemodynamic changes in pericardial tamponade (9).

Thermodilution Ejection Fraction

A specialized pulmonary artery catheter is available that uses a fast-response thermistor to measure the ejection fraction (EF) of the right ventricle (11). Rapid-response thermistors can record the temperature changes associated with each cardiac cycle. This produces a thermodilution curve like the one shown in Figure 14.5. The change in temperature between each plateau on the curve is caused by dilution of the cold indicator fluid by venous blood that fills the ventricle during diastole. Because the volume that fills the ventricles during diastole is equivalent

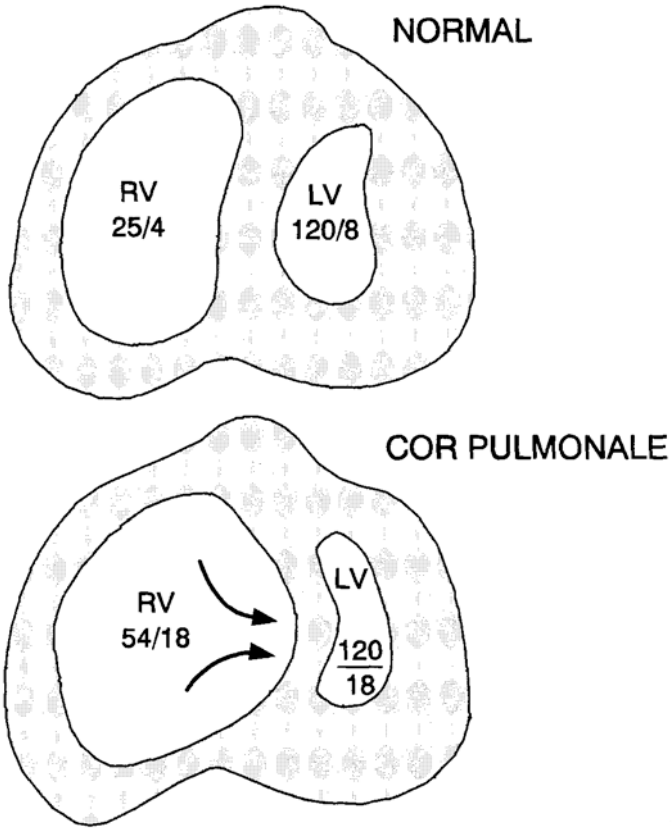

FIGURE 14.4 Interventricular interdependence: the mechanism whereby right heart failure can reduce diastolic filling of the left ventricle and increase the left-ventricular end-diastolic (wedge) pressure. *RV* = right ventricle; *LV* = left ventricle. The numbers in each chamber represent the systolic pressure as the numerator and the end-diastolic pressure as the denominator.

to the stroke volume, the temperature difference T} - T_2 is the thermal equivalent of the stroke volume (SV), and the temperature T} is thus a thermal marker of the end-diastolic volume (EDV). The ejection fraction is then equivalent to the ratio T} - T/T} (or SV /EDV). Once the EF is measured, the stroke volume can be measured in the usual fashion (as cardiac output divided by heart rate), and the EDV can be determined by rearranging Equation 14.1.

EDV = SV /EF

The normal right ventricular EF (RVEF) using thermodilution is 0.45 to 0.50, which is about 10% lower than the EF measured by radionuc1ide imaging (the gold standard). The normal right ventricular EDV (RVEDV) is 80 to 140 *mL/m²•*

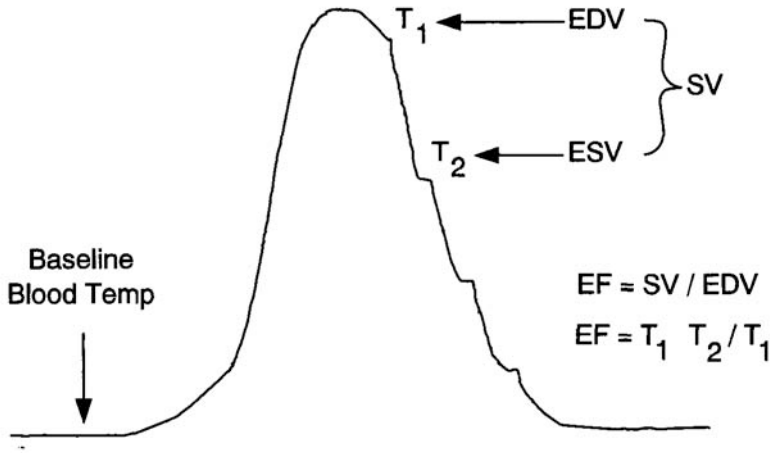

FIGURE 14.5 The thermodilution method of measuring the ejection fraction (*EF*) of the right ventricle using thermal equivalents for end-diastolic volume (*EDV*), end-systolic volume (*ESV*), and stroke volume (*SV*).

Since most cases of right heart failure represent systolic failure, the RVEF is expected to be less than 0.45, and the RVEDV is expected to be above 140 mL/m2 in cases of right heart failure (2). The response of RVEDV to a fluid challenge may also be diagnostic: volume infusion is expected to increase the RVEDV in patients with right heart failure, while in other patients, the RVEDV is unchanged after a fluid challenge (3).

Echocardiography
Cardiac ultrasound can be useful at the bedside for differentiating right from left heart failure. Three findings typical of right heart failure are (a) an increase in right-ventricular chamber size, (b) segmental wall motion abnormalities on the right, and (c) paradoxical motion of the interventricular septum.

B-TYPE NATRIURETIC PEPTIDE
Brain-type (B-type) natriuretic peptide (BNP) is a neurohormone that is released by the ventricular myocardium in response to ventricular volume and pressure overload. Plasma levels of BNP increase in direct relation to increases in ventricular end-diastolic volume and end-diastolic pressure (both right-sided and left-sided), and the rise in BNP produces both vasodilatation and an increase in renal sodium excretion (4).

Diagnostic Value
The plasma BNP level has proven to be an important tool for the diagnosis of heart failure. In patients who present with dyspnea of unknown etiology, a plasma BNP > 100 picograms/milliliter (pg/mL) can be used

as evidence of heart failure as a cause of the dyspnea (diagnostic accuracy = 84%) (15). In fact, in patients who present to the emergency department with dyspnea of unknown etiology, the plasma BNP level (using a cutoff level of 100 pg/mL) is the single most accurate predictor of the presence or absence of heart failure 05). Rapid determination of plasma BNP levels is available at the bedside using a fluorescence immunoassay kit (Triage; Biosite Diagnostics, San Diego, CA) that allows for timely identification of acute heart failure in the emergency department (15).

Plasma BNP levels also show a direct correlation with the severity of heart failure (14,16) [i.e., plasma levels are higher in patients with more advanced stages of heart failure (see Table 14.1)]. This correlation indicates that plasma BNP levels may be useful for monitoring the clinical course of heart failure.

Other Contributing Factors

Plasma BNP levels are influenced by gender, age, and renal function. This is demonstrated in Table 14.1. Plasma BNP levels are about 50% higher in females than in males, and plasma levels increase with advancing age in both sexes (4). Renal insufficiency also increases plasma BNP levels (because BNP is cleared by the kidneys), but levels usually do not pass the 100 pg/ mL threshold unless there is associated volume overload (see Table 14.1) (7).

TABLE 14.1 Plasma BNP Levels in Selected Conditions

Condition	Mean Plasma BNP (pg/mL)
Females—no CHF[a]	
Age 55–64	32
Age 75+	78
Males—no CHF[a]	
Age 55–64	20
Age 75+	48
Renal insufficiency[b]	
No volume overload	80
Volume overload	180
Heart failure[c]	
Mild	186
Moderate	791
Severe	2013

[a]From Reference 14.
[b]From Reference 17.
[c]From References 14,16.
Abbreviations: BNP = B-type natriuretic peptide, CHF = congestive heart failure, pg = picograms

What Role in *the ICU?*

Plasma BNP has been studied primarily in patients who present to emergency departments with possible heart failure. Few studies have been performed in ICU patients. One study of ICU patients with sepsis showed that plasma BNP levels were useful in identifying patients with cardiac dysfunction (8). However, it is unlikely that plasma BNP will replace more traditional methods of evaluating cardiac function in the ICU. Plasma BNP levels might prove useful for monitoring the effectiveness of treatment for heart failure in the ICU or to identify patients who develop fluid overload. Until further studies are conducted in the ICU, the plasma BNP assay will remain a tool for the emergency department.

MANAGEMENT STRATEGIES

The management of heart failure described here is meant for patients with advanced or decompensated heart failure, where the cardiac output is compromised (stage 3 in Figure 14.2). The approach here is specifically designed for ICU patients: it is based on invasive hemodynamic measurements rather than symptoms and uses only drugs that are given by continuous intravenous infusion 09-21). The hemodynamic drugs in this chapter are presented in detail in Chapter 16: the dose ranges and actions of each drug are shown in Table 14.2.

Left-Sided (Systolic) Heart Failure

The management of decompensated left-sided heart failure is traditionally designed for a systolic-type heart failure, even though some cases may involve diastolic failure. The recommendations here are based on three

TABLE 14.2 Drugs Used to Manage Acute, Decompensated Heart Failure in the ICU*

Drug	Dose Range	Principal Effect
Dobutamine	3-15 μg/kg/min	Positive inotropic effect and systemic vasodilatation
Dopamine	1-3 μg/kg/min	Renal vasodilatation and natriuresis
	3-10 μg/kg/min	Positive inotropic effect and systemic vasodilatation
	>10 μg/kg/min	Systemic vasoconstriction
Milrinone	50 μg/kg bolus, then 0.25-1 μg/kg/min	Positive inotropic effect, lusitropic effect, and systemic vasodilatation
Nitroglycerin	1-50 μg/min	Venous vasodilatation
	>50 μg/min	Arterial vasodilatation
Nitroprusside	0.3-2 μg/kg/min	Systemic vasodilatation

*Includes only drugs given by continuous intravenous infusion.

measurements: the pulmonary capillary wedge pressure (PCWP), the cardiac output (CO), and the arterial blood pressure (BP). Decompensated heart failure is associated with a high PCWP and a low CO, but the BP can vary. The management strategies that follow are based on the condition of the blood pressure (Le., high, normal, or low).

High Blood Pressure

Decompensated heart failure with elevated blood pressure is a common scenario in the early period after cardiopulmonary bypass surgery (22).

Profile: High PCWP fLow CO fHigh BP
Treatment: Vasodilator therapy with nitroprusside or nitroglycerin. If the PCWP remains above 20 mm Hg, add diuretic therapy with furosemide.

Vasodilators like nitroprusside and nitroglycerin augment cardiac output by reducing ventricular afterload. The overall effect is a decrease in arterial blood pressure, an increase in cardiac output, and a decrease in ventricular filling pressure (20). Nitroprusside is a more effective vasodilator than nitroglycerin, but drug safety is a concern. The major problem with nitroprusside is cyanide toxicity (23), which is more common than suspected (see Chapter 16) and is particularly prevalent following cardiopulmonary bypass surgery. Nitroprusside is also not advised in patients with ischemic heart disease because the drug can produce a "coronary steal syndrome" (4).

Nitroglycerin is a safer alternative to nitroprusside. Low infusion rates < 50 μg/min) produce venous vasodilation (which can reduce cardiac output further), and dose rates in excess of 50 μg/min are usually required to produce effective arterial vasodilation. The major drawback with nitroglycerin infusions is the development of tolerance, which can appear after 16 to 24 hours of continuous drug administration (4). Vasodilator therapy with angiotensin-converting-enzyme (ACE) inhibitors, while beneficial in the long-term management of left heart failure, is not recommended for the acute management of decompensated left heart failure (4).

Diuretic therapy with furosemide is indicated only if vasodilator therapy does not reduce the wedge pressure to the desired level. The desired wedge pressure in left heart failure is the highest pressure that will augment cardiac output without producing pulmonary edema. This is shown in Figure 14.6 as the highest point on the lower (heart failure) curve that does not enter the shaded (pulmonary edema) region. The desired or optimal wedge pressure in left h~art failure is 18 to 20 mm Hg (24). Therefore diuretic therapy is indicated only if the wedge pressure during vasodilator therapy remains above 20 mm Hg. The features of diuretic therapy for decompensated heart failure are described later.

Normal Blood Pressure

Decompensated heart failure with a normal blood pressure is the usual presentation of heart failure resulting from ischemic heart disease, acute myocarditis, and the advanced stages of chronic cardiomyopathy.

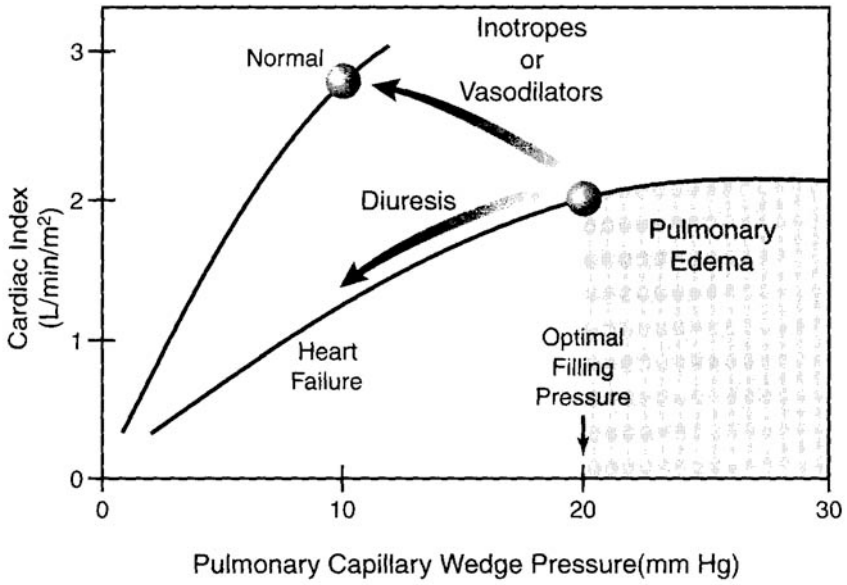

FIGURE 14.6 Ventricular function curves for the normal and failing left ventricle. Arrows show the expected changes associated with each type of drug therapy. The shaded area indicates the usual region where pulmonary edema becomes apparent.

Profile: High PCWP /Low CO/Normal BP
Treatment: Inodilator therapy with dobutamine or milrinone, or vasodilator therapy with nitroglycerin. If the PCWP does not decrease to <20 mm Hg, add diuretic therapy with furosemide.

Dobutamine and milrinone are called *inodilators* because they have both positive inotropic and vasodilator actions 09,21). Dobutamine is a ~-receptor agonist, while milrinone is a phosphodiesterase inhibitor. Both drugs augment cardiac output and reduce ventricular filling pressures. Blood pressure is usually unaffected in the usual doses, but dobutamine can increase blood pressure, and milrinone can promote hypotension. Dobutamine can increase myocardial 02 consumption (19), and this effect can be counterproductive in the ischemic myocardium (where oxygen supply is impaired) and in the failing myocardium (where 02 consumption is already increased). Milrinone has no reported effect on myocardial 02 consumption (19).
Because dobutamine can increase myocardial oxygen demands, vasodilator therapy (e.g., with nitroglycerin) has been recommended as a safer alternative to dobutamine, particularly in patients with ischemic heart disease (19,21). Milrinone may also be preferred to dobutamine because of its lack of effect on myocardial 02 consumption. Milrinone is also preferred to dobutamine in patients receiving beta-blocker drugs because its mechanism of action does not involve beta-receptors.

Diuretic therapy in this condition is similar in principle to that described for hypertensive heart failure: it is reserved for cases where the wedge pressure remains above 20 mm Hg despite inodilator or vasodilator therapy.

Low Blood Pressure
Decompensated heart failure accompanied by hypotension is the *sine qua 1101l* of cardiogenic shock. This condition is most often associated with cardiopulmonary bypass surgery, acute myocardial infarction, viral myocarditis, and pulmonary embolus (25).

Profile: High PCWP /Low CO fLow BP
Treatment: Dopamine in vasoconstrictor doses. Mechanical assist devices can be used as a temporary measure in selected cases (see later).

Hemodynamic drugs are notoriously unsuccessful in cardiogenic shock, with a mortality rate as high as 80% (24). Increasing blood pressure (to a mean pressure of 60 mm Hg) is a priority, and dopamine is a popular agent because it acts as a vasopressor in high doses (>10 μgf kg/min) and retains some positive inotropic actions associated with lower doses (5 to 10 μg/kg/min) (4,19,21). However, because low cardiac output states are accompanied by systemic vasoconstriction, druginduced vasoconstriction can further aggravate tissue hypoperfusion. Dobutamine can be added to dopamine to further enhance cardiac output, but the combined effects of dopamine and dobutamine on promoting tachyarrhythmias and increasing myocardial 02 consumption can be detrimental in the failing heart. Mechanical cardiac support is indicated in the management of cardiogenic shock when myocardial function is expected to improve spontaneously (as occurs in the early period following cardiopulmonary bypass surgery) or when a corrective procedure (such as coronary angioplasty) is planned. This approach can reduce the mortality in cardiogenic shock to about 60%, although this is not a consistent finding (25). Mechanical assist devices are described later in the chapter.

The Role of Diuretic Therapy
Although diuretic therapy with furosemide has been a cornerstone of management for chronic heart failure, diuretics should be used cautiously in the management of acute, decompensated heart failure. The reason for caution is the observation that intravenous furosemide often causes a decrease in cardiac output in patients with acute left heart failure (26-30). This effect is the result of a decrease in venous return and an increase in systemic vascular resistance. The latter effect is due to the ability of furosemide to stimulate renin release and raise circulating levels of angiotensin, a vasoconstrictor (31).
There are two management goals in decompensated heart failure:
1) augment cardiac output (to promote tissue perfusion), and
2) reduce

venous pressures (to eliminate the risk of edema formation). Vasodilator and inodilator drug therapy can achieve both goals, so these drugs should be used in the initial management of decompensated heart failure. Diuretic therapy with intravenous furosemide is indicated only when the first line drugs do not return the venous pressures to acceptable levels (i.e., a PCWP <20 mm Hg).

FUROSEMIDE BY CONTINUOUS INFUSION. Critically ill patients can have an attenuated response to furosemide (32). Several factors may be involved, including reduced drug transport by plasma proteins, reduced renal blood flow, and chloride depletion (furosemide acts by inhibiting chloride reabsorption in the Loop of Henle). Because the diuretic effect of furosemide is more closely related to its urinary excretion rate than to its plasma concentration (33), continuous infusion of the drug produces a more vigorous diuresis than bolus injection. The indications and dosage of continuous infusion furosemide are shown below.
Indication: Furosemide resistance (e.g., when 80 mg furosemide given as an IV bolus results in less than 2 liters of urine output in the ensuing 4 hours).
Dosage: Start with 100 mg furosemide as an IV bolus. Immediately follow with a continuous infusion of furosemide at 40 mg/hr. Double the dose rate every 12 hours if needed to achieve a urine output of at least 100 mL/h. The dose rate should not exceed a maximum of 169 mg/h (34).

NESIRITIDE.
Nesiritide (Natrecor) is a recombinant human B-type natriuretic peptide that was introduced in 2001 for the treatment of decompensated heart failure. This agent is a systemic vasodilator that augments cardiac output by reducing ventricular afterload. The recommended dose regimen is shown below (36).
Dosage: Give initial intravenous bolus of 2 μg/kg and follow with a continuous infusion at 0.01 μg/kg/min. This dose rate can be increased 0.01 μg/kg/min every 3 hours to a maximum dose of 0.03 μg/kg/min (36).
Clinical studies indicate that nesiritide is an effective vasodilator but offers no advantage over other vasodilators such as nitroglycerin (36). In fact, there is concern about a report showing an increase in short-term (30 day) mortality attributed to nesiritide (37). This prompted the Food and Drug Administration to issue a warning (in the summer of 2005) about the possible dangers of nesiritide. At the present time, the clinical value of nesiritide is unproven.

Diastolic Heart Failure

The incidence of decompensated heart failure in the ICU that is purely diastole in nature is not known, and it is likely that many cases of heart

failure treated as systolic failure have some component of diastolic dysfunction. There is no general agreement about the optimal treatment of diastolic heart failure (7), but there are two recommendations that seem valid based on the distinguishing features of diastolic failure. First, because systolic function is normal in diastolic heart failure, positive inotropic agents have no role in the treatment of diastolic heart failure. Second, because ventricular filling is impaired in diastolic heart failure, diuretic therapy can be counterproductive and can further impair ventricular filling and cardiac output. Diuretic therapy does not playa major role in the management of acute, decompensated heart failure, and this deserves particular emphasis for diastolic-type heart failure.
Since most cases of diastolic failure are the result of hypertensioninduced left ventricular hypertrophy, vasodilators have been a popular ingredient in treatment regimens for diastolic failure. Some vasodilator agents, such as nitroglycerin and milrinone, also have *lusitropic* actions that promote ventricular relaxation during diastole (7,21) and thus might be the preferred vasodilators for diastolic heart failure. Calcium channel blockers like verapamil are effective in diastolic failure caused by idiopathic hypertrophic cardiomyopathies (38), but these agents do not favorably improve diastolic function in other conditions that cause diastolic failure (39).

Right Heart Failure
Therapeutic strategies for right heart failure are similar in principle to those just described. The strategies below pertain only to primary right heart failure (e.g., following acute myocardial infarction) and not to right heart failure secondary to chronic obstructive lung disease. The PCWP and RVEDV are used as the focal points of management.
1) If PCWP is below 15 mm Hg, infuse volume until the PCWP or CVP increases by 5 mm Hg or either one reaches 20 mm Hg

2) If the RVEDV is less than 140 mL/m2, infuse volume until the RVEDV reaches 140 mL/m^2

3) If PCWP is above 15 mm Hg or the RVEDV is 140 mL/m^2 or higher, infuse dobutamine, beginning at a rate of 5 μg/kg/minute

4) In the presence of AV dissociation or complete heart block, institute sequential A-V pacing and avoid ventricular pacing

The response to volume infusion must be carefully monitored in right heart failure because aggressive volume infusion can overdistend the right ventricle and further reduce cardiac output through interventricular interdependence (see Figure 14.4).
Dobutamine is an effective agent in right heart failure (41,42).
Nitroprusside has been used in right heart failure, but it is not as effective as dobutamine (42).

MECHANICAL CARDIAC SUPPORT

In selected cases of life-threatening cardiac pump failure that is refractory to hemodynamic drug support, mechanical devices can be used to generate blood flow and reduce the workload of the heart. There are two methods of providing mechanical cardiac support: intra-aortic balloon counterpulsation and circulatory support with specialized pumps called *ventricular-assist devices* that are placed in parallel with one or both ventricles.

Intra-Aortic Balloon Counterpulsation

Intra-aortic balloon counterpulsation was introduced in 1968 as a method of promoting coronary blood flow in patients with acute myocardial infarction complicated by cardiogenic shock (43). (The term *counterpulsation* is a misnomer for the process of providing pulsatile flow during diastole.) This technique uses a sausage-shaped polyurethane balloon that is' attached to the distal end of a large-bore catheter. The catheter (with the balloon wrapped tightly around the distal end) is inserted percutaneously into the femoral artery in the groin and then advanced up the aorta until the tip lies just below the origin of the left subclavian artery. The balloon is available in various lengths to match body height. When properly placed, the balloon should extend from just below the left subclavian artery to just above the renal arteries. Correct balloon placement does not require fluoroscopy, which allows for timely placement of the device at the bedside.

Hemodynamic Effects

The intra-aortic balloon pump (IABP) uses helium, a low density gas, to inflate the balloon (inflation volume is generally 35 to 40 mL). Inflation begins at the onset of diastole, just after the aortic valve closes (the R wave on the ECG is a common trigger). The balloon is then deflated at the onset of ventricular systole, just before the aortic valve opens. This pattern of balloon inflation and deflation produces two changes in the aortic pressure waveform, as illustrated in Figure 14.7.

Inflation of the balloon increases the peak diastolic pressure and displaces blood toward the periphery. The increase in diastolic pressure increases the mean pressure in the aorta, which is the driving force for systemic blood flow. The increase in diastolic pressure should also augment coronary blood flow, because the bulk of coronary flow occurs during diastole. However, the IABP has been shown to increase coronary flow only in patients with hypotension (44).

Deflation of the balloon reduces the end-diastolic pressure, which reduces the impedance to flow when the aortic valve opens at the onset of systole. This decreases ventricular afterload and promotes ventricular stroke output.

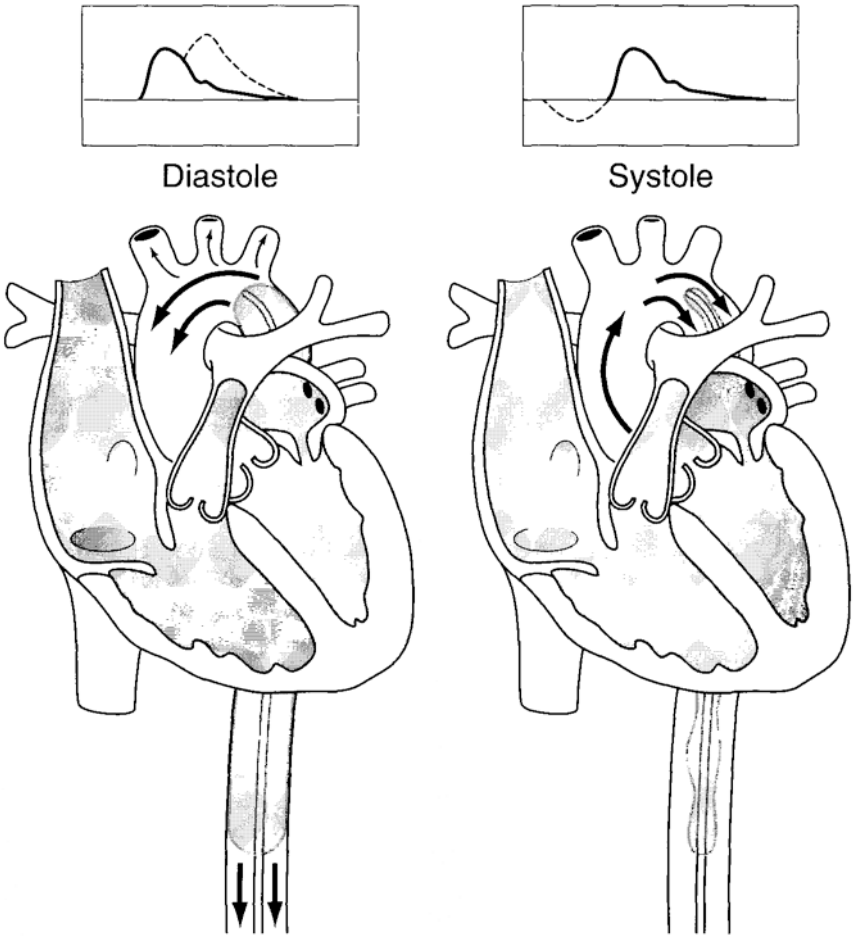

FIGURE 14.7 The effect of intra-aortic balloon counterpulsation on the aortic pressure waveform. The dotted lines indicate the change in aortic pressure produced by balloon inflation during diastole and balloon deflation just prior to systole. The arrows indicate the direction of blood flow.

The IABP thus promotes systemic blood flow in two ways: by increasing the driving pressure for systemic blood flow in the aorta and by reducing the impedance to ventricular ejection during systole.

Indications &. *Contraindications*
In general, IABP support is indicated when cardiac pump failure is lifethreatening and either pump function is expected to improve spontaneously, or a corrective procedure is planned. Most cases of IABP support are for cardiogenic shock following cardiopulmonary bypass surgery or acute myocardial infarction (45,46). Other indications include unstable angina, acute mitral insufficiency, and planned cardiac transplantation.

Contraindications to IABP support include aortic insufficiency, aortic dissection, renal insufficiency, and a recently-placed (within 12 months) prosthetic graft in the thoracic aorta (46).

Complications

The incidence of complications from IABP support varies in different reports from 10 to 50%, with serious complications reported in 5 to 25% of cases (46-48). The most common and feared complication is leg ischemia, which is reported in as many as 25% of cases (47,48). Leg ischemia can involve the ipsilateral or contralateral leg and can appear while the catheter is in place or within hours after the catheter is removed. Most cases are the result of *ill-situ* thrombosis at the catheter insertion site, and about 75% of cases require surgical thrombectomy to restore limb flow (47,48).

The risk of leg ischemia mandates close monitoring of both distal pulses and sensorimotor function in both legs. Loss of distal pulses alone does not always mandate removal of the balloon catheter. If IABP support is life-sustaining and sensorimotor function in both legs is intact, the device can be left in place as long as sensorimotor function in the legs is carefully monitored (48). Loss of sensorimotor function in the legs should always prompt immediate removal of the device.

Other complications of IABP support include spinal cord ischemia, visceral ischemia, renal insufficiency, catheter-related infection, balloon rupture, arterial injury, peripheral neuropathy, and pseudoaneurysm (46-48).

Ventricular Assist Devices

A ventricular assist device (VAD) is a pump (usually nonpulsatile) that is placed in parallel with either the right ventricle (RVAD), the left ventricle (LVAD), or both ventricles (BiVAD) (49-51). The pump is adjusted to provide a total systemic flow of 2.0 to 3.0 L/min/m^2. The use of VADs is limited by the need for intraoperative placement: most are used for cardiogenic shock following cardiopulmonary bypass surgery. The duration of postoperative support is one to 4 days. Complications occur in over 50% of patients and most often include bleeding or systemic embolism. Most patients can never be weaned from pump support, but as many as one-third of patients progress and outlive the need for pump support (51). VADs are also used for long-term support (as long as one year) in cardiac transplant candidates, and newer devices can be used outside the hospital environment.

THE FUTURE

The treatment of acute, decompensated heart failure is basically the same today as it was 20 years ago. This is a concern because none of the hemodynamic drugs used to treat acute heart failure has demonstrated the

ability to alter the clinical course of the illness (52). The problem may be that the hemodynamic modulation of heart failure does not protect the myocardium from ongoing damage or decay. This concern has led to changes in the management of chronic heart failure, where the emphasis is shifting from the use of drugs that improve hemodynamic status (e.g., vasodilators) to the use of drugs that protect the myocardium from injury (e.g., beta-blockers). A similar focus on cardioprotection is now being recommended for the management of acute heart failure (52).

Levosimendan

Levosimendan is an intravenous inodilator that augments cardiac output via positive inotropic and systemic vasodilator actions (53). This drug is unique because animal studies demonstrate its ability to protect the myocardium from ischemic injury (54). Furthermore, early clinical trials indicate that treatment of acute heart failure with levosimendan has a survival benefit (53). Levosimendan is not currently approved for clinical use in the United States, but this will be remedied quickly if the survival benefit in early clinical trials is corroborated.

A FINAL WORD

The approach to advanced or decompensated heart failure in the ICU is best guided by invasive hemodynamic measurements and by the type of heart failure involved (systolic, diastolic, left-sided, or right-sided failure). The following points deserve emphasis.

The combination of an increase in ventricular filling pressure and a decrease in cardiac output will identify decompensated heart failure but will not distinguish between systolic and diastolic heart failure.

The management of acute, decompensated heart failure should augment cardiac output and reduce ventricular filling pressures while producing little or no increase in myocardial 02 consumption.

Diuretic therapy with intravenous furosemide can be counterproductive in acute, decompensated (low output) heart failure because cardiac output is often adversely affected. Diuretic therapy should not playa major role in the management of acute heart failure, particularly if the failure is due to diastolic dysfunction.

If cardiogenic shock is identified, mechanical cardiac support should be initiated as soon as possible, if indicated.

Remember that the current management of acute heart failure is designed to treat the hemodynamic consequences of heart failure and is not directed at the pathologic process in the myocardium. While this approach can achieve temporary hemodynamic improvement, it may not improve survival or otherwise alter the course of the cardiac pathology.

References

Chapter 15

CARDIAC ARREST

Medicine cannot, except over a short period, increase the population of the world. Bertrand Russell

In 1960, an article was published in the *Journal of the American Medical Association* that would eventually change the way we approach the dying process. The article, titled "Closed-Chest Cardiac Massage" 0), was the birth of what is known today as *cardiopulmonary resuscitation* (CPR). Despite being unsuccessful in a majority of attempts (see Figure 15.1) (2), CPR has grown

to become a universally accepted practice. In fact, it is considered a human right and is withheld only upon request.
This chapter describes the mechanical and pharmacologic interventions involved in the management of cardiac arrest. Much of the information is taken from the most recent American Heart Association Guidelines for Cardiopulmonary Resuscitation, which are available on the Internet (see Reference 3).

BASIC LIFE SUPPORT
Basic life support has three components: achieving a patent airway, delivering periodic lung inflations, and promoting circulation with chest compressions. These components are often referred to as the *ABCs* of life support (Airway, Breathing, and Circulation).

Airway Patency
Tracheal intubation (which is considered a component of advanced life support) is the preferred method of maintaining a patent airway in unconscious patients with cardiac arrest. Prior to intubation, an oropharyngeal airway (an S-shaped device passed over the tongue and into the pharynx) can be used to keep the flaccid tongue from falling back and occluding the oropharynx. Delays to intubation should be minimized whenever possible.

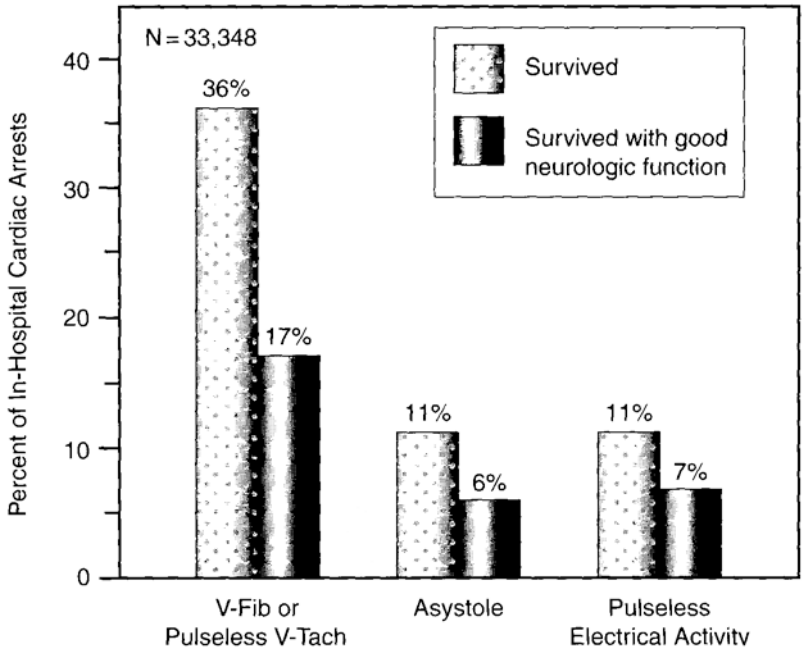

FIGURE 15.1 Outcomes of in-hospital cardiac arrest (grouped according to initial cardiac rhythm) reported by the National Registry of Cardiopulmonary Resuscitation, which includes 253 hospitals in the U.S. and Canada. *N* = total number of subjects included in the report; *V-Fib* = ventricular fibrillation, *V-Tach* = ventricular tachycardia. (From Reference 2.)

Ventilation

Lung inflations are usually delivered with a self-inflating bag that is connected at one end to a continuous flow of oxygen, and at the other end, to a face mask or endotracheal tube. The lungs are inflated by compressing the bag with one or both hands (one-way valves at each end of the bag ensure that the volume is directed to the patient). Following each lung inflation, the bag re-inflates spontaneously (in about one second). The current guidelines for CPR state that the lungs should be inflated 8 to 10 times per minute without pausing for chest compressions, and the inflation volume should be delivered in one second (4). This is a slower rate than previously recommended, for reasons described in the next section.

Avoiding Hyperventilation

One of the important discoveries about CPR in recent times is the tendency to over-ventilate patients during CPR and the negative impact of this practice on the success of CPR. The problem is the increase in positive intrathoracic pressure created by large tidal volumes and rapid

respiratory rates because this can impede ventricular filling (by reducing venous inflow into the thorax), which limits the ability of chest compressions to augment cardiac output. High intrathoracic pressures can also reduce coronary perfusion pressure (4,5), which is an important determinant of outcome in cardiac arrest. These adverse circulatory effects could contribute to the low survival rates following CPR.

The use of high ventilatory rates is commonplace during CPR. In one survey, ventilatory rates above 20 breaths/min were recorded in over half of the cases of CPR (6), and in another survey, the average rate of ventilation during CPR was 30 breaths/min, which is 3 times the recommended rate (5). Such rapid rates are problematic because there is insufficient time for alveolar emptying after each lung inflation, and the air that accumulated in the lungs creates a positive end-expiratory pressure (PEEP) that adds further to the effects of positive-pressure ventilation on intrathoracic pressures. The PEEP created by rapid breathing, which is also called *intrinsic PEEP,* is described in more detail in Chapter 26.

High inflation volumes are also commonplace during CPR. The standard ventilation bags used during CPR have a volume capacity of 1,600 mL when fully inflated (7), and two-handed bag compression (which is standard during CPR) will expel most of this volume into the lungs, at least when the bag is connected to an endotracheal tube (some volume is lost when face masks are used because of the incomplete seal on the face). This is three times greater than the normal tidal volume in an average-sized adult (about 7 mL/kg, or 500 mL in a 70 kg subject). The current guidelines for CPR do not include a specific recommendation for the size of tidal volumes (prior guidelines recommended tidal volumes of 10 to 15 mL/kg, which is excessive), but volumes of 6 to 8 mL/kg seem reasonable. One-handed compression of standard size ventilation bags will expel a volume of about 800 mL (7), and this may be the appropriate method of lung inflation during CPR.

THE INSPIRATORY IMPEDANCE THRESHOLD DEVICE. A specialized valve has been developed that reduces the influence of positive-pressure lung inflations on intrathoracic pressure. When placed between the ventilation bag and the patient, this valve prevents positive pressure lung inflations from entering the thorax during the decompression phase of CPR (the time between chest compressions). This reduces mean intrathoracic pressures and should improve coronary and systemic blood flow during CPR. A small clinical trial using this *inspiratory impedance threshold device* has shown improved short-term survival in patients with pulseless electrical activity (8). Larger trials are underway.

In summary, hyperventilation is a common and potentially lifethreatening problem during CPR. To minimize the adverse circulatory effects of hyperventilation, avoid using lung inflation rates above 10 breaths/min, and consider using smaller-volume bag compressions to limit tidal volumes. If the cardiac arrest occurs in a patient with an indwelling arterial catheter, you can observe the influence of different ventilatory rates and volumes on the blood pressure to determine if ventilation is adversely affecting systemic blood flow.

Chest Compressions

Chest compressions are performed by placing the heel of the dominant hand on the sternum in the center of the chest, with the non-dominant hand on top. The elbows should be locked so that both arms are kept straight, and the shoulders should be positioned directly above the point of contact. The sternum is then depressed at least 1.5 to 2 inches inward. When the compression is released, the sternum should be allowed to recoil completely before the next compression. The recommended rate of chest compressions is at least 100 per minute (4), and each compression should be maintained for half of the total compression-release cycle. With a lung inflation rate of 10 breaths/minute, the ratio of chest compressions to lung inflations is 10:1.

Although this sounds simple enough, maintaining a rate of 100 compressions per minute requires one compression every 0.6 seconds, which is not possible to perform accurately without a stop watch! In any event, allowing full recoil of the chest wall after each compression is an important feature because the decompression phase of CPR (the time between chest compressions) is the time when venous blood can return to the heart.

ADVANCED LIFE SUPPORT

Advanced life support (also called advanced cardiac life support, ACLS) includes a variety of interventions, including airway intubation, mechanical ventilation, defibrillation, and drugs given during cardiac arrest (9). The material in this section focuses on the use of defibrillation and cardiac arrest drugs to manage patients with pulseless cardiac arrest. This is summarized in Figure 15.2, which is taken from the most recent (2005) guidelines published by the American Heart Association.

Defibrillation

Direct-current (DC) cardioversion is the treatment of choice for ventricular tachycardia (V-tach) and ventricular fibrillation (V-fib), and it is the single most effective resuscitative measure for improving survival in cardiac arrest (see Figure 15.1). The time elapsed from the cardiac arrest to the first electric shock is the most important factor in determining survival (11,12). This is demonstrated in Figure 15.3. Note that 40% of patients survived when the first shock was delivered 5 minutes after the arrest, while only 10% of patients survived if defibrillation was delayed until 20 minutes after the arrest. These results emphasize the importance of avoiding delays in delivering the first electric shock.

Protocol

Some of the important recommendations for defibrillation are outlined in Table 15.1. The effective strength of electric shocks (which is expressed in units of energy, or joules) depends on the type of waveform delivered. Newer defibrillators deliver biphasic shocks, which are effective at lower

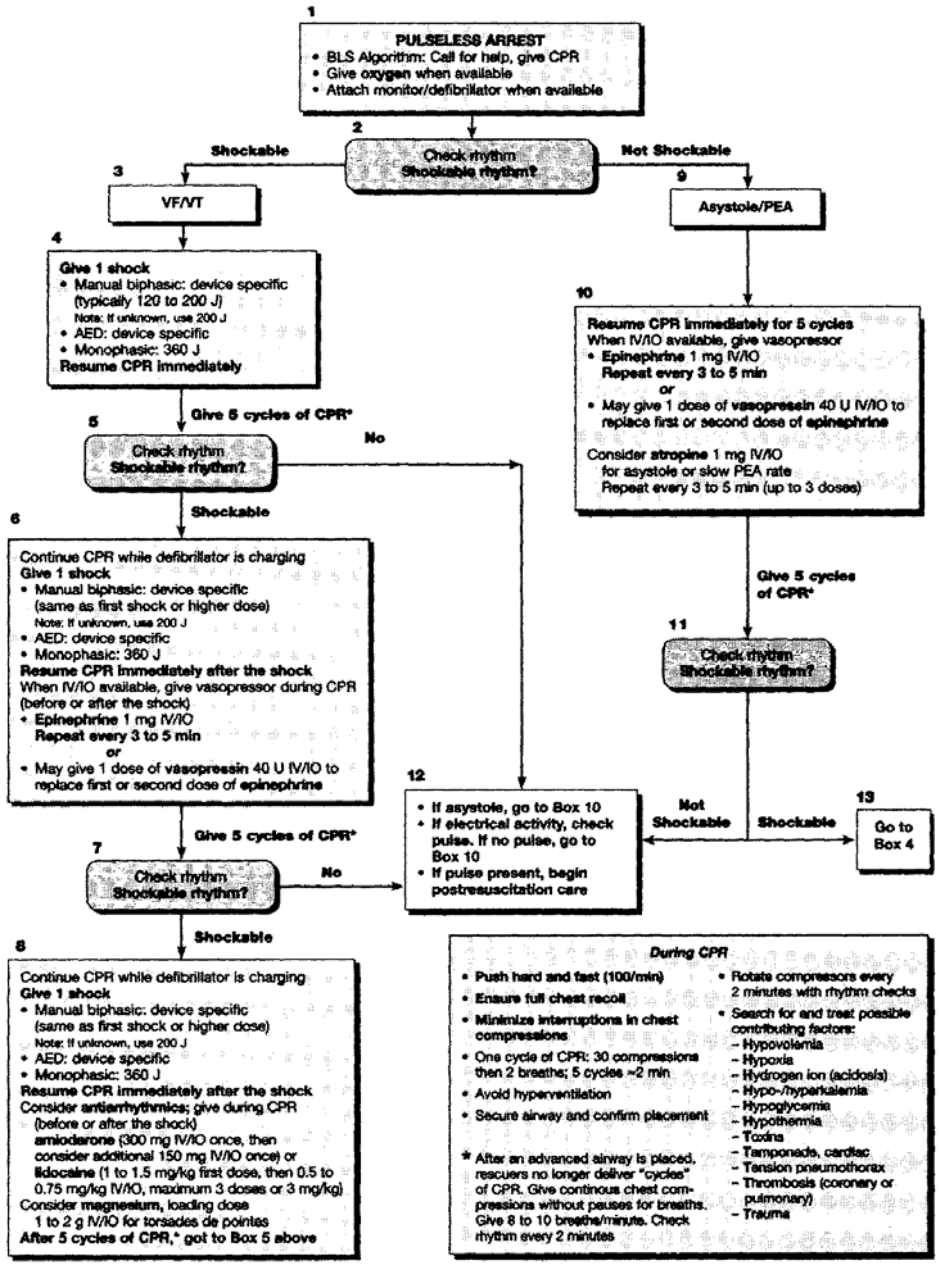

FIGURE 15.2 Algorithm for the management of pulseless cardiac arrest due to ventricular fibrillation (*VF*), ventricular tachycardia (*VT*), pulseless electrical activity (*PEA*), and ventricular asystole. From the 2005 American Heart Association Guidelines for CPR (see Reference 10).

energy levels than the monophasic shocks used by older defibrillators. The recommended energy level for the first shock is 200 joules for biphasic shocks (unless otherwise specified by the defibrillator manufacturer) and 360 joules for monophasic shocks (11).

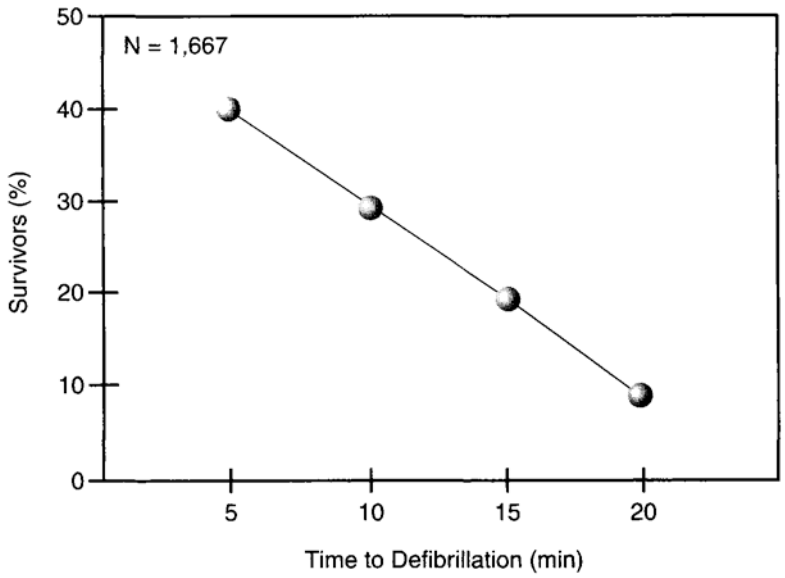

FIGURE 15.3 The relationship between survival rate and time elapsed from the cardiac arrest to the onset of defibrillation in patients with ventricular fibrillation. *N* = number of subjects studied. (From Larsen MP et al. Predicting survival from out-of-hospital cardiac arrest: a graphic model. Ann Emerg Med 1993;22:1652.)

The timing of the first shock depends on the setting. For pulseless V-fib or V-tach that occurs outside the hospital, a brief period (1.5 to 3 minutes) of CPR is recommended before defibrillation when the response interval is greater than 5 minutes **(1)**. Otherwise (including all in-hospital arrests), immediate defibrillation is recommended.

TABLE 15.1 Some Facts About Defibrillation

1. If the cardiac arrest occurs outside the hospital and the response time is > 5 minutes, a brief period (1.5-3 min) of CPR is recommended prior to the first shock.
2. The recommended energy level of each shock is determined by the type of waveform.
a) For biphasic waveforms, use 200 joules.
b) For monophasic waveforms, use 360 joules.
3. There is no evidence that increasing the energy level in successive shocks more effective than maintaining the energy level of the initital shock.
4. Because delivering each shock requires an interrruption of CPR (which can be detrimental), a single-shock strategy may be preferable to the traditional triple-shock strategy.

From Reference 11.

TABLE 15.2 Cardiac Arrest Drugs: Indications and Dosage

Drug	Dosage (IV or 10)	Indications
Vasopressors:		
Epinephrine	1 mg first dose and repeat every 3 to 5 min if needed.	Asystole, PEA, and shock-resistant VF or VT.
Vasopressin	40 units as a single dose.	Can replace the first or second dose of epinephrine.
Antiarrhythmic agents		
Amiodarone	300 mg first dose, then 150 mg once if needed.	VF or pulseless VT that is refractory to defibrillation and vasopressors.
Lidocaine	1-1.5 mglkg first dose, then 0.5-0.75 mglkg to a total of 3 doses or 3 mg/kg.	Alternative to amiodarone.
Magnesium	1-2 9 over 5 min	Pulseless polymorphic VT (torsades de pointes) with prolonged OT interval.
Atropine	1 mg first dose. Repeat every 3 to 5 min if needed to total of 3 doses.	Bradyarrhythmias, or as an adjunct to vasopressors for asystole and PEA.

From Reference 10.
Abbreviations: IV = intravenous, 10 = intraosseous, VF = ventricular VT = ventricular tachycardia, PEA = pulseless electrical activity.

If the first shock is ineffective, two additional shocks can be attempted (don't forget to perform CPR between successive shocks). There is no evidence that increasing the energy levels in successive shocks is more effective than maintaining the energy level of the initial shock. If the second shock is unsuccessful, a vasopressor should be administered (see Table 15.2): either epinephrine O mg IV, repeated every 3 to 5 minutes) or vasopressin (40 units IV as a single dose) is recommended. If the V-fib or V-tach persists after the third shock, an antiarrhythmic agent should be administered: either amiodarone (300 mg IV, followed by 150 mg IV if needed) or lidocaine O to 1.5 mg/kg IV as first dose, followed by 0.5 to 0.75 mg/kg IV if needed up to a total dose of 3 mg/kg) is recommended. Because delivering each electric shock requires an interruption of CPR (which can be detrimental), a single-shock strategy may be preferable to the traditional triple-shock strategy (11).

Automated External Defibrillators

The introduction of the automated external defibrillator (AED) represents a significant advance in the use of DC cardioversion. The benefit of the AED is its ability to analyze a cardiac rhythm and determine if

cardioversion is appropriate. When the two AED electrode pads are placed on the chest (one on the right anterior chest wall and the other on the left lateral chest wall), sensors in the pads act like precordial leads to record the cardiac rhythm. The AED analyzes the rhythm and then displays a prompt informing the operator if defibrillation is indicated (the operator does not see the cardiac rhythm). If defibrillation is indicated, the operator simply presses a button to deliver the shock. The machine automatically selects the strength of the pulse. After the shock is delivered, the machine will again analyze the cardiac rhythm and determine if a second shock is necessary. This sequence can continue until three shocks are delivered.
The benefit of the AED is the ability of untrained personnel (who are unable to interpret the cardiac rhythm) to initiate defibrillation (1). It also saves the time spent preparing to record the cardiac rhythm. These devices have been used primarily for cardiac arrests that occur outside the hospital, but they are also available in many hospitals as well. The ability to deliver rapid DC cardioversion should make AEDs popular in virtually all settings.

Drug Administration During CPR

Intravenous Sites

Peripheral veins are preferred to central veins for drug administration during CPR because cannulation of peripheral veins does not require interruption of CPR (O). Drugs given via peripheral veins should always be injected as a bolus, followed by a 20 mL bolus of an intravenous fluid (0). The extremity should be elevated for 10 to 20 seconds to facilitate drug delivery to the heart. If the initial drug injection is unsuccessful, central venous cannulation can be performed for subsequent drug administration. This latter maneuver reduces the transit time for drugs to reach the heart by 1 to 2 minutes (O).

Alternate Sites

When venous access is not readily available, drugs can be delivered by puncturing a marrow cavity (usually in the sternum) or by injection through an endotracheal tube. The intraosseous route is preferred to the airway route because drug absorption from the airways is erratic (O). However, the airway route seems favored by most critical care practitioners (probably because it is easier), at least in adults.

ENDOTRACHEAL DRUG ADMINISTRATION. The drugs that can be given via the endotracheal route are atropine, epinephrine, vasopressin, and lidocaine. The endotracheal dose of each drug should be 2 to 2.5 times the recommended intravenous dose (10), and injection of the drug into the endotracheal tube is as effective as more distal injection into the airways (9). All drugs injected into the airways should be diluted in 5 to 10 mL of water or isotonic saline. Water may be the preferred diluent because of enhanced drug absorption (9,10).

Vasopressor Drugs

One of the management goals in cardiac arrest is to promote systemic vasoconstriction and thereby direct blood flow to the coronary and cerebral circulations. Two vasopressor drugs are used for this purpose: epinephrine and vasopressin. As shown in Figure 15.2, vasopressor drugs are recommended for most cases of pulseless cardiac arrest, including those due to asystole, pulseless electrical activity, and V-fib or V-tach that persists after the initial defibrillation attempt. Despite the almost universal use of vasopressors in cardiac arrest, there is no evidence that vasopressor drugs improve survival in cardiac arrest (10).

Epinephrine

Epinephrine (which is a beta-receptor agonist in low doses and an alpha-receptor agonist in high doses) is the traditional vasopressor used in cardiac arrest. The recommended intravenous dose of epinephrine is 1 mg (10 mL of a 1:10,000 solution), repeated every 3 to 5 minutes if necessary. The recommended dose for endotracheal injection is 2 to 2.5 mg. Epinephrine is poorly absorbed from the airways, and the reduced serum concentration can produce predominant beta-receptor stimulation and unwanted cardiac stimulation. For this reason, endotracheal injection of epinephrine is not advised (10).

Vasopressin

Vasopressin is a non-adrenergic vasoconstrictor that can be used as a single dose (40 units given as an intravenous bolus) to replace the first or second dose of epinephrine (see Figure 15.2). This strategy has two potential benefits: 0) vasopressin acts as a cerebral vasodilator, and (2) there is no risk of unwanted cardiac stimulation from epinephrine. However, several clinical trials have shown no survival benefit when vasopressin is substituted for epinephrine (13), and vasopressin causes coronary vasoconstriction, which is a reason to avoid its use. Vasopressin should be considered when the endotracheal route is used for drug delivery because epinephrine can cause unwanted cardiac stimulation when administered via this route.

Antiarrhythmic Agents

Amiodarone

Clinical studies involving adults with out-of-hospital cardiac arrests due to refractory V-fib have shown that a single dose of intravenous amiodarone given in the field improves survival to hospital admission when compared to placebo (4) or intravenous lidocaine 05). Unfortunately, amiodarone did not improve survival to hospital discharge in either study. Despite having no long-term survival benefit, intravenous amiodarone is now recommended for cases of V-fib and pulseless V-tach that are refractory to defibrillation and vasopressor drugs (O). The initial dose is 300 mg (intravenous or intra osseous), followed by a second dose of 150 mg if needed (the time between doses is not specified).

Amiodarone can produce hypotension and bradycardia (4), but these side effects have been minimized by a new aqueous formulation of amiodarone that does not contain vasoactive solvents.

Lidocaine
Intravenous lidocaine has been the traditional antiarrhythmic agent used for shock-resistant cases of V-fib and pulseless V-tach. However, because amiodaTOne seems to produce better results for short-term survival 05), lidocaine is now recommended only as an alternative to amiodarone (O). The recommended dosage of lidocaine is 1 to 1.5 mg/kg (intravenous or intraosseous) as an initial dose, then 0.5 to 0.75 mg/kg every 5 to 10 minutes if needed, to a maximum of 3 doses or 3 mg/kg. Despite its long history of use in cardiac arrest, lidocaine has no documented impact on survival (or any measure of clinical outcome) in cardiac arrest.

Magnesium
Intravenous magnesium is effective in terminating polymorphic V-tach (also called " torsades de pointes") when this arrhythmia is associated with a prolonged QT interval. For cardiac arrest associated with this rhythm, the magnesium dose (intravenous or intraosseous) is 1 to 2 grams infused over 5 minutes. The recognition and treatment of torsades de pointes is described in Chapter 18.

Atropine
Atropine is a well-known anticholinergic agent that is recommended as an adjunct to vasopressor therapy for cardiac arrest associated with asystole or pulseless electrical activity (see Figure 15.2). The intravenous dose is 1 mg, which can be repeated every 3 to 5 minutes to a total dose of 3 mg (which is the dose that produces complete vagal blockade) (O). The rationale for the use of atropine in this situation is the possibility that asystole or pulseless electrical activity could be precipitated by heightened vagal tone. The efficacy of atropine in these conditions is unproven.

MONITORING DURING CPR
The goal of the resuscitation effort is to restore adequate perfusion of the vital organs, particularly the heart and central nervous system. Unfortunately, it is not possible to directly measure blood flow (global or regional) during CPR, so surrogate measurements are used. These measurements, which are described below, are limited and sometimes misleading.

Arterial Pulse and Pressure
Despite their popularity, the arterial pulse and pressure are not reliable markers of blood flow during CPR. This is demonstrated by the pressure tracings in Figure 15.4. The tracings in this figure were recorded

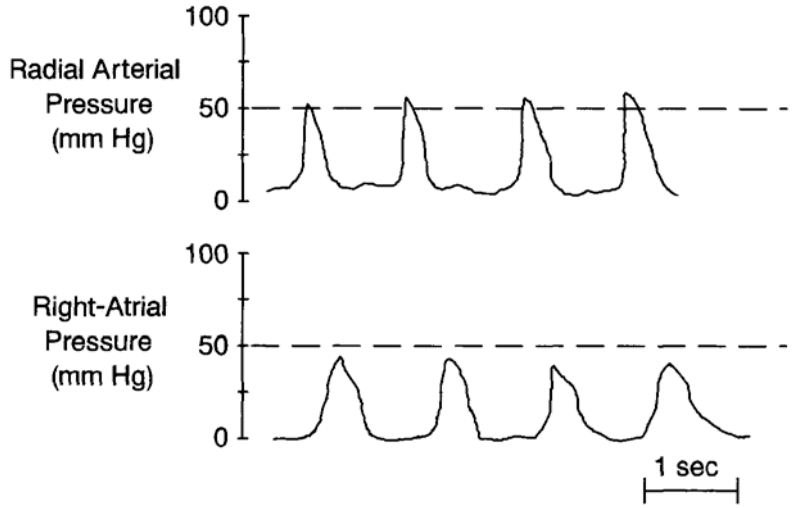

FIGURE 15.4 The influence of chest compressions on arterial and central venous (right atrial) pressure tracings in a patient with asystolic cardiac arrest. The chest compressions produce an arterial pressure wave, but the arterial and right atrial pressures are similar, so there is no pressure gradient to drive systemic blood flow.

from a patient who had an indwelling radial artery catheter and central venous catheter and had just been pronounced dead from asystolic cardiac arrest. The tracings show the effect of chest compressions on the arterial pressure and central venous (right atrial) pressure. If the arterial blood pressure is considered in isolation, the size of the pressure pulse (50 mm Hg systolic pressure) would be interpreted as indicating that the chest compressions were successful in promoting systemic blood flow. However, note that the central venous pressure is about the same as the arterial pressure, so there is no pressure gradient between the arterial and venous circuits, and thus there is no blood flow in the systemic circulation. (Remember from Chapter 1 that flow in a tube requires a pressure gradient along the tube). Therefore Figure 15.4 shows that it is possible to have an arterial pulse and blood pressure in the absence of peripheral blood flow during CPR.

Coronary Perfusion Pressure

The pressure gradient that drives coronary blood flow, which is called the coronary perfusion pressure (CPP) is the difference between the aortic diastolic pressure and the right-atrial pressure. Clinical studies have shown that a CPP (15 mm Hg during CPR is associated with a successful outcome 06,17). When CPR is performed on a patient with indwelling arterial and central venous catheters, the CPP can be estimated by using the peripheral arterial diastolic pressure as a substitute for the aortic diastolic pressure.

End-Tidal $PC0_2$

The excretion of carbon dioxide in exhaled gas is a direct function of pulmonary blood flow or cardiac output (see Chapter 2, Figure 2.7), and the partial pressure of CO_2 in end-expiratory gas (the end-tidal $PC0_2$) can be used as an indirect indicator of the cardiac output generated during CPR 06,18-20). The end-tidal $PC0_2$ is easily measured at the bedside using commercially-available infrared devices called capnometers that are connected to indwelling endotracheal tubes (see Chapter 20 for a detailed description of the end-tidal $PC0_2$ measurement).

An increase in end-tidal $PC0_2$ during CPR can serve as an indication that the resuscitation effort is successful in promoting cardiac output. This is consistent with clinical studies showing that an increase in end-tidal $PC0_2$ during CPR is predictive of a successful outcome 06,18-20). This is demonstrated in Figure 15.5, which shows the changes in end-tidal PCO_z during CPR in survivors and nonsurvivors of cardiac arrest. As expected, the end-tidal PCO_z is very low (indicating a low cardiac output) at the onset of CPR in both groups. In patients who survived, the end-tidal PCO_z more than doubled (from 12 to 31 mm Hg) after 20 minutes of CPR, whereas in the patients who did not survive, the end-tidal PCO_z decreased during CPR. This demonstrates the value of the end-tidal PCO_z as a prognostic marker for CPR. A threshold of 10 mm Hg for end-tidal PCO_z can be used to predict outcome (e.g., when end-tidal $PC0_2$ does not rise above 10 mm Hg after 15 to 20 minutes of CPR, the resuscitative effort is unlikely to be successful).

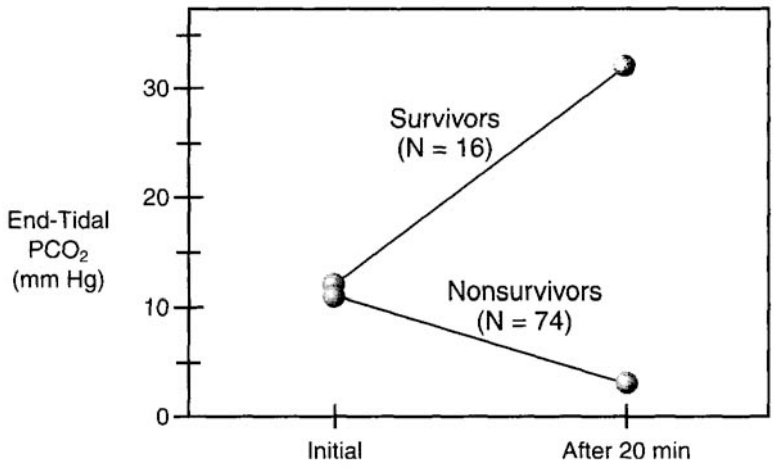

FIGURE 15.5 Changes in end-tidal PCO_2 during CPR in survivors and nonsurvivors of cardiac arrest due to pulseless electrical activity. Data points represent the mean end-tidal PCO_2 for each group. (From Wayne MA, Levine RL, Miller CC. Use of end-tidal carbon dioxide to predict outcome in prehospital cardiac arrest. Ann Emerg Med 1995;25:762–767.)

Venous Blood Gases

Clinical studies have shown that, during CPR, arterial blood gas analysis often reveals a respiratory alkalosis (indicating operator-induced hyperventilation), while venous blood gas analysis shows a metabolic acidosis (indicating systemic hypoperfusion) (21,22). Therefore venous blood gas analysis is more appropriate for evaluating tissue perfusion during CPR. Unfortunately, the time required to perform blood gas analysis limits the value of this test during CPR.

How Long to Resuscitate

There is little doubt that CPR is inappropriately prolonged in a significant percentage of resuscitative efforts. The problem with prolonged CPR is that survivors are often left with severe neurologic deficits. Identifying the appropriate time to discontinue CPR will achieve the optimal goal of CPR, which is to produce survivors who are able to interact with their surroundings and are capable of independent existence.

Ischemic Time and Neurolonic Recovery

The risk of functional impairment in any of the major organs is directly related to the duration of the ischemic insult. The ischemic time following cardiac arrest includes the time from onset of the arrest to onset of CPR (arrest time) and the duration of the resuscitative effort (CPR time). The influence of these two time periods on neurologic recovery is shown in

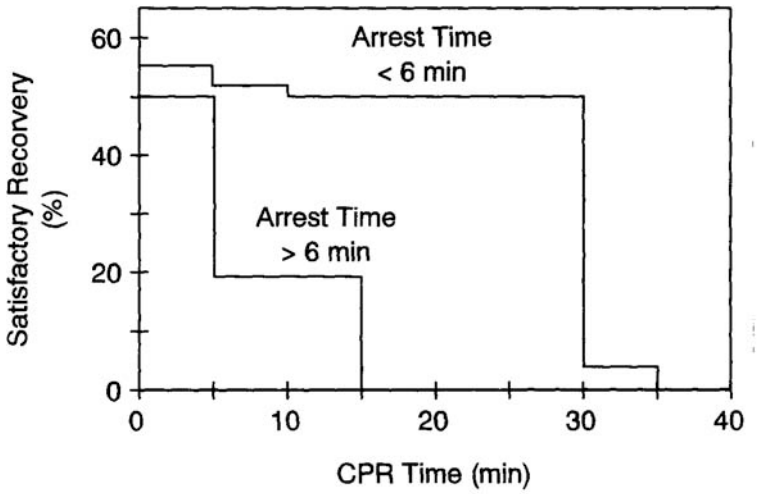

FIGURE 15.6 The incidence of satisfactory neurologic recovery as a function of the time from cardiac arrest to onset of CPR (arrest time), and the duration of the resuscitative effort (CPR time). (From Abramson NS, Safar P, Detre KM, et al. Neurologic recovery after cardiac arrest: effect of duration of ischemia. Crit Care Med 1985;13:930–931.)

Figure 15.6 (23). Note that when the arrest time is less than 6 minutes, at least half of the survivors had a satisfactory neurologic recovery when CPR was continued for as long as 30 minutes. However, if the arrest time exceeded 6 minutes, more than 15 minutes of CPR always produced neurologic impairment in the survivors. Thus if the goal of CPR is to produce functional survivors, then CPR can be continued for 30 minutes if the time to onset of CPR is less than 6 minutes, but if there is a delay to onset of CPR longer than 6 minutes, CPR should be terminated after 15 minutes.

POST-RESUSCITATION MANAGEMENT

The immediate goal of CPR is to restore spontaneous circulation, but this does not ensure a satisfactory recovery. This section describes some concerns in the post-resuscitation management that will help to optimize the recovery from cardiac arrest.

Avoiding Fever

Animal studies show that ischemic brain injury is aggravated by increased body temperature (24), and clinical studies show that increased body temperature after CPR is associated with an unfavorable neurologic outcome (25). These studies suggest that it is wise to avoid increased body temperature following cardiac arrest. The value of antipyretic therapy after CPR has not been studied, but fever reduction with acetaminophen 00 to 15 mg/kg per dose, 3 to 4 times a day) seems reasonable in patients with incomplete neurologic recovery after cardiac arrest. Acetaminophen must be given enterally and should not be given to patients with hepatic dysfunction. Cooling blankets are problematic because they can induce shivering (which is counterproductive) and can provoke vasospasm in diseased coronary arteries (26).

Therapeutic Hypothermia

Clinical studies have shown that induced hypothermia can improve neurologic outcome in patients who remain comatose after successful resuscitation of out-of-hospital cardiac arrest due to V-fib or pulseless V-tach (27,28). External cooling should be considered to improve neurologic function in patients who do not awaken after cardiac arrest, but there are strict eligibility criteria for this intervention. These are listed in Table 15.3, along with important features of the methodology. The hypothermia should be initiated as soon as possible after the resuscitation using an external cooling device. The target body temperature is 32°C to 34°C (89.6°F to 93.2°F), and this should be maintained for no less than 12 hours and no longer than 24 hours (27). Core body temperature can be monitored using tympanic temperatures or bladder temperatures. External cooling can provoke shivering, which is counterproductive because it increases body temperature. Therefore shivering should be suppressed by administering a neuromuscular blocker (e.g., atracurium).

TABLE 15.3 Induced Hypothermia after Cardiac Arrest

Eligible patients

Patients with out-of-hospital cardiac arrest due to VF or pulseless VT who remain comatose after successful resuscitation.

Inclusion

All of the following criteria must be satisfied.

a) Cardiac arrest is cardiac in origin.

b) Body temperature is not reduced.

c) Patient is hemodynamically stable.

d) Patient is intubated and on a ventilator.

Methodology

1. Cooling should begin within 1-2 hr after CPR.
2. Use cooling blanket to achieve a body temperature of 32°C-34°C (89.6°F-93.2°F).
3. Use sedation and neuromuscular blockade to avoid shivering.
4. Watch for hyperkalemia and hyperglycemia during hypothermia.
5. Maintain hypothermia for 24 hr, and then allow passive rewarming.

The information in this table is taken from References 27 and 28.

Hypothermia is associated with hyperkalemia (usually mild and without clinical impact) and hyperglycemia (27), so attention to the serum potassium and glucose is warranted during hypothermia. Rewarming from hypothermia should be passive.

Therapeutic hypothermia, as indicated, has been adopted in many ICUs, but only a limited number of patients are eligible for this intervention by current criteria. In one study, only 8% of patients who survived cardiac arrest were suitable for treatment (27). Studies are needed to determine if the eligibility criteria for this intervention can be expanded.

Glyc emic Control

Several clinical studies have documented that hyperglycemia following cardiac arrest is associated with a poor neurologic outcome (29,30). However, there are no studies to show that control of hyperglycemia after cardiac arrest improves neurologic outcome. Strict control of hyperglycemia is, however, associated with reduced morbidity and mortality in ICU patients (31). Based on these observations, the most recent American Heart Association Guidelines for CPR state that strict control of blood glucose levels is a reasonable practice in the post-resuscitation period (30). As an adjunct to this practice, dextrose-containing intravenous solutions should be avoided whenever possible. Remember that hypoglycemia can also be injurious to the central nervous system, so careful monitoring of blood glucose is necessary during aggressive management of hyperglycemia.

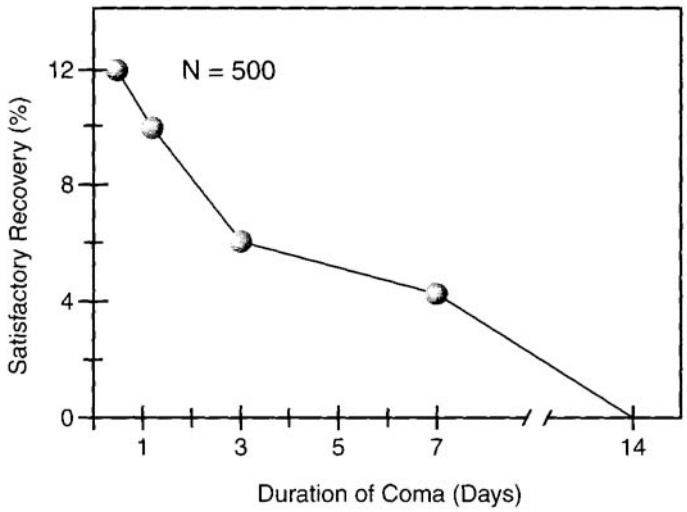

FIGURE 15.7 The relationship between the duration of non-traumatic coma and the incidence of favorable neurologic recovery. N = number of study subjects. (From Levy DE, Caronna JJ, Singer BH, et al. Prognosis in non-traumatic coma. Ann Intern Med 1981;94:293–301.)

Predicting Neurologic Recovery

In patients who do not awaken immediately after CPR, the single most important determination (for families as well as physicians) is the likelihood of neurologic recovery. The following are some prognostic factors that can help identify patients who are likely (and unlikely) to achieve a satisfactory neurologic recovery.

Duration of Coma

Failure to regain consciousness after CPR has prognostic significance if the coma persists for longer than 4 to 6 hours (32). The relation between prolonged coma and neurologic recovery is demonstrated in Figure 15.7 (32). The data in this graph are summarized in the following statements:

Only a small percentage of patients will recover fully if their coma persists for longer than 4 to 6 hours after cardiac arrest.

If a patient is not awake 24 hours after a cardiac arrest, there is only a 10% chance of satisfactory neurologic recovery. This is reduced to a 5% chance of recovery if the coma persists for 72 hours after CPR.

There is virtually no chance for a full neurologic recovery for a patient who is comatose 2 weeks after a cardiac arrest.

Although full neurologic recovery is unlikely for patients with coma 24 hours after cardiac arrest, most ICU physicians seem to use the 72 hour point of persistent coma to inform families of the poor prognosis.

Prognosis can also be expressed using the Glasgow Coma Score (which is described in Chapter 50): a score of less than 5 points (with 3 points being the lowest possible score) on the third day following cardiac arrest will identify patients with little or no chance of neurologic recovery (33).

Other Prognostic Signs
A review of 11 studies involving patients who did not awaken immediately after CPR identified four clinical signs that act as independent predictors of death or poor neurologic recovery (34). These are listed below.

No corneal reflex at 24 hours.
No pupillary light reflex at 24 hours.
No withdrawal to pain at 24 hours.
No motor response at 24 hours.

Note that each of these signs, if present, allows prediction of a poor outcome at 24 hours after cardiac arrest. Unfortunately, it is unlikely that these criteria will improve the disturbing tendency of physicians to avoid or delay the realization that a patient will never improve under their care.

A FINAL WORD
Despite its popularity, cardiopulmonary resuscitation is a failure as a resuscitative measure in most cases of cardiac arrest. The only practice that shows any evidence of success is timely defibrillation for ventricular fibrillation and pulseless ventricular tachycardia. When cardiac arrest is due to catastrophic pump failure (as occurs with asystole and pulseless electrical activity), the success rate of CPR is dismal. This is not unexpected, because chest compressions fail to generate adequate levels of systemic or regional blood flow, and cardiac arrest drugs add little to the resuscitative effort. Overall, CPR enjoys a popularity that far exceeds its efficacy.
Two caveats about CPR deserve mention. First, avoid hyperventilating patients during CPR, because this can impair the ability of chest compressions to generate blood flow. Also avoid prolonging CPR beyond a reasonable time period, because the goal of CPR is not just a functioning heart, but a functioning heart in a functioning person.

REFERENCES

Chapter 16

HEMODYNAMIC DRUG INFUSIONS

This chapter contains a brief description of five popular drugs given by continuous intravenous infusion to support the circulation. Each is listed below in order of presentation. Drugs marked by an asterisk have a dosage chart included in the chapter.
Dobutamine*
Dopamine*
Nitroglycerin*
Nitroprusside*
Norepinephrine
DRUG INFUSION RATES

Because the drugs in this chapter are given by continuous infusion, the recommended dose of each drug is expressed as a dose rate, either in micrograms per minute (μg/min) or micrograms per kilogram per minute (μg/kg/min). These drugs are first diluted in one of the common intravenous fluids, and the rate of infusion of these solutions is then set to achieve the desired dose rate. This is accomplished using the drug concentration in the infusate, as demonstrated in Table 16.1. In this case, the desired dose rate (R) is expressed in μg/min, and the drug concentration (C) in the infusate is expressed in μg/mL. The ratio R/C determines the infusion rate of the drug solution in mL/min. Drug infusions are often delivered in microdrops (1 mL = 60 microdrops) to improve the precision of drug dosing. To convert the infusion rate from mL/min to microdrops/minute requires a multiplier of 60

(mL/min X 60 = microdrops/min). The volumetric equivalent of microdrops/minute is mL/hr (i.e., microdrops/minute X *60/60* = mL/hr).

TABLE 16.1 Determining Drug Infusion Rates

If the desired dose rate = R μg/min and the drug concentration in the infusate = C μglmL, then:

Infusion rate = R / C (mL/min)

= R / C x 60 (microdrops/min)

DOBUTAMINE

Dobutamine is a synthetic catecholamine that is used as a positive inotropic agent to increase cardiac stroke output in patients with severe, decompensated heart failure.

Actions

Dobutamine is a potent beta 1-receptor agonist and a weak beta 2-receptor agonist: the beta 1 stimulation produces positive inotropic and chronotropic effects, and the beta 2 stimulation produces peripheral vasodilatation. As demonstrated in Figure 16.1, dobutamine causes a dose-dependent increase in stroke volume (upper graph) accompanied by a decrease in cardiac filling pressures (lower graph). Heart rate may be increased or

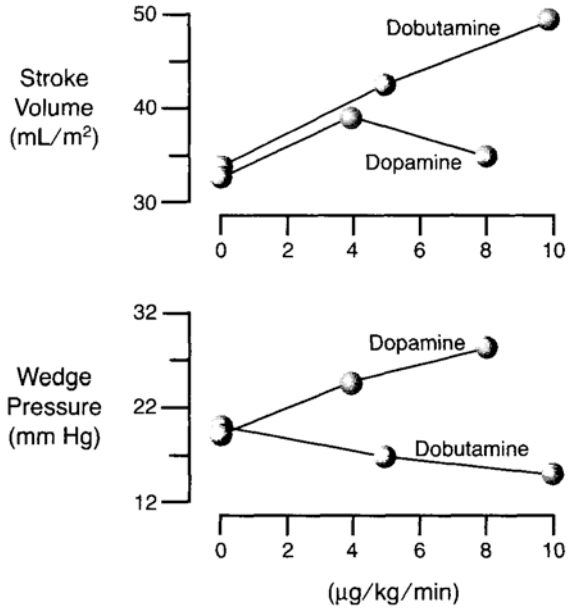

FIGURE 16.1 Effects of dobutamine and dopamine on cardiac performance in patients with severe heart failure. (From Leier CV, et al. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 1978;58:466–475.)

decreased (the latter effect is due to reflex withdrawal of sympathetic tone in response to the increased cardiac output). The increase in cardiac stroke output is usually accompanied by a proportional decrease in systemic vascular resistance: as a result, the arterial blood pressure usually remains unchanged 0,3).
The cardiac stimulation produced by dobutamine is often accompanied by an increase in both cardiac work and myocardial 02 consumption (2). These effects can be deleterious in heart failure because cardiac work and myocardial energy needs are already heightened in the failing myocardium (2).

Clinical Uses
Dobutamine is used primarily in patients with decompensated heart failure due to systolic dysfunction who also have a normal blood pressure. The drug is effective in both right-sided and left-sided heart failure. Because dobutamine does not usually raise the blood pressure, it is not recommended (at least as monotherapy) in patients with cardiogenic shock. The unfavorable effects of dobutamine on myocardial energetics have created a preference for vasodilator drug infusions (e.g., nitroglycerin) for the acute management of decompensated heart failure (2). (See Chapter 14 for more information on the management of heart failure.)

Dosage and Administration
A dobutamine dose chart is shown in Table 16.2. The drug is available in 250-mg vials and is infused in a concentration of 1 mg/mL. The usual dose range is 3 to 15 μg/kg/min 0), but doses as high as 200 μg/kg/min have been used safely (4). The response can be variable in critically **ill** patients (5), and elderly patients may show an attenuated response (6).

TABLE 16.2 Dobutamlne Dosage Chart

Infusate: Premixed solutions of dobutamine in DsW are available with drug concentrations of 0.5, 1, 2, and 4 mglmL. The infusion chart below is for 1mg/mL.

Usual dose: 3-15 μg/kg/min

	Body Weight (kg)						
Dose	40	50	60	70	80	90	100
(μg/kg/mln)	Infusion Rate (mL/hr)						
2.5	6	8	9	11	12	14	15
5	12	15	18	21	24	27	30
7.5	18	23	27	32	36	41	45
10	24	30	36	42	48	54	60
12.5	30	38	45	53	60	68	75
15	36	45	54	63	72	81	90

Therapy should be driven by hemodynamic end-points and not by pre-selected dose rates.

Incompatibilities

An alkaline pH inactivates catecholamines such as dobutamine (1), and thus sodium bicarbonate or other alkaline solutions should not be administered with dobutamine.

Adverse Effects

The principal side effect of dobutamine is tachycardia and ventricular ectopic beats (1). The tachycardia is usually mild, and the ectopic beats are usually benign.

Contraindications

Dobutamine (like all positive inotropic agents) is contraindicated in patients with hypertrophic cardiomyopathy (1). It should also be avoided (if possible) in patients with a history of malignant ventricular tachyarrhythmias.

DOPAMINE

Dopamine is an endogenous catecholamine that serves as both a neurotransmitter and a precursor for norepinephrine synthesis. When given as an exogenous drug, dopamine activates a variety of receptors in a dose-dependent manner. This creates a variety of dose-dependent drug effects (7), as described next.

Actions

At low dose rates (< = 3 μg/kg/min), dopamine selectively activates dopamine-specific receptors in the renal and splanchnic circulations, resulting in increased blood flow in these regions (2). Low-dose dopamine also directly affects renal tubular epithelial cells, causing an increase in urinary sodium excretion (natriuresis) that is independent of the changes in renal blood flow (8).

At intermediate dose rates (3 to 10 μg/kg/min), dopamine stimulates beta-receptors in the heart and peripheral circulation, producing an increase in myocardial contractility, an increase in heart rate, and peripheral vasodilatation. The overall result is an increase in cardiac output. This effect is demonstrated in Figure 16.1 (upper graph). Note that the contractile response to dopamine is modest when compared to dobutamine.

At high dose rates (>10 μg/kg/min), dopamine produces a progressive activation of alpha-receptors in the systemic and pulmonary circulations, resulting in progressive pulmonary and systemic vasoconstriction. This vasopressor effect, by virtue of increasing ventricular afterload, counteracts the cardiac stimulation produced by intermediate-dose dopamine.

Figure 16.1 (upper graph) shows the loss in cardiac output augmentation that occurs when the dopamine dose is progressively increased.
The effects of dopamine on the pulmonary capillary wedge pressure are shown in Figure 16.1 (lower graph). There is a dose-dependent increase in the wedge pressure, which is independent of the changes in stroke volume. This effect may be the result of dopamine-induced vasoconstriction in pulmonary veins. This ability to constrict pulmonary veins makes the pulmonary capillary wedge pressure an unreliable measure of left-ventricular filling pressure during high-dose dopamine infusion. (See Chapter 10 for a detailed description of the pulmonary capillary wedge pressure.)

Clinical Uses
Dopamine is often used in situations where both cardiac stimulation and peripheral vasoconstriction are desired. The classic example of this is cardiogenic shock. Dopamine is also used to correct the hypotension in septic shock, but norepinephrine has become the preferred vasopressor in this condition (see later).
Low-dose dopamine is often used in an attempt to prevent or reverse acute renal failure. This is not appropriate. While low-dose dopamine does promote renal blood flow and urine output in healthy subjects, these effects are minimal or absent in patients with acute renal failure, particularly oliguric renal failure (8). As a result, low dose dopamine is NOT recommended for the prevention or reversal of acute renal failure in the ICU (8). (This topic is discussed again in Chapter 31.)

Dosage and Administration
A dose chart for dopamine is shown in Table 16.3. Commercial preparations of dopamine are concentrated drug solutions (containing 40 mg or 80 mg dopamine HCl per mL) provided in small-volume vials (5 mL or 10 mL). These preparations must be diluted to prevent intense vasoconstriction during drug infusion. In Table 16.3, the original dopamine solution is diluted 100-fold in isotonic saline to prepare the infusate. Dopamine infusions should always de delivered into large, central veins.
The dosing regimen for dopamine is weight-based, and dosing should be based on *ideal body weight,* not actual body weight (2,7). (For reasons that are unclear, the distinction between ideal and actual body weight is not mentioned for other hemodynamic drugs with weightbased dosing regimens.). As shown in Table 16.3, there are two recommended dose ranges for dopamine: 3 to 10 μg/kg/min is recommended for augmenting cardiac output, and> 10 μg/kg/min is recommended to increase the blood pressure. (Low-dose dopamine is not included in Table 16.3 because of the lack of efficacy mentioned previously.)
Incompatibilities
Like dobutamine, dopamine is inactivated by an alkaline pH, so alkaline fluids should not be infused along with dopamine.

TABLE 16.3 Dopamine Dosage Chart

Infusate: Use 10 mL vial containing 80 mg/mL dopamine HCL. Add to one of isotonic saline (final concentration = 800 μg/mL).
Dose rates: 3-10 μg/kglmin to augment cardiac output; > 10 μg/kg/min to increase blood pressure.

	Ideal Body Weight (kg)						
Dose	40	50	60	70	80	90	100
(μg/kg/min)	Infusion Rate (mL/hr)						
1	3	4	5	5	6	7	8
3	9	11	14	16	18	20	23
5	15	19	23	26	30	34	38
10	30	38	45	53	60	68	75
15	45	56	68	79	90	101	113
20	60	75	90	105	120	135	150

Adverse Effects

Tachyarrhythmias are the most common adverse effects of dopamine infusions. Sinus tachycardia is common (7) but rarely is severe enough to prompt a change in drug or dose rate. Malignant tachyarrhythmias (e.g., multifocal ventricular ectopics, ventricular tachycardia) can also occur but are uncommon.

The most feared complication of dopamine infusion is ischemic limb necrosis, which is usually caused by drug extravasation into perivascular tissues. Using large, central veins for dopamine infusions will prevent this complication. Extravasation of the drug through a peripheral vein can be treated with a local injection of phentolamine (5 to 10 mg in 15 mL saline) (7).

Other adverse effects of dopamine infusions include allergic reactions to the sulfite preservative used to prevent oxidative decomposition of dopamine (7), increased intraocular pressure (9), and delayed gastric emptying, which could predispose to nosocomial pneumonia.

NITROGLYCERIN

Nitroglycerin is an organic nitrate (glyceryl trinitrate) that relaxes vascular smooth muscle and produces a generalized vasodilation.

Actions

The actions of nitroglycerin on vascular smooth muscle are mediated by nitric oxide (11). This is illustrated in Figure 16.2. Nitroglycerin binds to the surface of endothelial cells and undergoes two reduction reactions to form

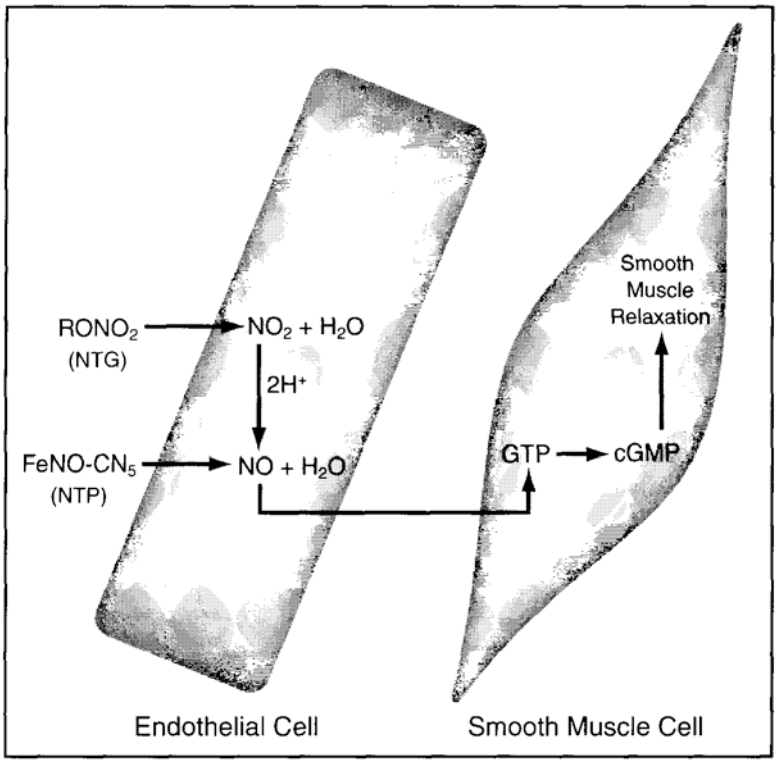

FIGURE 16.2 The biochemical mechanism for the vasodilator actions of nitroglycerin (NTG) and nitroprusside (NTP). Chemical symbols: nitroprusside ($Fe\text{-}NO\text{-}CN_5$), organic nitrate ($RONO_2$), inorganic nitrite (NO_2), nitric oxide ($NO^{\bullet}$), guanosine triphosphate (GTP), cyclic guanosine monophosphate (cGMP).

nitric oxide. The nitric oxide then moves out of the endothelial cells and into adjacent smooth muscle cells, where it produces muscle relaxation by promoting the formation of cyclic guanosine monophosphate (cGMP).

Vasodilator Effects

Nitroglycerin has a dose-dependent vasodilator effect involving arteries and veins in the systemic and pulmonary circulations (12,13). When the drug is given by continuous infusion, venous vasodilator effects are prominent at low dose rates (<40 μg/min), and arterial vasodilator effects predominate at high dose rates (> 200 μg/min). At intermediate dose rates (40 to 200 μg/min), a mixture of venous and arterial vasodilation occurs. At low dose rates, nitroglycerin produces a decrease in cardiac filling pressures (i.e., central venous pressure and wedge pressure) with little or no change in cardiac output. As the dose rate is increased through the intermediate dose range, the cardiac output begins to rise as a result of progressive arterial vasodilation. Further increases in the dose rate will eventually produce a drop in blood pressure. The hemodynamic

effects of intravenous nitroglycerin have a rapid onset and short duration, which permits rapid dose titration.

Antiplatelet Effects

Nitrates inhibit platelet aggregation, and nitric oxide is believed to mediate this effect as well (14). Because platelet thrombi play an important role in the pathogenesis of coronary insufficiency, the antiplatelet actions of nitroglycerin have been proposed as the mechanism for the antianginal effects of the drug (14). This would explain why the antianginal effects of nitroglycerin are not shared by other vasodilator drugs.

Clinical Uses

Intravenous nitroglycerin has two principal uses in the leu: O) to reduce edema formation and augment cardiac output in patients with acute, decompensated heart failure, and (2) to relieve chest pain in patients with persistent or unstable angina.

Dosage and Administration

A nitroglycerin dose chart is shown in Table 16.4. The infusion rates in this chart are based on a drug concentration of 400 μg/mL in the infusate.

Adsorption to Plastics

Nitroglycerin binds to soft plastics such as polyvinylchloride (PVC), which is a common constituent in the plastic bags and tubing used for intravenous infusions. As much as 80% of the drug can be lost by

TABLE 16.4 Nitroglycerin Dosage Chart

Infusate: Add 50 mg or 100 mg nitroglycerin to 500 mL isotonic saline to achieve a drug concentration of 100 μg/mL or 200 μg/mL.

Dose rate: Start at 5 μg/min, and increase dose rate by 5 μg/min every 5 min to desired effect.

Caution: Do NOT use polyvinylchloride (PVC) infusion sets to prevent drug loss via adsorption to PVC. Use only glass bottles and polyethylene

Dose Rate	Infusion Rate (mL/hr)	
(μg/min)	100 μg/mL	200 μg/mL
5	3	–
10	6	3
20	9	6
40	24	18
80	48	36
160	96	72
320	–	96

adsorption to PVC in standard intravenous infusion systems (2). Nitroglycerin does not bind to glass or hard plastics like polyethylene (PET), so drug loss via adsorption can be eliminated by using glass bottles and PET tubing. Drug manufacturers often provide specialized infusion sets to prevent nitroglycerin loss via adsorption.

Drug Dosing

Nitroglycerin should be started at a dose rate of 5 to 10 μg/min. The rate is then increased in 5 μg/min increments every 5 minutes until the desired effect is achieved. The effective dose will vary in each patient, and the infusion should be guided by the selected end-point and not the infusion rate. However, the dose requirement should not exceed 400 μg/min in most patients. High dose requirements (e.g., > 350 μg/min) are often the result of drug loss via adsorption or nitrate tolerance (see below).

Contraindications

Nitroglycerin should not be used in patients who have taken a phosphodiesterase inhibitor for erectile dysfunction within the past 24 hours (longer for some preparations) because of the high risk of hypotension when these agents are combined.

Adverse Effects

Adverse Hemodynamic Effects

Nitroglycerin-induced increases in cerebral and pulmonary blood flow can be problematic. The increase in cerebral blood flow can lead to increased intracranial pressure and symptomatic intracranial hypertension (15). In patients with lung disease, the increase in pulmonary blood flow can be problematic when the increased flow occurs in lung regions that are poorly ventilated. This increases shunt fraction and can aggravate hypoxemia. This effect can be prominent when nitroglycerin is used in patients with acute respiratory distress syndrome (16).

The venodilating effects of nitroglycerin can promote hypotension in hypovolemic patients and in patients with acute right heart failure due to right ventricular infarction. In either of these conditions, aggressive volume loading is required prior to initiating a nitroglycerin infusion.

Methemoalobinemia

Nitroglycerin metabolism produces inorganic nitrites (see Fig. 16.2), and accumulation of nitrites can lead to oxidation of the heme-bound iron moieties in hemoglobin to create methemoglobin. Fortunately, clinically significant methemoglobinemia is not a common complication of nitroglycerin infusions, and occurs only at very high dose rates 05). (The diagnosis of methemoglobinemia is described in Chapter 20.)

Solvent Toxicity

Nitroglycerin does not readily dissolve in aqueous solutions, and nonpolar solvents such as ethanol and propylene glycol are required to keep the

drug in solution. These solvents can accumulate during prolonged infu· sions. Both ethanol intoxication (17) and propylene glycol toxicity (8) have been reported as a result of nitroglycerin infusions. Propylene glycol toxicity may be more common than suspected because this solvent makes up 30 to 50% of some nitroglycerin preparations 05). Clinical manifestations include altered mental status, metabolic acidosis, and hemolysis. The propylene glycol level in blood is needed to confirm the diagnosis.

Nitrate Tolerance

Tolerance to the vasodilator and antiplatelet actions of nitroglycerin is a well-described phenomenon and can appear after only 24 hours of continuous drug administration 05). The underlying mechanism is unclear, but there is evidence that inactivation of nitric oxide by oxygen radicals may be involved (9). One study showed that concomitant use of hydralazine prevented nitrate tolerance (20), but the significance of this is unclear. The most effective measure for preventing or reversing nitrate tolerance is a daily drug-free interval of at least 6 hours (15).

NITROPRUSSIDE

Nitroprusside is a rapidly-acting vasodilator that is favored for the treatment of severe. life-threatening hypertension. The popularity of this drug is limited, however, by a significant risk of toxicity, as described later.

Actions

The vasodilator actions of nitroprusside, like those of nitroglycerin, are mediated by nitric oxide (11). The nitroprusside molecule, which is shown at the top of Figure 16.3, contains one nitrosyl group (NO). When nitroprusside enters the bloodstream, the nitrosyl group is released as nitric oxide, which then follows the pathway shown in Figure 16.2 to produce vasodilation.

Like nitroglycerin, nitroprusside dilates both arteries and veins, but it is less potent than nitroglycerin as a venodilator and more potent as an arterial vasodilator. The vascular responses are prompt and short lived, which allows for rapid dose titration. Vasodilator effects are often evident at low dose rates (0.5 μg/kg/min), but blood pressure reduction usually requires higher dose rates (~1 μg/kg/min). Nitroprusside has variable effects on cardiac output in subjects with normal cardiac function (21), but it consistently improves cardiac output in patients with decompensated heart failure (21,22).

Clinical Uses

Nitroprusside is used to treat severe hypertension when rapid blood pressure control is desirable (e.g., hypertensive emergencies). It can also be used to treat decompensated heart failure (22) and is effective in treating severe heart failure due to aortic stenosis (23), where vasodilator therapy has traditionally been discouraged.

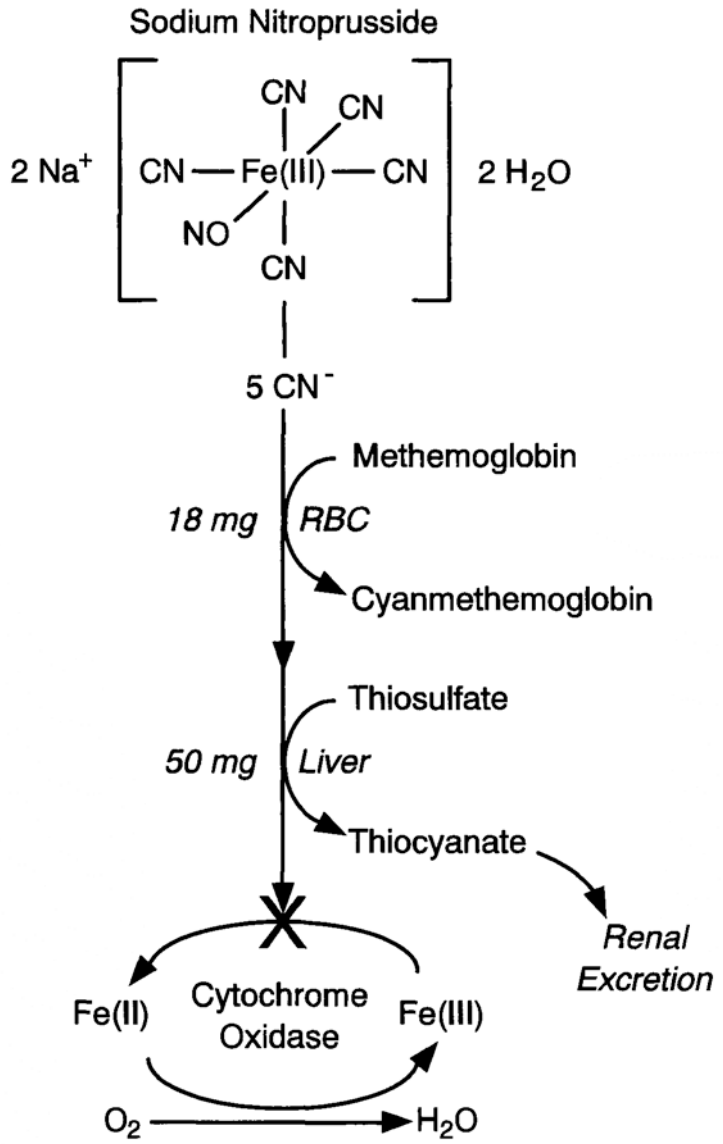

FIGURE 16.3 The fate of cyanide ions (CN^-) released into the bloodstream by the nitroprusside molecule.

Cyanide Intoxication

Nitroprusside infusions carry a considerable risk of cyanide intoxication. In fact, cyanide accumulation is common during therapeutic infusions of nitroprusside (15,24,25). The origin of the cyanide is the nitroprusside molecule, which is a ferricyanide complex that contains 5 cyanide atoms bound to an oxidized iron core (see the upper part of Figure 16.3).

When nitroprusside disrupts to release nitric oxide and exert its actions, the cyanide is released into the bloodstream. The fate of this cyanide is shown in Figure 16.3. Two chemical reactions help to remove cyanide from the bloodstream. One involves the binding of cyanide to the oxidized iron in methemoglobin. The other reaction involves the transfer of sulfur from a donor molecule (thiosulfate) to cyanide to form a thiocyanate compound, which is then cleared by the kidneys. The latter (transulfuration) reaction is the principal mechanism for removing cyanide from the human body.

Healthy adults have enough methemoglobin to bind the cyanide in 18 mg of nitroprusside and enough thiosulfate to bind the cyanide in 50 mg of nitroprusside (15). This means that the human body has the capacity to detoxify 68 mg of nitroprusside. At a nitroprusside infusion of 2 μg/kg/minute (therapeutic range) in an SO-kg adult, this 68 mg capacity is reached 500 minutes (8.3 hours) after the onset of infusion. This limited capacity for cyanide removal is reduced further by thiosulfate depletion, which is common in smokers and postoperative patients 05,24). Once the capacity for removal is exceeded, the free cyanide will combine with the oxidized iron in cytochrome oxidase and block the utilization of oxygen in the mitochondria.

Clinical Manifestations

The clinical manifestations of cyanide intoxication are shown in Table 16.5. One of the early signs of cyanide accumulation is nitroprusside tachyphylaxis 05). Signs of impaired oxygen use (i.e., a decrease in oxygen extraction ratio and lactic acidosis) often do not appear until the late stages of cyanide intoxication (26). As a result, the absence of lactic

TABLE 16.5 Diagnosis and Treatment of Cyanide Intoxication

Clinical manifestations	Early stages:	Behavioral changes
		Impaired 02 extraction
		Nitroprusside tachyphylaxis
	Late stages:	Obtundation and coma
		Generalized seizures
		Lactic acidosis
Laboratory diagnosis	Toxicity	Blood cyanide level
	Mild	0.5-2.5 μg/mL
	Severe	> 2.5 μglmL
	Fatal	> 3.0 μg/mL
*Management:**	Amyl nitrate inhaler for one min, or	
	Sodium nitrite: 300 mg IV over 15 min plus	
	Sodium thiosulfate: 12.5 g IV over 15 min	

From Hall AH, Rumack BH. Clinical toxicology of cyanide. AnnEmerg Med

• A *Cyanide Antidote Kit* is available from Eli Lilly & Co.

acidosis during nitroprusside infusion does not exclude the possibility of cyanide accumulation 05,24).

Diagnosis
Whole blood cyanide levels can be used to document cyanide intoxication, as shown in Table 16.5. However, the results of cyanide assays are not immediately available (a STAT specimen usually requires 3 to 4 hours to be processed) (24), so immediate decisions regarding cyanide intoxication are often based on the clinical presentation. Nitroprusside tachyphylaxis is an important early marker of cyanide accumulation.

Treatment
Treatment of cyanide intoxication should begin with the inhalation of 100% oxygen. The Cyanide Antidote Kit (Eli Lilly & Co.) can be used as described in Table 16.5 (27). This kit uses nitrates and nitrites (which oxidize the iron in hemoglobin to produce methemoglobin) to promote cyanide binding to methemoglobin and also uses thiosulfate to clear cyanide from the bloodstream.
Because nitrite therapy creates methemoglobinemia, alternative methods of cyanide binding have been explored. The affinity of cyanide for cobalt has led to the use of hydroxocobalamin 000 mL of a 5% solution infused over 15 minutes) (28), which combines with cyanide to form cyanocobalamin (vitamin B_{12}), which is then excreted in the urine. This strategy is popular in Europe, but the lack of a suitable hydroxocobalamin preparation has hampered its use in the United States.

Thiocyanate Intoxication
The most important mechanism for cyanide removal involves the formation of thiocyanate, which is slowly excreted in the urine. When renal function is impaired, thiocyanate can accumulate and produce a toxic syndrome that is distinct from cyanide intoxication (15,24). The clinical features include anxiety, confusion, pupillary constriction, tinnitus, hallucinations, and generalized seizures (15,24). Thiocyanate can also produce hypothyroidism by blocking the thyroid uptake of iodine (24).
The diagnosis of thiocyanate toxicity is established by the serum thiocyanate level. Normal levels are below 10 mg/L, and clinical toxicity is usually accompanied by levels above 100 mg/L (24). Thiocyanate intoxication can be treated by hemodialysis or peritoneal dialysis.

Dosage and Administration
A dose chart for nitroprusside is shown in Taple 16.6. Note that thiosulfate is added to the nitroprusside infusate to limit cyanide accumulation. About 500 mg of thiosulfate should be added for every 50 mg of nitroprusside (24). Nitroprusside should be started at a low dose rate (0.2 μg/kg/ min) and then titrated upward every 5 minutes to the desired result.

TABLE 16.6 Nitroprusside Dosage Chart

Infusate: Add 50 mg nitroprusside to 250 mL DsW for a drug concentration of 200 μg/mL. Add 500 mg thiosulfate.
Dosage: Start at 0.2 μg/kglmin and titrate upward to desired effect. Effective dose rates are usually between 0.5 and 5 μg/kg/min. Maximum dose allowed 10 μg/kg/min for 10 min.

	Body Weight (kg)					
Dose Rate	50	60	70	80	90	100
(μg/kg/min)	Infusion Rate (mL/hr)					
0.2	4	4	5	6	7	8
0.5	7.5	9	11	12	14	15
1	15	18	21	24	27	30
2	30	36	42	48	54	60
3	45	54	63	72	81	90
5	75	90	105	120	135	150

Satisfactory control of hypertension usually requires dose rates of 2 to 5 μg/kg/min, but the dose rate should be kept below 3 μg/kg/min if possible to limit cyanide accumulation (21). In renal failure, the dose rate should be kept below 1 μg/kg/min to limit thiocyanate accumulation (21). The maximum allowable dose rate is 10 μg/kg/min for only 10 minutes.

NOREPINEPHRINE

Norepinephrine is a popular vasopressor that is often used to correct hypotension when other measures (e.g., volume infusion, dopamine) fail (29). **It** is the preferred vasopressor agent in septic shock (30).

Actions

Norepinephrine stimulates alpha receptors and produces a dosedependent increase in systemic vascular resistance. Although the drug can stimulate cardiac beta -receptors over a wide range, the effects on cardiac output are variable (29). The vasoconstrictor response to norepinephrine is usually accompanied by a decrease in organ blood flow, particularly in the kidneys (29,30). This is not the case in septic shock, where norepinephrine can increase blood pressure without causing a decrease in renal blood flow or a deterioration in renal function (30,31).

Clinical Uses

Norepinephrine is traditionally used as the last measure for cases of hypotension that are refractory to volume infusion and other hemodynamic

drugs (e.g., dobutamine, dopamine). Norepinephrine is the vasopressor of choice in septic shock (30) and should be added when hypotension is not corrected by appropriate volume infusion. Despite the ability to correct hypotension, vasopressor drugs (including norepinephrine) do not improve survival in shock states, including septic shock (30).

Dosage and Administration

Norepinephrine is usually supplied as norepinephrine bitartrate, but the dosage is expressed in terms of norepinephrine (2 mg norepinephrine bitartrate = 1 mg norepinephrine) (29). Dextrose-containing fluids are recommended as the diluent for norepinephrine (29). Two milligrams of norepinephrine can be added to 500 mL of diluent to achieve a drug concentration of 4 μg/mL. The initial dose rate can be as low as 1 *μg/* min (15 microdrops/min) and titrated upward to the desired effect. The effective dose rate in septic shock is usually between 0.2 and 1.3 *μg/kg/* min (about 1 to 10 μg/min for a 70 kg patient), but dose rates as high as 5 μg/kg/min may be required (30).

Incompatibilities

Norepinephrine, like all catecholamines, is inactivated at an alkaline pH (29), so alkaline fluids should not be given with norepinephrine.

Adverse Effects

Adverse effects of norepinephrine include local tissue necrosis from drug extravasation and intense systemic vasoconstriction with worsening organ function. As for the latter effect, whenever a vasoconstrictor drug is required to correct hypotension, it is often difficult to distinguish between adverse drug effects and adverse disease effects.

Finally, norepinephrine bitartrate contains sulfites to prevent oxidative decomposition (29), and allergic reactions to sulfites have been reported (particularly in patients with asthma).

REFERENCES