

SPECIAL article

New Concepts in the Diagnosis and Fluid Treatment of Circulatory Shock

Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture

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SHOCK is a clinical syndrome characterized by protracted prostration, pallor, coldness and moistness of the skin, collapse of the superficial veins, alterations in mental status, and suppression of the formation of urine.¹ The systolic arterial pressure is usually less than 90 mm Hg or has declined more than 50 mm Hg from the basal level and the urine flow is less than 20 ml/hour. The urine is typically iso-osmolar. The ratio between urine osmolality and plasma osmolality, which reflects the tubular concentrating function of the nephron, is characteristically

less than 1.5. The basic mechanism underlying all forms of acute circulatory shock is reduction of effective blood flow and inadequate tissue perfusion with decreased delivery of oxygen to the capillary exchange bed.² The clinical signs of shock reflect primary perfusion failure. Reduction in peripheral blood flow accounts for cold, cyanotic extremities; reduction in cerebral blood flow for altered mental alertness; reduction in renal perfusion for diminution in both the quantity and quality of urine that is excreted; and reduction in coronary blood for compromised myocardial oxygen supply and electrocardiographic S-T and T-wave changes which are indicative of myocardial ischemia. In most instances cardiac output and consequently arterial blood pressure is reduced.

With reduction in tissue perfusion and decreased delivery of oxygen to the capillary exchange bed, oxidative metabolism is impaired. There is decreased formation of high energy phosphate bonds and an increase in the permeability of cellular membranes. The cellular sodium pump fails and sodium enters and potassium escapes from the cells. The cells swell and ultimately there is rupture of lysosomal mem-

This study was supported by United States Public Health Service Research Grant GM-16462 from the National Institute of General Medical Sciences, ENG 77-24007 from the National Science Foundation, and the Cardiopulmonary Laboratory Research Foundation.

Received from the Division of Critical Care Medicine and the Institute of Critical Care Medicine, University of Southern California School of Medicine, the Los Angeles County/USC Medical Center, and the Center for the Critically Ill, Hollywood Presbyterian Medical Center, Los Angeles, California. Accepted for publication October 20, 1978.

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branes with release of lytic enzymes and autodigestion.³

In the absence of metabolic oxygen, the anaerobic pyruvate-lactate shunt is activated and this accounts for the production of excesses of lactic acid and intracellular acidosis. The magnitude of lactic acidosis corresponds to the severity of the oxygen deficit. Arterial blood lactate therefore provides a quantitative measure of the oxygen deficit and, in turn, of the severity of perfusion failure. In patients who present with clinical signs of perfusion failure, the concentration of lactate in arterial blood characteristically exceeds 2 mmol/L.^{4,5} When lactate concentrations increase from 2 to 8 mmol/L, survival progressively decreases from approximately 90% to 10%⁶ (Fig 1). Lactic acidosis, therefore, is a *sine qua non* of oxygen deficit and presently represents the best single objective measure of perfusion failure (shock).⁷

Classification of Circulatory Shock

In the new classification of circulatory shock, we recognized that deficits in tissue perfusion originate from one of four categories of hemodynamic deficits: hypovolemia, cardiac failure, defects in the distribution of blood flow, and vascular obstruction (Table 1).²

Hypovolemic shock accounts for the vast majority of instances of acute circulatory shock in patients who are hospitalized and it is due to a primary deficit in intravascular volume.⁸ The volume of blood within the intravascular space is depleted to the extent that effective tissue perfusion cannot be maintained. Although the body can survive with 15% of the total hepatic mass, 25% of the renal mass, 30% of the red blood cell mass, and less than 50% of the pulmonary

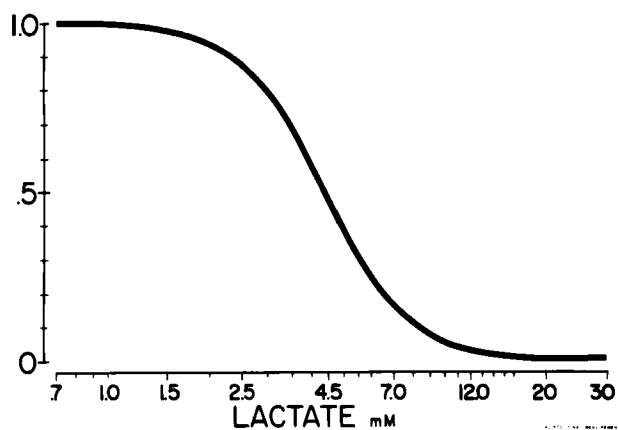


Fig 1. Statistical probability of survival in relationship to the concentration of arterial blood lactate.

TABLE 1
Reclassification of Shock States

Type of shock	Cause
Hypovolemic shock	
Exogenous	Blood loss due to hemorrhage Plasma loss due to burn, inflammation Electrolyte loss due to diarrhea, dehydration
Endogenous	Extravasation due to inflammation, trauma, application of a tourniquet, anaphylaxis, and pheochromocytoma
Cardiogenic shock	Myocardial infarction Cardiac failure Arrhythmia
Distributive shock	
High or normal resistance (increased venous capacitance; selective or general)	Bacillary shock Barbiturate intoxication CNS injury Ganglionic blockade
Low resistance (arteriovenous shunt)	Inflammatory vasodilation due to pneumonia, peritonitis, abscess; reactive hyperemia
Obstructive shock (by anatomic site and mechanism)	
a. Vena cava	1. Compression
b. Pericardium	2. Tamponade
c. Cardiac chambers	3. Ball-valve thrombus
d. Pulmonary circuit	4. Embolism
e. Aorta	5. Dissecting aneurysm

parenchyma, an acute reduction of plasma volume to less than 70% of normal threatens immediate survival.⁹ Hypovolemia follows the endogenous or exogenous loss of blood, plasma and/or electrolyte fluids.

Cardiogenic shock represents primary pump failure. Cardiac rhythm, myocardial contractility, or myocardial work capability is compromised to the extent that cardiac output is critically reduced.

Impaired distribution of blood flow is the third category of hemodynamic defects accounting for shock. Two major subsets of distributive defects are recognized: low-resistance and high-resistance distributive defects. In the low-resistance defect, blood is either shunted from the arterial to the venous circulation¹⁰ or transverses capillaries without effective exchange of oxygen at the cellular level.¹¹ This defect is commonly observed in patients with peritonitis or in the presence of one or more abscesses caused by Gram-positive pyogenic organisms. The high resistance defect is characterized by the intra-

vascular sequestration of blood, particularly in the venous capacitance circuit and represents a selective form of relative hypovolemia.^{10, 12} In such patients with "relative hypovolemia," the total intravascular volume may be normal or near normal but the capacity of the intravascular space is expanded. This is typically the case in patients with bacterial shock and/or patients who present with perfusion failure after barbiturate intoxication.^{13, 14}

Finally, an impediment or obstruction to the main stream of blood flow represents an obstructive defect. This is the case in pulmonary embolism, dissecting aortic aneurysm, or pericardial tamponade. In these pathologic conditions, it is the obstruction to blood flow which precludes effective tissue perfusion and therefore accounts for the shock state.

The primary mechanism for initiating circulatory shock may be any one of these four categories of hemodynamic defects. However, the subsequent course and especially perpetuation of the shock state almost invariably involves the recruitment of other deficits. In cardiogenic shock, for instance, when there is a reduction in myocardial contractility and reduction in cardiac output, a distributive defect arises because of arteriolar constriction. At the same time, the venous return is decreased because of alterations in the venous capacitance bed. Exogenous and especially endogenous adrenergic stimulation may increase venular constriction. Consequently, capillary hydrostatic pressure is increased and this accounts for extravasation of fluid from the intravascular space into the interstitial space.¹⁵ The intravascular volume is therefore depleted as it is in hypovolemic shock. During hypovolemic shock, reduced coronary perfusion, increased susceptibility to bacterial infection, and disseminated intravascular coagulation may perpetuate the shock state by cardiogenic, distributive, and obstructive mechanisms.

Fluid Administration

Because hypovolemia predominates as the initial cause of shock and as a complication accounting for progression of cardiogenic, distributive, or obstructive types of shock, volume replacement represents the single most important therapeutic intervention (except for cardiopulmonary resuscitation and arrest of bleeding). However, the volume that may be safely administered is contingent on the patient's cardiac competence. This is especially true in older patients. Clinical guidelines for rapid volume replacement are therefore of primary importance if acute cardiac de-

compensation and pulmonary edema are to be prevented. The routine measurement of the central venous pressure and the pulmonary artery and the pulmonary artery wedge pressure allows the clinician to detect limitations in cardiac competence and therefore provides an important guide for volume repletion. The pulmonary artery wedge pressure, and to a lesser extent the central venous pressure, reflect not only vascular volume but also the effectiveness with which the heart ejects the volume which is returned to it from the venous capacitance circuit. Central venous pressure measurements are useful but may be misleading in patients with significant impairment in left ventricular competence or in patients with advanced pulmonary disease. In young, previously healthy patients and in the absence of historical, physical, electrocardiographic, or radiologic signs of heart disease, the central venous pressure represents a reliable guide to volume repletion. However, in critically ill or injured patients with known cardiac or pulmonary disease who present with clinical signs of circulatory shock, the routine use of a pulmonary artery catheter is warranted.

Fluid Challenge

The response to fluid administration should be systematically assessed in patients with circulatory shock by a technique of fluid challenge. A volume of 50, 100, or 200 ml of fluid is administered over a 10-minute interval through a peripheral venous catheter.¹⁶ Fluid challenge is also indicated in patients in whom the initial pulmonary artery diastolic or wedge pressure or central venous pressure is increased if the patient presents with clinical signs of circulatory shock. Central venous pressure and pulmonary artery wedge pressure, on occasion, may be increased rather than decreased after massive blood or fluid loss in elderly patients with limited cardiac reserve because of compromised coronary blood flow and therefore, impaired cardiac competence. If the central venous pressure (CVP) is less than 8 cm H₂O, 200 ml of fluid is administered through a peripheral vein over a 10-minute interval (Table 2). When the CVP is greater than or equal to 8 cm H₂O but less than 14 cm of H₂O, 100 ml of fluid is administered over a 10-minute interval of time. When the CVP is greater than or equal to 14 cm of H₂O, 50 ml of fluid is administered over a 10-minute period. A "5-2" rule is employed with a central venous pressure catheter during volume administration. If at any time during the infusion the CVP rises by more than 5 cm of H₂O, the infusion

TABLE 2
Guidelines for Fluid Challenge Utilizing Central Venous Pressure Monitoring

Fluid challenge: CVP, cm H ₂ O (5-2 rule)		
Observe CVP for 10 min	<8 cm H ₂ O	200 ml × 10 min
	<14 cm H ₂ O	100 ml × 10 min
	≥14 cm H ₂ O	50 ml × 10 min
		Peripheral IV
During infusion 0-9 min	>5 cm	STOP
Following infusion	>2 cm < 5 cm	Wait 10 min
	>2 cm	Wait STOP
	≤2 cm	Continue infusion

should be discontinued. Following the infusion, if the CVP has risen by less than 5 cm but more than 2 cm of H₂O, the patient is observed for a 10-minute interval. If the CVP persistently exceeds 2 cm H₂O of the starting value, the patient is monitored but no additional fluid is administered. If it declines to within 2 cm H₂O of the starting value, the fluid challenge is resumed. In each instance, the pressure value immediately preceding the fluid challenge serves as the reference measurement. Fluid is administered until either the hemodynamic signs of shock are corrected or the central venous pressure "5-2" rule is violated.

A "7-3" rule is employed when measurements of pulmonary artery diastolic (P_{PAD}) or "wedge" (P_{PAW}) pressure are available (Table 3). The P_{PAD} is a valid indication of left-sided filling pressures in the absence of pulmonary hypertension. However, when pulmonary diastolic pressure exceeds wedge pressure by more than 5 mm Hg and if changes in P_{PAW} do not closely correspond to simultaneous changes in P_{PAD}, P_{PAW} should be utilized. Measurement of P_{PAD} decreases the risk of pulmonary vascular injury and pulmonary infarction caused by prolonged inflation of the balloon of the flow-directed pulmonary artery (Swan-Ganz) catheter.^{17,18} When the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is less than 12 mm Hg, 200 ml of fluid is administered over a 10-minute interval through a peripheral intravenous catheter. If the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is greater than 12 mm Hg but less than 16 mm Hg, 100 ml of fluid is administered. If the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is equal to or greater than 16 mm Hg, a 50-ml aliquot of fluid is administered. The pulmonary artery pressure is monitored during the infusion and the "7-3" rule is utilized: If the pulmonary artery diastolic or pulmonary artery wedge pressure increases by 7 mm Hg at any time during the infusion and remains at this level for more than 1 minute, the infusion is stopped. If following the 10-

TABLE 3
Guidelines for Fluid Challenge Utilizing Pulmonary Artery Diastolic or Pulmonary Artery Wedge Pressure Monitoring

Fluid challenge: P _{PAW} , P _{PAD} mm Hg (7-3 rule)		
Observe P _{PAD} /P _{PAW} for 10 min	<12 mm Hg	200 ml × 10 min
	<16 mm Hg	100 ml × 10 min
	≥16 mm Hg	50 ml × 10 min
During infusion 0-9 min	>7 mm Hg	STOP
Immediately following 10 min infusion	>3 < 7 mm Hg	Wait 10 min
	>3 mm Hg	Wait STOP
	≤3 mm Hg	Continue infusion

minute infusion, the pulmonary artery diastolic pressure or the pulmonary wedge pressure has increased by less than 7 mm Hg but more than 3 mm Hg, the patient is observed for 10 minutes. If the pulmonary pressure persistently exceeds 3 mm Hg of the starting value, the patient is monitored but fluid challenge is suspended. However, if the pulmonary pressure declines to within 3 mm Hg of the starting value, the fluid challenge is resumed. Once again, the pressure value recorded immediately preceding the most recent 10-minute interval of fluid infusion serves as the reference measurement. Fluid administration by the "7-3" rule is continued until either the hemodynamic signs of shock are reversed or the "7-3" rule is violated. When the safe limits of fluid challenge are exceeded and perfusion failure persists, a trial of therapy with inotropic drugs, such as digitalis glycosides, vasodilator (afterload reducing) agents, or mechanical circulatory assistance may be justified. If such interventions improve myocardial performance with a decline in central venous and pulmonary artery pressure, fluid challenge may then be resumed.

Selection of Fluids

During acute, massive hemorrhage both red blood cells and plasma are lost and should be replaced with whole blood or, preferably, reconstituted washed red

blood cells and plasma protein solution. Four hours after acute hemorrhage, the intravascular volume is often increased by fluid transfer from the extravascular compartment into the intravascular compartment. Accordingly, hemoglobin and hematocrit concentrations are reduced. If the plasma volume has been expanded with crystalloid solutions after acute hemorrhage, red blood cells are subsequently administered. When both the hemoglobin and the protein concentration are reduced, we presently advise that both red blood cells and albumin or plasma protein fraction be administered. When plasma losses are caused by inflammatory processes such as peritonitis, or pancreatitis, or after blunt trauma to an extremity, the hemoglobin and hematocrit concentrations may be increased but the protein concentration may be decreased. Solutions of albumin or plasma protein fraction are presently utilized for fluid challenge under these conditions. Excessive losses of chloride during vomiting and selective losses of sodium in patients with diarrhea, in which electrolyte concentrations may be depleted but hematocrit and plasma concentrations are both increased, are presently managed by infusions of physiologic (0.9%) sodium chloride solutions with appropriate additions of potassium and minor cations.

Colloid Osmotic Pressure

The major risk of rapid volume expansion during circulatory shock is pulmonary edema. Our concepts of pulmonary edema have been greatly modified in the last several years by clinical investigations which have quantitated the relationships between the capillary hydrostatic pressure and the colloid osmotic (oncotic) pressure.

E. H. Starling, in 1896,¹⁹ defined the quantitative changes in fluid flux between the capillary membrane and the interstitium, as follows:

$$F_i = K(P_c - P_i) - (\Pi_c - \Pi_i)$$

in which:

F_i = fluid pressure favoring filtration of fluid into the interstitium;

K = Membrane permeability coefficient;

P = hydrostatic pressure;

c = capillary;

i = interstitium;

Π = colloid osmotic (oncotic) pressure.

The larger the fluid pressure (F_i), the greater the likelihood of extravasation of fluid into the interstitium and *edema* formation.

Pulmonary edema may be brought about *either* by an increase in the pulmonary capillary hydrostatic pressure or by a decrease in the colloid osmotic (protein) pressure of the fluid within the capillary. A classic study by Guyton and Lindsey²⁰ illustrates the relationship between the colloid osmotic pressure and the capillary hydrostatic pressure. In dogs with normal plasma protein concentrations, pulmonary edema developed when the left atrial pressure or pulmonary capillary hydrostatic pressure was increased to levels exceeding 25 mm Hg. When the plasma protein concentration was reduced to approximately one-half, by dilution of plasma with physiologic salt solution, pulmonary edema developed when the left atrial pressure was elevated to levels of 11 mm Hg. With the availability of practical methods for the clinical measurement of colloid osmotic (oncotic) pressure (COP) in plasma or serum^{21, 22}, it is now possible to quantitate precisely this additional variable that determines the transport of fluid across the pulmonary capillary and hence the likelihood of pulmonary edema.

Normal colloid osmotic pressure of plasma is 25 mm Hg in the upright subject.^{21, 22} The colloid osmotic pressure declines to 21 mm Hg in the supine individual after 4 hours of bed rest because of loss of the normal gravimetric gradient and reabsorption of hypo-oncotic fluid from the interstitial space. Pulmonary capillary pressure may be estimated from the pulmonary artery wedge (PAW) pressure. An estimate of the average pressure relationships in the pulmonary capillary is shown in Fig 2. At the arteriolar end of the pulmonary capillary in the mid-lung of the supine subject, the normal pressure is estimated to be 15 mm Hg. At the venous end of the pulmonary capillary, the estimate of hydrostatic pressure is 7 mm Hg. The lung is unique as an organ because it provides

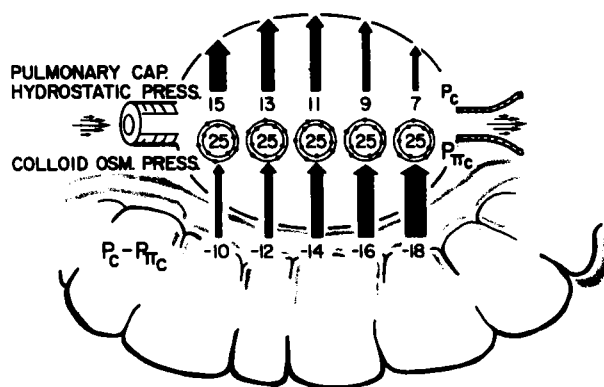


Fig 2. Normal colloid osmotic pressure-pulmonary hydrostatic pressure relationships in the central portion of the lung. Colloid osmotic-hydrostatic pressure gradient ranges from 10 mm Hg at the arteriole to 18 mm Hg at the venule.

mechanisms for maintaining its tissue spaces relatively dry in contrast to systemic tissues. The intravascular colloid osmotic-pulmonary hydrostatic pressure gradient, which, in the supine subject normally ranges from 10 to 18 mm Hg, accounts for the capability of the lung to minimize accumulation of fluid in the alveolar and interstitial spaces. As Staub and associates²³ have demonstrated, the lymphatic system of the lung also has an important role in maintaining a gradient of fluid flow by which extravascular lung water is drained into the venous system. Both the force and the rate of lymph flow are increased when fluid filtration is increased. Normally, the interstitial protein osmotic pressure is one-half or less than that of plasma colloid osmotic pressure and constitutes another important variable for maintenance of normal gradients.²⁴ When capillary filtration is augmented and the volume of interstitial fluid is increased, the interstitial colloid osmotic pressure is reduced. Together with increased lymphatic flow, this provides an important safety factor which decreases the risk of alveolar pulmonary edema.

When left ventricular end-diastolic pressure (left-sided filling pressure) is increased, pulmonary hydrostatic pressure is correspondingly increased. If pulmonary hydrostatic pressure exceeds the colloid osmotic pressure, there is a net gradient of outward fluid flow and, consequently, pulmonary edema (Fig 3). This is in part tempered by the simultaneous changes in lymphatic flow and interstitial colloid osmotic pressure which we have already described. When osmotic pressure is reduced following loss or dilution of plasma proteins, pulmonary edema may occur with only mild increases or even in the absence of increased left ventricular filling pressure. Decreases

in colloid osmotic pressure may be due to increases in permeability of pulmonary or systemic capillaries,²⁵ failure of hepatic production or mobilization of plasma albumin,²⁶ major losses of blood or plasma due to hemorrhage or inflammation,²⁷⁻²⁹ or to the reduction of plasma proteins by the administration of large amounts of crystalloid (non-colloid containing) fluid.³⁰

Oncotic-Hydrostatic Pressure Gradient

Our earlier studies have demonstrated very predictable relationships between the production of acute pulmonary edema and the algebraic difference between the colloid osmotic pressure and the pulmonary artery wedge pressure which we have referred to as the COP-PAW gradient.³¹⁻³³ This presumes that there is no major defect in pulmonary capillary permeability of the type observed with heroin intoxication,³⁴ salicylate overdose,³⁵ bacterial lung infection,³⁶ or aspiration pneumonitis.³⁷ Permeability pulmonary edema may be distinguished from hemodynamic (oncotic-hydrostatic) pulmonary edema by sampling endobronchial fluid.^{38,39} The COP of endobronchial fluid is typically less than 50% of plasma COP and is usually less than 60% of that of plasma in patients with hemodynamic pulmonary edema. However, it exceeds 90% of that of plasma in patients with permeability pulmonary edema.

The colloid osmotic pressure (COP) and the pulmonary artery wedge pressure should be measured simultaneously. If the colloid osmotic pressure-hydrostatic pressure difference is persistently greater than 8 mm Hg, it is unlikely that the patient will develop acute pulmonary edema. When the difference between the COP and the PAW ranges from 4 to 8 mm Hg, the risk of pulmonary edema is significantly increased. If the difference between the COP and the PAW is persistently less than 3 mm Hg for more than 12 hours, pulmonary edema is almost invariably observed (Table 4). When pulmonary edema is reversed in patients, the colloid osmotic hydrostatic pressure gradient is increased to levels of 8 mm Hg or more; in patients who fail to respond to treatment, the colloid osmotic pressure-hydrostatic pressure gradient typically remains less than 3 mm Hg.³⁰

The practical implication of these new developments in the context of this presentation, relates to the prevention of acute pulmonary edema in patients during fluid repletion. The colloid osmotic pressure and the pulmonary artery wedge pressure should be

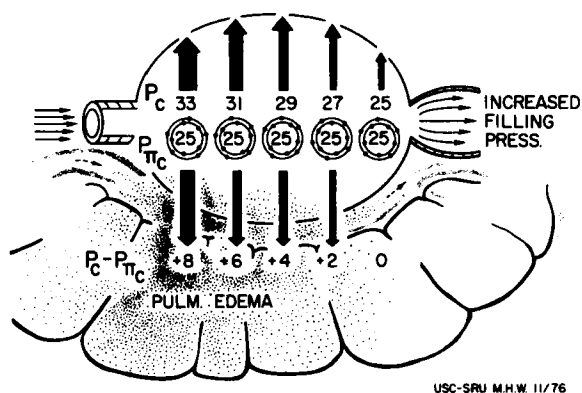


Fig 3. Colloid osmotic-hydrostatic pressure relationships during pulmonary capillary hypertension secondary to left ventricular failure. Pulmonary hydrostatic pressure exceeds colloid osmotic pressure; consequently, fluid extravasates from the intravascular space into the interstitial and alveolar spaces.

TABLE 4
Colloid-Hydrostatic Pressure Gradient Versus
Roentgenographic Severity of Pulmonary Edema*

COP-PAW (mm Hg)	No. of patients	Grade of pulm. edema	Grade 2+ or greater	% Significance	p
-12 to 0.1	9	2.8+	8/9	89	<0.05
0 to 5.9	15	2.2+	8/15	53	<0.001
≥6.0	25	0.8+	5/25	20	<0.05

* Pulmonary edema was graded from the chest roentgenogram using a scale of 0 (absent) to 4+ (florid alveolar edema) for 49 patients with acute cardiorespiratory failure.

measured simultaneously when patients are resuscitated by infusion of blood, electrolytes, or crystalloid fluids. The COP-PAW gradient should be maintained at levels exceeding 7 mm Hg by either manipulating the left ventricular filling pressure or by the use of colloid-containing fluids.

Acute Cardiogenic Pulmonary Edema

Acute pulmonary edema, when caused by left ventricular failure, represents a form of acute perfusion failure (shock) characterized by metabolic acidemia, lactic acidemia, and a reduction in forward blood flow.⁴⁰ Extensive investigations of patients with acute cardiogenic pulmonary edema in our unit have revealed a reduction rather than an expansion of the intravascular blood volume in these patients.^{41, 42} With the increase in the capillary hydrostatic pressure above the colloid osmotic pressure, and the production of a negative COP-PAW gradient, large quantities of fluid, which are low in protein content, extravasate from the intravascular space into the interstitial and alveolar spaces of the lung during acute heart failure. As much as one-half of the plasma volume may be lost from the intravascular spaces into the interstitial space and alveoli of the lung.^{43, 44} Indeed, the volume deficit which accompanies acute pulmonary edema may occasionally be so marked that the patient may present with acute circulatory failure which is due to primary hypovolemic shock. Seven patients with ischemic heart disease with unequivocal clinical signs of acute left ventricular failure, radiographic signs of acute pulmonary edema, hypoxemia combined with respiratory and metabolic acidemia, hypovolemia, and peripheral circulatory failure with hypotension have been studied by our group.⁴⁵ Reduction in intravascular volume, documented in each case, together with reduction in ventricular filling pressures, aggravated the low cardiac output state and produced the circulatory failure (shock). Perfusion

failure was promptly reversed after infusion of 5% human serum albumin in amounts ranging from 0.5 to 2.0 L *without* exacerbation of the pulmonary edema (Table 5). Responsiveness to furosemide, a potent loop diuretic, was then restored.

Hypovolemia requiring fluid repletion is an uncommon complication in patients who present with acute pulmonary edema. Nevertheless, the fact that acute circulatory failure may occasionally be reversed by volume infusion, provides important confirmation of the important role of volume depletion in patients with acute cardiogenic pulmonary edema.

Summary and Conclusion

The primary defect underlying all forms of acute circulatory failure (shock) is reduction of effective blood flow with inadequate tissue perfusion and a decrease in the delivery of oxygen to the capillary exchange bed. Lactic acid accumulates as a result of anaerobic metabolism and provides a quantitative measurement of the perfusion failure and the oxygen deficit. Hypovolemia is the most frequent cause of acute circulatory failure (shock) with lactic acidosis seen in the general hospital and is due to a primary deficit in the intravascular blood volume.

Routine measurement of the central venous pressure and/or the pulmonary artery pressure provides clinical guidelines for volume repletion in patients with acute circulatory failure and allows the clinician to detect limitations in cardiac competence prior to the development of acute pulmonary edema. Large volumes of fluid may be safely administered utilizing the "5-2" and "7-3" rules of fluid challenge.

Recent investigations in our unit have emphasized the importance not only of the pulmonary hydrostatic pressure but also the colloid osmotic pressure in the production of acute pulmonary edema. A colloid osmotic-hydrostatic pressure gradient which is persist-

TABLE 5
Reversal of Acute Perfusion Failure in Seven Patients with
Acute Cardiogenic Pulmonary Edema by Infusion of Plasma
Albumin

	Mean arterial pressure (mm Hg)	P _{PAW} (mm Hg)	Plasma volume (ml/kg)	Total blood volume (ml/kg)
Initial measurement	69	9.4	36.9	56.8
Post-albumin infusion	81	14.7	46.0	67.2
		p < 0.05	p < 0.05	p < 0.05

ently less than 3 mm Hg for 12 hours, is almost always associated with acute pulmonary edema.

Acute pulmonary edema, when caused by left ventricular failure, represents a form of acute perfusion failure (shock) with metabolic acidemia, lactic acidemia, and a reduction in forward flow. Large quantities of fluid may be lost from the intravascular space into the interstitial and the alveolar spaces during the production of acute cardiogenic pulmonary edema. Measurement of the intravascular volume demonstrates a reduction rather than an expansion of the plasma volume.

Acute pulmonary edema is not fundamentally different from other types of shock in which the shock state is initiated by one primary defect, and during the course of its progression, other mechanisms are called into action. In the instance of acute cardiogenic pulmonary edema, the primary defect is cardiac pump failure and the secondary defects include hypovolemia and distributive defects associated with expansion of the venous capacitance bed and arterial vasoconstriction. The volume deficit may occasionally be so great during acute cardiogenic pulmonary edema that fluid repletion may be required as an initial therapeutic intervention to restore effectiveness of conventional treatment of myocardial failure with diuretic agents and digitalis glycoside.

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Potency of Pancuronium and Its Metabolites

To determine the potency of pancuronium and its metabolites 3-OH-, 17-OH-, and 3,17-OH-pancuronium, cumulative dose-response curves were determined in five anesthetized patients with each drug. The ED₅₀ (dose required for a 50% depression of twitch tension) was established for each drug. Pancuronium (ED₅₀ = 0.041 mg/kg) was 2 times more potent than 3-OH-pancuronium (ED₅₀ = 0.082 mg/kg), 50 times more potent than 17-OH-pancuronium (ED₅₀ = 2.0 mg/kg), and 54 times more potent than 3,17-OH-pancuronium (ED₅₀ = 2.15 mg/kg). In 21 additional patients, one equipotent dose of either pancuronium or one of its metabolites was given as an intravenous bolus. Onset time and duration of neuromuscular blockade from 3-OH- and 3,17-OH-pancuronium did not differ significantly from that of pancuronium: 17-OH-pancuronium had a shorter duration of action than did pancuronium. Although pancuronium tended to have a slightly longer elimination half-life, the pharmacokinetics of the four drugs did not differ significantly. The elimination half-lives were 110, 68, 73, and 71 minutes for pancuronium and its 3-OH, 17-OH, and 3,17-OH derivatives, respectively. The authors conclude that although pancuronium is more potent than its 3-OH, 17-OH, and 3,17-OH metabolites, the pharmacokinetics of these three metabolites do not differ from each other and from that of pancuronium. (Miller RD, Agoston S, Booij LHD, et al: *The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man*. *J Pharmacol Exp Ther* 207:539-543, 1978)