Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update

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Objective: To provide the American College of Critical Care Medicine with updated guidelines for hemodynamic support of adult patients with sepsis.

Data Source: Publications relevant to hemodynamic support of septic patients were obtained from the medical literature, supplemented by the expertise and experience of members of an international task force convened from the membership of the Society of Critical Care Medicine.

Study Selection: Both human studies and relevant animal studies were considered.

Data Synthesis: The experts articles reviewed the literature and classified the strength of evidence of human studies according to study design and scientific value. Recommendations were drafted and graded levels based on an evidence-based rating system described in the text. The recommendations were debated, and the task force chairman modified the document until <10% of the experts disagreed with the recommendations.

Conclusions: An organized approach to the hemodynamic support of sepsis was formulated. The fundamental principle is that clinicians using hemodynamic therapies should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis by monitoring a combination of variables of global and regional perfusion. Using this approach, specific recommendations for fluid resuscitation, vasopressor therapy, and inotropic therapy of septic in adult patients were promulgated. (Crit Care Med 2004; 32:1928–1948)

Key Words: sepsis; hemodynamic support; fluid resuscitation; vasopressor therapy; inotropic therapy

Shock occurs when the circulatory system fails to maintain adequate cellular perfusion. Shock is a syndrome that may arise from any of several initiating causes; as this syndrome progresses, a common pattern comprising an array of symptoms, signs, and laboratory abnormalities that result from hypoperfusion emerges. If shock is not reversed, irreversible cellular damage may ensue.

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce hemodynamic decompensation. Septic shock is primarily a form of distributive shock and is characterized by ineffective tissue oxygen delivery and extraction associated with inappropriate peripheral vasodilation despite preserved or increased cardiac output (1). In septic shock, a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution occurs due to the inflammatory response to infection. Even after the restoration of intravascular volume, microcirculatory abnormalities may persist and lead to maldistribution of cardiac output (2). About half of the patients who succumb to septic shock die of multiple organ system failure (1). Most of the rest have progressive hypotension with low systemic vascular resistance refractory to vasopressor agents (3). Although myocardial dysfunction is not uncommon, death from myocardial failure is rare (1).

Cellular dysfunction in sepsis is the final outcome of a process with multiple stimuli. Prominent mechanisms include cellular ischemia, disruption of cellular metabolism by the effects of inflammatory mediators, and toxic effects of free radicals (3). Activation of caspas and induction of heat shock proteins may lead to apoptotic cell death. In early shock, compensatory mechanisms are activated in an attempt to restore pressure and flow to vital organs. When these compensatory mechanisms begin to fail, damage to cellular membranes, loss of ion gradients, leakage of lysosomal enzymes, proteolysis due to activation of cellular proteases, and reductions in cellular energy stores occur and may result in cell death (3). Once enough cells from vital organs have reached this stage, shock can become irreversible, and death can occur despite eradication of the underlying septic focus.
Therapy of septic shock may be viewed as having three main components. The initial priority in managing septic shock is to maintain a reasonable mean arterial pressure and cardiac output to keep the patient alive. Then the nidus of infection must be identified and eliminated, using antimicrobial therapy in all cases and surgical drainage whenever indicated. Another therapeutic goal is to interrupt the pathogenic sequence leading to septic shock. While these latter goals are being pursued, adequate organ system perfusion and function must be maintained, guided by cardiovascular monitoring. The purpose of this practice parameter is to provide guidelines for hemodynamic support in sepsis to maintain adequate organ system and cellular perfusion.

**PURPOSE AND STRUCTURE OF PRACTICE PARAMETERS FOR HEMODYNAMIC SUPPORT IN SEPSIS**

These practice parameters were developed by a panel convened by the American College of Critical Care Medicine of the Society of Critical Care Medicine, and updated by a similar panel, to assist health care providers in the management of hemodynamic support for patients with sepsis and septic shock. These guidelines are intended for adult patients and do not cover all conceivable clinical scenarios. Nonetheless, they do represent an attempt to review the state of knowledge concerning hemodynamic therapy of sepsis and to supplement specific therapeutic recommendations with guidelines about how to optimize therapy and how to evaluate the results of therapeutic interventions. The information and recommendations are predicated upon an expert-based review of the available scientific data, clinical investigations, and outcomes research. Where such data are unavailable or limited in scope, consensus was attained by considering published expert opinion and discussion among a wide range of experts. The citations of human studies have been annotated into levels of scientific support as per Cochrane group recommendations (4) as follows:

- Level I: large, randomized trials with clear-cut results; low risk of false-positive (α) error or false-negative (β) error
- Level II: small, randomized trials with uncertain results; moderate to high risk of false-positive (α) error and/or false-negative (β) error
- Level III: nonrandomized, contemporaneous controls
- Level IV: nonrandomized, historical controls and expert opinion
- Level V: case series, uncontrolled studies, and expert opinion

The strength of the recommendations has been graded as modified from the guidelines of Evidence-Based Medicine Working Group as follows: (5)

- A: Supported by at least two level I investigations
- B: Supported by only one level I investigation
- C: Supported by level II investigations only
- D: Supported by at least one level III investigation
- E: Supported by level IV or level V investigations only

Hemodynamic therapy of sepsis has been considered in each of three categories: fluid resuscitation, vasopressor therapy, and inotropic therapy. Since the initial formulation of the guidelines, a randomized, double-blind, placebo-controlled, multiple-center trial of recombinant human activated protein C has been completed (6). Although this trial showed that treatment with recombinant activated protein C is effective in patients with septic shock, activated protein C is not a hemodynamic therapy per se, nor was hemodynamic instability a requisite for inclusion in the trial. Thus, consideration of activated protein C and other therapies not directed at hemodynamic stabilization is outside the scope of these practice parameters.

An algorithm outlining an approach to hemodynamic support of patients with septic shock based on the recommendations in these parameters is shown in Figure 1.

**BASIC PRINCIPLES**

Septic shock requires early, vigorous resuscitation. An integrated approach directed at rapidly restoring systemic oxygen delivery and improving tissue oxygenation has been demonstrated to improve survival significantly in septic shock (7). Although the specific approach that is used may vary, there are critical elements that should be incorporated in any resuscitative effort. Therapy should be guided by parameters that reflect the adequacy of tissue and organ perfusion. Fluid infusion should be vigorous and titrated to clinical end points of volume repletion. Systemic oxygen delivery should be supported by ensuring arterial oxygen saturation, maintaining adequate concentrations of hemoglobin, and using vasoactive agents directed to physiologic and clinical end points.

Patients with septic shock should be treated in an intensive care unit. Continuous electrocardiographic monitoring should be performed for detection of rhythm disturbances, and pulse oximetry is useful to detect fluctuations in arterial oxygenation. Urine output is monitored continuously as well. Laboratory measurements such as arterial blood gases, serum electrolytes, complete blood counts, coagulation variables, and lactate concentrations should be done early and repeated as indicated.

In shock states, estimation of blood pressure using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure (3). These catheters also allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information. Such monitoring facilitates the administration of large quantities of fluids and potent vasopressor and inotropic agents to critically ill patients (3).

Although patients with shock and mild hypovolemia may be treated successfully with rapid fluid replacement, right heart catheterization may be useful to provide a diagnostic hemodynamic assessment in patients with moderate or severe shock. In addition, because hemodynamics can change rapidly in sepsis, and because noninvasive evaluation is frequently incorrect in estimating filling pressures and cardiac output, pulmonary artery catheterization is often useful for monitoring the response to therapy.

**Goals and End Points of Hemodynamic Support in Septic Patients**

Shock represents the failure of the circulatory system to maintain adequate delivery of oxygen and other nutrients to tissues, causing cellular and then organ dysfunction. Thus the ultimate goals of hemodynamic therapy in shock are to
Figure 1. Suggested algorithm for hemodynamic support of adult patients with severe sepsis and septic shock. SBP, systolic blood pressure; MAP, mean arterial pressure; ICU, intensive care unit; BP, blood pressure; HR, heart rate; Hgb, hemoglobin. *Adequate cardiac filling pressures can be assessed by response of cardiac output (CO) to increases of pulmonary artery occlusion pressure. Maximal benefit is usually achieved at pulmonary artery occlusion pressure 12–15 mm Hg. Variation in arterial pressure with respiration can also be used to identify patients who would benefit from increased fluid administration. †Cardiac output can be assessed by echocardiography or by measuring cardiac index and/or mixed-venous oxygen saturation with a pulmonary artery catheter. ‡Perfusion can be assessed using a combination of clinical and laboratory variables, as described in the text. §A corticotropin stimulation test is recommended. See text for details.
restore effective tissue perfusion and to normalize cellular metabolism.

In hypovolemic, cardiogenic, and extracardiac obstructive shock, hypotension results from a decrease in cardiac output, with consequent anaerobic tissue metabolism. Septic shock, the prototypical form of distributive shock, is different and more complicated. In septic patients, tissue hypoperfusion results not only from decreased perfusion pressure attributable to hypotension but also from abnormal shunting of a normal or increased cardiac output (3). Cellular alterations may also occur. Hemodynamic support of sepsis thus requires consideration of both global and regional perfusion.

The practical import of the complexity of hemodynamics in sepsis is that the goals of therapy are much more difficult to define with certainty than in other forms of shock in which global hypoperfusion is the dominant pathology. In cardiogenic shock, for example, the goal of therapy is to increase cardiac output, although the degree of hypoperfusion may vary in different organs. Indexes of regional perfusion usually correlate well with indexes of global perfusion, and both can be used to monitor the effects of therapy. In sepsis, maldistribution of a normal cardiac output can impair organ perfusion, and maldistribution of blood flow within organs due to perturbation of resistance vessel tone or microvascular obstruction can exacerbate organ dysfunction. To add to the complexity, mediators of sepsis can perturb cellular metabolism, leading to inadequate utilization of oxygen and other nutrients despite adequate perfusion. One would not expect such abnormalities to be corrected by hemodynamic therapy.

Despite the complexity of the pathophysiology of sepsis, an underlying approach to the hemodynamic support of sepsis can be formulated, with the understanding that the basic principles of the approach are more important than the specific recommendations, which will certainly change as our understanding of sepsis improves. For example, although which variables most accurately reflect the effects of therapy in septic patients may be uncertain, it should be apparent that therapeutic efficacy should be assessed by monitoring a combination of variables. Similarly, although specific end points may be arguable, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle.

An important recent trial supports early goal-directed therapy in sepsis. A total of 263 patients with severe sepsis or septic shock were randomized to receive either 6 hrs of early goal-directed therapy or standard therapy in the emergency department before admission to the intensive care unit (7). The resuscitation strategy involved rapid administration of intravenous fluids targeted to a central venous pressure of 8–12 mm Hg, correction of anemia to a hematocrit ≥30%, vasopressor agents as necessary to maintain mean arterial pressure ≥65 mm Hg, and administration of dobutamine in an attempt to achieve a central venous oxygen saturation ≥70%. Patients assigned to early goal-directed therapy had a significantly higher central venous oxygen saturation, lower lactate concentration and base deficit, and significantly lower Acute Physiology and Chronic Health Evaluation II scores, indicating less severe organ dysfunction (7). More importantly, in-hospital mortality rate was significantly decreased in the group assigned to early goal-directed therapy, from 46.5% to 30.5% (p = .009) (7). This study provides strong support for the notion that therapy for sepsis should be initiated as early as possible and should be directed toward clearly defined goals.

Index of Global Perfusion

Bedside clinical assessment provides a good indication of global perfusion. Septic shock is by definition characterized by hypotension, which generally refers to a mean arterial pressure below 60–70 mm Hg in adults. Mean arterial pressure is preferable to systolic pressure because of its closer relationship to the autoregulatory limits of organ blood flow (3). In interpreting any given level of arterial pressure, however, the chronic level of pressure must be considered. Hypotension is usually accompanied by tachycardia.

Indications of decreased perfusion include oliguria, clouded sensorium, delayed capillary refill, and cool skin. Some caution is necessary in interpreting these signs in septic patients, however, since organ dysfunction can occur in the absence of global hypoperfusion.

In most forms of shock, elevated blood lactate concentrations reflect anaerobic metabolism due to hypoperfusion, but the interpretation of blood lactate concentrations in septic patients is not always straightforward. Some studies in animal models of sepsis have found normal high-energy phosphate concentrations (8) but others have not (9); the differences may relate to the severity of the septic model, with more severe sepsis being associated with depletion of adenosine triphosphate despite maintenance of systemic oxygen delivery and tissue oxygenation. A number of studies have indicated that increasing either global (10) or regional (11) oxygen delivery fails to alter elevated lactate concentrations in patients with sepsis. A number of studies have suggested that elevated lactate may result from cellular metabolic alterations rather than from global hypoperfusion in sepsis (12, 13). Accelerated glycolysis with high pyruvate production (14), inhibited pyruvate dehydrogenase, and decreased clearance by the liver may contribute to elevated lactate concentrations. Nonetheless, although lactate concentrations should not be considered to represent tissue hypoxia in the strict sense, the prognostic value of elevations of blood lactate has been well established in septic shock patients (15–17). The trend of lactate concentrations is a better indicator than a single value (15, 16). It is also of interest to note that blood lactate concentrations are a better prognostic indicator than oxygen-derived variables (calculated oxygen delivery and consumption) (18).

Mixed venous oxyhemoglobin saturation (SVo2) can be measured in patients with a right heart catheter in place, either intermittently by sampling blood from the pulmonary artery port or continuously using a fiberoptic oximeter. SVo2 is dependent on cardiac output, oxygen demand, hemoglobin, and oxygen saturation. SVo2 reflects the balance between oxygen delivery and consumption and can decrease when oxygen delivery falls in relation to the oxygen requirements of the tissues. The normal SVo2 value is 70–75% in critically ill patients, but SVo2 can be elevated in septic patients due to maldistribution of blood flow, and so values must be interpreted in the context of the wider hemodynamic picture. Nonetheless, if SVo2 remains low despite achievement of other end points of resuscitation, this suggests increased oxygen extraction and therefore potentially incomplete resuscitation.
recent study showed that monitoring of central venous oxygen saturation (ScvO2) can be a valuable guide to early resuscitation (7).

**Indexes of Regional Perfusion**

Adequacy of regional perfusion is usually assessed clinically by evaluating indexes of organ function, such as myocardial ischemia, decreased urine output, increased blood urea nitrogen and creatinine, an abnormal sensorium, increased serum concentrations of transaminases, lactic dehydrogenase, and bilirubin, and prolonged clotting tests (3). Methods of measuring regional perfusion more directly have been under investigation, with a focus on the splanchic circulation, for several reasons. First, the hepatosplanchic circulation may be compromised early in acute circulatory failure. Measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of septic patients, suggesting that hepatosplanchnic oxygen supply may be inadequate in some patients, even when more global variables appear adequate (19). Second, the gut (especially the stomach) may be accessible to monitoring systems. Third, the countercurrent flow in the gut microcirculation increases the risk of mucosal hypoxia. Finally, the gut may have a higher critical oxygen delivery threshold than other organs (20), and gut ischemia increases intestinal permeability.

Gastric tonometry is a method to assess regional perfusion in the gut that employs a balloon in the stomach to measure intramucosal Pco2. Gastric mucosal Pco2 is influenced directly by systemic arterial Pco2, however, and so use of gastric-arterial Pco2 difference has been proposed as the primary tonometric variable of interest, although even this measure is not a simple measure of gastric mucosal hypoxia (21). Despite its complexity, tonometry is a reasonably good predictor for the ultimate outcome of critically ill patients (22–26). Its utility to guide therapy in patients with sepsis and septic shock, however, has not been proven. More recently, capnography in the sublingual area, a technique that is less invasive and easier to use, has been shown to yield tissue Pco2 measurements that correlate with those obtained by gastric tonometry (27).

**FLUID RESUSCITATION IN SEPSIS**

**Goals and Monitoring of Fluid Resuscitation**

Septic shock is characterized by decreased effective capillary perfusion resulting from both global and distributive abnormalities of systemic and microcirculatory blood flow. An important factor contributing to the impairment in tissue perfusion is hypovolemia (13, 28–30). The initial phases of experimental and clinical septic shock present as a low cardiac output syndrome with low filling pressures and evolve to a hyperdynamic state only after volume repletion (13, 28). Increased blood and plasma volumes are associated with increased cardiac output and enhanced survival from septic shock (31). Failure to appreciate the degree of underlying hypovolemia may result in a low cardiac output.

Large fluid deficits exist in patients with septic shock. Up to 6–10 L of crystalloid solutions or 2 to 4 L of colloid solutions may be required for initial resuscitation in the first 24 hrs (7, 32). Volume repletion in patients with septic shock produces significant improvement in cardiac function and systemic oxygen delivery, thereby enhancing tissue perfusion and reversing anaerobic metabolism (33). Despite sepsis-induced myocardial depression, cardiac index will usually improve by 25–40% during fluid resuscitation (34). In approximately 50% of septic patients who initially present with hypotension, fluids alone will reverse hypotension and restore hemodynamic stability (35).

In sepsis, increases in interstitial fluid volume may already exist and venous capacitance changes play a major role in contributing to hypovolemia, and so repleting the interstitial space, which may have a role in hemorrhagic shock, does not appear to be as important. Intravascular volume can be repleted through the use of packed red cells, crystalloid solutions, and colloid solutions.

The goal of fluid resuscitation in septic shock is restoration of tissue perfusion and normalization of oxidative metabolism. Increasing cardiac output and oxygen delivery is dependent on expansion of blood and plasma volume. Fluid infusion is best initiated with predetermined boluses (250–500 mL every 15 mins) titrated to clinical end points of heart rate, urine output, and blood pressure. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Filling pressures should be increased to a level associated with maximal increases in cardiac output. In most patients with septic shock, cardiac output will be optimized at pulmonary artery occlusion pressures between 12 and 15 mm Hg (34). Increases above this range usually do not significantly enhance end-diastolic volume or stroke volume and increase the risk for developing pulmonary edema. If only central venous pressure is available, levels of 8–12 mm Hg should be targeted (7).

In patients requiring mechanical ventilation, changes in arterial pressure during mechanical breaths may also serve as a useful indicator of underlying hypovolemia (36–38). The effects of increased pleural pressure on ventricular filling are accentuated in preload-deficient states, resulting in cyclic decreases in systolic arterial pressure and widening of the arterial pulse pressure. When these changes are present, they appear to be predictive of fluid responsiveness in septic patients with circulatory failure (37, 38). These measurements require that the patient have minimal or absent spontaneous respiratory efforts, which may necessitate the use of neuromuscular blocking agents (37, 38).

Far more important than the specific method of monitoring is the use of that method in a dynamic fashion. Evaluation of the response to fluid infusion is much more useful than one measurement at a single time point. This is particularly true in unstable patients, since cardiac and vascular compliance may change over time.

Resuscitation should be titrated to end points of oxygen metabolism and organ function. Associations have been observed between improved survival and increased levels of central venous oxygen saturation, systemic oxygen delivery, reversal of lactic acidosis, and increases in gastric intramucosal pH (7, 18, 24, 39). However, the specific choice of end points remains controversial.

**Fluid Resuscitation Therapies**

**Crystalloids.** The crystalloid solutions used most commonly for resuscitation are 0.9% sodium chloride (normal saline) and lactated Ringer’s solution. The lactate content of Ringer’s solution is rapidly metabolized during resuscitation and...
does not significantly affect the use of arterial lactate concentration as a marker of tissue hypoperfusion (40).

The volume of distribution of normal saline and Ringer’s lactate is the extracellular compartment. Under ideal conditions, approximately 25% of the infused amount will remain intravascular while the rest is distributed to the extravascular space. Clinically, 100–200 mL of intravascular volume expansion can be expected after the infusion of 1 L of isotonic crystalloids (41, 42). Resuscitation from septic shock frequently requires crystalloid volumes ranging from 6 to 10 L during the initial 24-hr period, which results in significant hemodilution of plasma proteins and decreases in colloid osmotic pressure.

Hypertonic saline solutions have a sodium content ranging from 400 to 2400 mOsm/L. Hypertonic solutions have potentially advantageous physiologic effects including improved cardiac contractility and precapillary vasodilation (43). The primary risk when using these fluids is iatrogenically induced hypertonic states due to sodium load. Experience with hypertonic solutions in septic shock is limited.

Colloids. Many different colloidal solutions are available, including plasma protein fraction, albumin, gelatins, dextrans, and hydroxyethyl starch. The principal solutions used in clinical resuscitation are albumin and hydroxyethyl starch.

Albumin is a naturally occurring plasma protein that accounts for approximately 80% of the plasma colloid osmotic pressure in normal subjects. Human serum albumin is available in the United States in 5% and 25% solutions; other concentrations are available in Europe. The 5% solution, rather than the 25% solution, should be used for initial resuscitation. After 1 L of 5% albumin, plasma volume expansion ranges from 500 to 1000 mL (41, 42). Mobilization of extravascular volume is required for effective increases in intravascular volume when using 25% albumin. If fluid is successfully mobilized from the interstitial space, a 100-ml aliquot can produce increases of 400–500 mL in the intravascular volume 1 hr after infusion (42). In the setting of increased vascular permeability such as septic shock, significantly smaller amounts of fluid may be mobilized.

The recently completed Saline versus Albumin Fluid Evaluation (SAFE) trial randomized 6,997 critically ill patients to resuscitation with albumin or saline. There was no difference in 28-day mortality rate (20.9% with albumin vs. 21.1% with saline) (44).

Hydroxyethyl starch is a synthetic colloid formed from hydroxyethyl-substituted branched-chain amylopectin. It is available in the United States a 6% solution of normal saline with a colloid osmotic pressure of approximately 30 mOsm/L (45). One liter of hydroxyethyl starch solution expands plasma volume by 700 mL to 1 L with as much as 40% of maximum volume expansion persisting for 24 hrs (41).

There have been reports suggesting that hydroxyethyl starch molecules may adversely affect renal function by causing tubular injury (46, 47). In patients with sepsis, resuscitation with hydroxyethyl starch solution, as compared with gelatin, resulted in significantly higher serum creatinine concentrations without associated differences in the need for renal replacement (47). Studies in other groups of patients have not observed differences in renal function when hydroxyethyl starch solution was compared with other fluids (48–51). Importantly, these studies were done with a variety of hydroxyethyl starch solutions, each with different physical properties that may have different effects on renal tubular cells. Additional investigations are required to reconcile these divergent observations.

Hydroxyethyl starch can cause dose-dependent decreases in factor VIII activity and prolongation of partial thromboplastin time. Although these changes appear to be primarily dilutional, there have been reports of increased bleeding, primarily in patients undergoing cardiac surgery (52). However, only minor clotting abnormalities and no increased incidence of bleeding have been noted in patients with hypovolemic and septic shock (52).

Efficacy

Patients with septic shock can be successfully resuscitated with either crystalloid or colloids. Increases in cardiac output and systemic oxygen delivery are proportional to the expansion of intravascular volume achieved. When crystalloids and colloids are titrated to the same level of filling pressure, they are equally effective in restoring tissue perfusion (32). Resuscitation with crystalloid solutions will require two to four times more volume than colloids and may require slightly longer periods to achieve desired hemodynamic end points. Colloid solutions are much more expensive than crystalloid solutions. Five percent albumin and 6% hydroxyethyl starch solution are equivalent with respect to the amount of fluid required during resuscitation.

Complications

The major complications of fluid resuscitation are pulmonary and systemic edema. These complications are related to three principal factors: a) increases in hydrostatic pressures; b) decreases in colloid osmotic pressure; and c) increases in microvascular permeability associated with septic shock. The controversy concerning crystalloid and colloid resuscitation revolves around the importance of maintaining plasma colloid osmotic pressure. Large volume crystalloid resuscitation results in significant decreases in plasma colloid osmotic pressure, whereas plasma colloid osmotic pressure is maintained with colloid infusion (32). In experimental studies, decreases in plasma colloid osmotic pressure increase extravascular fluid flux in the lungs and lower the level of hydrostatic pressure associated with lung water accumulation (53, 54). Some, but not all, clinical reports have observed a correlation between decreases in the colloid osmotic pressure-pulmonary artery occlusion pressure gradient and the presence of pulmonary edema (55–57). Several clinical studies have randomized subjects to crystalloid or colloid infusion and examined the development of pulmonary edema with mixed results, demonstrating either no differences between solutions or an increased incidence of pulmonary edema with crystalloids (32, 58, 59). Experimental reports in septic models demonstrate no increase in extravascular lung water when hydrostatic pressures are maintained at low levels, indicating that in sepsis the primary determinant of extravascular fluid flux appears to be microvascular pressure rather than colloid osmotic pressure (60). Together, these data suggest that when lower filling pressures are maintained there is no significant difference in the development of pulmonary edema with crystalloids or colloids. However, if higher filling pressures are required to optimize cardiac performance in patients with ventricular dysfunction, colloids may mitigate against extravascular fluid flux (32).
The acute respiratory distress syndrome occurs in 30–60% of patients with septic shock. Of concern has been the possibility that in the setting of increased microvascular permeability, colloid particles could migrate into the interstitium where they would favor fluid retention in the lung and worsen pulmonary edema. A number of studies, including a variety of models of increased microvascular permeability, as well as clinical studies in patients with septic shock and the acute respiratory distress syndrome, have not found evidence of increased lung water or compromised lung function with colloids (32, 61–63).

Systemic edema is a frequent complication of fluid resuscitation. The relative roles of increased microvascular permeability, increases in hydrostatic pressure, and decreases in plasma colloid osmotic pressure in the development of this complication during sepsis are unclear. Tissue edema may reduce tissue oxygen tensions by increasing the distance for diffusion of oxygen into cells. During experimental peritonitis, crystalloid therapy was associated with increased endothelial cell swelling and decreased systemic capillary cross-sectional area when compared with colloid infusion (64). In contrast, other studies comparing the impact of large volume crystalloid infusion on skeletal muscle and intestinal oxygen metabolism have observed no impairment of oxidative metabolism despite significant edema formation (60, 65). The integrity of the gastrointestinal mucosa as a barrier to bacterial translocation also does not appear to be affected by decreases in colloid osmotic pressure and the development of tissue edema following crystalloid resuscitation. A comparison of crystalloid and colloid resuscitation in thermal injury found that the extent of resuscitation and not the choice of fluids was the major determinant of bacterial translocation (66).

Finally, there have been multiple meta-analyses of the clinical studies comparing crystalloids with colloids, which have examined the effect of resuscitation with these solutions on mortality rate. The results have been conflicting, with some of the reports suggesting differences in mortality rate favoring crystalloids, whereas others have shown no differences (67–69). These differences reflect the poor quality of many of the underlying studies, the heterogeneity in patient populations, and the fact that none of the clinical studies was ever designed with mortality as an end point.

**Transfusion Therapy**

The optimal hemoglobin and hematocrit for patients with septic shock is uncertain. This is a major clinical issue since hemoglobin concentrations usually range between 8 and 10 g/dL in patients with septic shock. The decrease in hemoglobin is related to several factors including ineffective erythropoiesis and hemodilution. Decreases in hemoglobin in the range of 1–3 g/dL can be expected during resuscitation of septic shock with either crystalloids or colloids (32).

In most patients, this degree of anemia is well tolerated because the associated decrease in blood viscosity decreases afterload and increases venous return thereby increasing stroke volume and cardiac output. The decrease in blood viscosity may also compensate for other rheologic changes that occur in patients with septic shock and may enhance microvascular blood flow. However, several factors may affect the ability of the patient to tolerate the decrease in hematocrit and should be considered. Cardiac dysfunction will limit the increase in cardiac output in response to decreased viscosity and may result in inadequate levels of systemic oxygen delivery. In markedly hypermetabolic states, the increase in cardiac output may not be adequate to compensate for the decrease in arterial oxygen content, potentially compromising systemic oxygen metabolism. The inability to extract oxygen, related either to anatomical abnormalities such as in coronary artery diseases or physiologic abnormalities in sepsis, may result in greater dependence on oxygen content to maintain oxidative metabolism (70, 71).

To date, studies examining the effects of transfusing critically ill patients with hemoglobin concentrations in the range of 8–10 g/dL have not demonstrated any consistent benefit in tissue perfusion. The majority of trials have demonstrated no significant increase in systemic oxygen consumption when the major effect of transfusion therapy is to increase oxygen content (72–74). Other studies suggest that increasing oxygen content by transfusion therapy is not as effective in restoring splanchnic perfusion as it is in increasing cardiac output (75). Indeed, the transfusion of aged, more rigid, red cells has been associated with decreased gastric intramucosal pH and may accentuate the rheologic abnormalities seen in sepsis (76). Blood transfusion may also have immunosuppressive effects (77). Moreover, a study randomizing critically ill patients to transfusion thresholds of 7 or 10 g/dL failed to demonstrate any differences in clinically significant outcomes (78).

Accordingly, the optimal hemoglobin for patients with hemodynamically significant sepsis has not been defined. Most patients will tolerate hemoglobin concentrations in the range of 8–10 g/dL. Some patients, however, may have clinical variables that suggest a need for increased oxygen delivery, including excessive tachycardia, cardiac dysfunction, significant underlying cardiac or pulmonary disease, severe mixed venous oxygen desaturation, or failure to clear lactic acidosis. Patients with sepsis and hemodynamic instability tend to be in the second category. Such patients were excluded from the randomized trials of transfusion thresholds and may benefit from higher hemoglobin concentrations. Although no data exist to support transfusion to a predefined threshold, most experts recommend maintenance of hemoglobin concentrations in the 8–10 g/dL range in patients with sepsis and hemodynamic instability.

**Vasopressor Therapy**

**Goals and Monitoring of Vasopressor Therapy.** When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated (79). Vasopressor therapy may also be required transiently to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been attained. Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin.

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness. Blood pressure, however, does not always equate to blood flow, and the precise level of mean arterial pressure to aim for is not necessarily the same in all patients. Animal studies suggest that below a mean arterial pressure of 60 mm Hg, autoregulation in the coronary, renal, and central nervous system vascular beds is compromised. When organ autoregulation is lost, organ flow becomes linearly dependent on pressure (80, 81).
Thus, maintenance of a mean arterial pressure of 60 mm Hg is usually required to maintain and optimize flow (82–84). Loss of autoregulation can occur at different levels in different organs, however, and thus some patients may require higher blood pressures to maintain adequate perfusion. In addition, the degree to which autoregulation is intact in septic patients is uncertain. It is important to supplement end points such as blood pressure with assessment of regional and global perfusion by a combination of the methods outlined previously.

Particular attention should be paid to certain peripheral circulations during vasopressor infusion. Vasopressor therapy to augment renal perfusion pressure has been shown to increase urine output and/or creatinine clearance in a number of open-label clinical series; the targeted mean blood pressure varied but was as high as 75 mm Hg (85–95). However, significant improvements in renal function with an increase in renal perfusion pressure have not been demonstrated in prospective, randomized studies. A recent study compared vasopressor therapy targeted to 65, 75, and 85 mm Hg in patients with septic shock and found no significant effect on systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchic perfusion (96). Vasopressors should be titrated to the minimum level required to optimize urine flow; in some patients this can be achieved with a mean arterial pressure of 60 or 65 mm Hg.

The gastrointestinal tract, particularly perfusion of the splanchnic bed and the integrity of the gut mucosa, occupies a key position in the pathogenesis of multiple organ failure in sepsis. The effects of vasopressor agents on splanchic circulation may play a role in their selection for a given patient.

Whether a potent vasopressor also has positive inotropic effects is of clinical importance in patients with low cardiac output (97). If vasopressor infusion impairs stroke volume, addition of an inotropic agent such as dobutamine should be considered (91).

**Individual Vasopressor Agents**

**Dopamine.** Dopamine is the natural precursor of norepinephrine and epinephrine. Dopamine possesses several distinct dose-dependent pharmacologic effects. At doses <5 μg·kg⁻¹·min⁻¹, the predominant effect of dopamine is to stimulate dopaminergic DA₁ and DA₂ receptors to cause vasodilation in the renal, mesenteric, and coronary beds. Infusion of low doses of dopamine increases glomerular filtration rate, renal blood flow, and sodium excretion (98, 99). At doses of 5–10 μg·kg⁻¹·min⁻¹, β₁-adrenergic effects predominate, increasing cardiac contractility and heart rate. Dopamine causes the release of norepinephrine from nerve terminals, which contributes to its effects on the heart. At doses >10 μg·kg⁻¹·min⁻¹, α₁-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure. It should be recognized, however, that there is a great deal of overlap in these effects, particularly in critically ill patients.

The hemodynamic effects of dopamine in patients with septic shock have been reported in a number of open labeled trials. Dopamine has been shown to produce a median increase in mean arterial pressure of 24% in patients who remained hypotensive after optimal fluid resuscitation (29, 100–111). Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume, and to a lesser extent to an increase in heart rate (29, 100–111). The median dose of dopamine required to restore blood pressure was 15 μg·kg⁻¹·min⁻¹. In most studies central venous, pulmonary artery, and pulmonary occlusion pressures, systemic vascular resistance index, and pulmonary artery resistance index were unchanged. In patients with elevated pulmonary artery occlusion pressures, dopamine may further increase occlusion pressure by increasing venous return. Patients receiving dopamine infusion rates >20 μg·kg⁻¹·min⁻¹ did show increases in right heart pressures as well as heart rate. Dopamine has been shown to improve right ventricular contractility in patients with underlying right ventricular failure (112).

Dopamine increases pulmonary shunt fraction, probably due to the increase in cardiac output, which can reopen vessels in poorly ventilated areas of the lung (104, 110). PaO₂, however, remains relatively constant, which may be due to hemodynamic improvement and/or an increased mixed venous oxygen saturation (104, 105, 110).

Dopamine has been shown to increase oxygen delivery, but its effects on calculated or measured oxygen consumption have been mixed (100–102). Oxygen extraction ratio typically decreases, suggesting no improvement in tissue oxygenation (100, 102). This may be due to a failure to improve microcirculatory flow in vital organs or lack of a meaningful tissue oxygen debt in some patients (102).

The effect of dopamine on splanchnic perfusion as assessed by gastric tonometric variables has also been mixed. Increases in splanchnic blood flow have been reported but have not always been associated with increases in splanchnic oxygen consumption or effects on gastric intramucosal pH (100, 103, 113, 114). One pilot study reported that despite an increase in both systemic oxygen delivery and systemic oxygen consumption with dopamine, gastric intramucosal pH was reduced (101). The authors speculated that dopamine might have redistributed blood flow within the gut, reducing mucosal blood flow and increasing mucosal oxygen debt. Decreased gastric mucosal blood flow was reported with dopamine in another study, but gastric PCO₂, gastric arterial PCO₂ difference, and calculated intramucosal pH were unchanged (115).

In laboratory animals and healthy volunteers, low doses of dopamine increase renal blood flow and glomerular filtration rate and inhibit proximal-tubular resorption of sodium, which result in natremia (116). With this physiologic rationale, low-dose dopamine is commonly administered to critically ill patients in the belief that it reduces the risk of renal failure by increasing renal blood flow. This issue has now been addressed by an adequately powered randomized clinical trial, which enrolled 328 critically ill patients with early renal dysfunction (urine output <0.5 mL·kg⁻¹·hr⁻¹ over 4 hrs, creatine >150 μmol/L or an increase of >80 μmol/L over 24 hrs) (117). Patients were randomized to low (“renal”) dose dopamine (2 μg·kg⁻¹·min⁻¹) or placebo, and the primary end point was peak serum creatinine. No difference was found in either the primary outcome (peak serum creatinine 245 vs. 249 μmol/L, p = .92), other renal outcomes (increase in creatinine, need for renal replacement), urine output (increased in both groups, perhaps due to furosemide administration), time to recovery of normal renal function, or secondary outcomes (survival to either intensive care unit or hospital discharge, intensive care unit stay, hospital stay, arrhythmias) (117). Thus, the available data do not support administration
of low doses of dopamine solely to maintain renal function.

In summary, dopamine appears to be very effective in increasing mean arterial pressure in patients who remain hypotensive after optimal volume expansion. Since mean arterial pressure increases primarily as a result of increasing cardiac index, dopamine may be particularly useful in patients who are hypotensive with compromised cardiac function or cardiac reserve. The major undesirable effects of dopamine are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. Other side effects include increased pulmonary artery occlusion pressure, increased pulmonary shunt, and the potential for decreased prolactin release and consequent immunosuppression (118).

**Norepinephrine.** Norepinephrine is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. Norepinephrine usually causes a clinically significant increase in mean arterial pressure attributable to its vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance. Norepinephrine generally increases cardiac output by 10–20% and increases stroke volume by 10–15% (85, 86, 89, 91, 93, 119). Clinical studies have reported either no change (85, 86, 89, 93, 112) or modest increases (1–3 mm Hg) (92, 94, 101, 103, 106) in pulmonary artery occlusion pressure. Mean pulmonary arterial pressure is either unchanged (86, 89, 91, 94, 106) or increased slightly (93, 94, 106, 112). The combination of norepinephrine with dobutamine may be attractive in the setting of sepsis. In one study, addition of norepinephrine in patients with septic shock unresponsive to dobutamine significantly improved both mean arterial pressure and cardiac output (120).

Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. In open labeled trials, norepinephrine has been shown to increase mean arterial pressure in patients who remained hypotensive after fluid resuscitation and dopamine (86, 89, 91, 93, 94, 103, 106, 112, 121). Reported doses have ranged from 0.01 to 3.3 μg·kg\(^{-1}\)·min\(^{-1}\) (91, 93). Thus, large doses of the drug may be required in some patients with septic shock, possibly due to α-receptor down-regulation in sepsis (122).

In the only randomized trial comparing vasopressor agents, 32 volume-resuscitated patients with hyperdynamic sepsis syndrome were prospectively randomized to receive either dopamine or norepinephrine to achieve and maintain normal hemodynamic and oxygen transport parameters for ≥6 hrs (106). Dose dopamine administration (10–25 μg·kg\(^{-1}\)·min\(^{-1}\)) resulted in successful treatment in only 31% of patients whereas norepinephrine administration (1.5 ± 1.2 μg·kg\(^{-1}\)·min\(^{-1}\)) was successful in 95% (p < .001). Of the 11 patients who did not respond to dopamine, ten responded when norepinephrine was added (106).

In patients with hypotension and hypovolemia, that is, during hemorrhagic or hypovolemic shock, the vasoconstrictive effects of norepinephrine can have detrimental effects on renal hemodynamics, with the potential for renal ischemia (123–125). The situation may differ in hyperdynamic septic shock (92). Norepinephrine has a greater effect on efferent than afferent renal arteriolar resistance and increases the filtration fraction. Several studies have shown increases in urine output, creatinine clearance, and osmolar clearance in patients with septic shock treated with norepinephrine alone or norepinephrine added to dobutamine (29, 85, 88, 92, 94, 101, 106, 112). These studies support the hypothesis that in fluid-resuscitated patients with septic shock, norepinephrine may optimize renal blood flow and renal vascular resistance (85, 92, 94).

Although early studies in patients with only mildly elevated serum lactate concentrations showed no significant changes over a relatively short period of time (1–3 hrs) with norepinephrine, (89, 101, 103, 112) in a later study in which initial lactate concentrations were elevated (4.8 ± 1.6 mmol/L), a statistically and clinically significant decrease (2.9 ± 0.8 mmol/L) was observed at the end of the 6-hr study period (106). The results of these studies suggest that the use of norepinephrine does not worsen and can even improve tissue oxygenation of patients with septic shock.

Results of studies of the effects of norepinephrine on splanchic blood flow in patients with septic shock have been mixed. In one study, the effect of norepinephrine on splanchic blood flow was unpredictable (103), whereas another study showed that septic patients who switched from dobutamine to norepinephrine or from dobutamine and norepinephrine to norepinephrine alone had a decrease in cardiac output and a parallel decrease in splanchic blood flow (100). In these studies, however, splanchic oxygen consumption remained unchanged (100, 103, 126). One pilot study found that gastric mucosal pH was significantly increased during a 3-hr treatment with norepinephrine whereas it was significantly decreased during treatment with dopamine (101). A more recent study compared the effects of norepinephrine, epinephrine, and dopamine in 20 patients with septic shock (127). In the ten patients with moderate shock, no differences in splanchic blood flow or gastric-arterial PCO\(_2\) difference were observed (127). In the ten with severe shock, cardiac index was higher and the effects of norepinephrine and dopamine were similar, but splanchic blood flow was lower despite a higher cardiac index with epinephrine than with norepinephrine (127).

In summary, the clinical experience with norepinephrine in septic shock patients strongly suggests that this drug can successfully increase blood pressure without causing a deterioration in cardiac index and organ function (128). Used in doses of 0.01–3 μg·kg\(^{-1}\)·min\(^{-1}\), norepinephrine reliably improves hemodynamic variables in most patients with septic shock. The effect of the drug on oxygen transport variables cannot be determined fully from the available data. However, other clinical variables of peripheral perfusion, such as urine flow and lactate concentration, are significantly improved in most studies. Unfortunately, only one report was controlled (106), and whether using norepinephrine in septic shock patients affects mortality rate as compared with dopamine or epinephrine still requires a prospective clinical trial. The available data do not support a detrimental effect of norepinephrine, however. In a recent multivariate analysis including 97 septic shock patients, mortality rate was favorably influenced by the use of norepinephrine as part of the hemodynamic management; use of high-dose dopamine, epinephrine, or dobutamine had no significant effect (129). When the use of norepinephrine is contemplated, it should be used early and not withheld as a last resort (130).

**Phenylephrine.** Phenylephrine, a selective α-1 adrenergic agonist, has been used by rapid intravenous administration to treat supraventricular tachycardia by causing a reflex vagal stimulation to the heart resulting from a rapid increase in...
blood pressure. It is also used intravenously in anesthesia to increase blood pressure. Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis. However, there are concerns about its potential to reduce cardiac output and lower heart rate in these patients.

Unfortunately, only a few studies have evaluated the use of phenylephrine in hyperdynamic sepsis. As such, guidelines on its clinical use are limited. One study in normotensive hyperdynamic septic patients showed that short-term administration of phenylephrine at a dosage of 70 µg/min increased mean arterial pressure, cardiac output, and stroke volume (131). In a dose–response study, phenylephrine administered to normotensive hyperdynamic septic patients in incremental doses of 0.5–8 µg·kg⁻¹·min⁻¹ increased mean arterial pressure, systemic vascular resistance, and stroke index, whereas no change was seen in cardiac index (132). Heart rate was slightly but significantly lower, with a decrease ranging from 3 to 9 beats/min. This study found no statistically significant changes in either oxygen delivery or consumption overall, but a clinically significant (>15%) increase in oxygen consumption was seen in eight of ten patients in at least one dosage.

Only one study has evaluated the effects of phenylephrine in treating hypotension associated with sepsis (95). In a small study of 13 patients with hyperdynamic septic shock (baseline cardiac index 3.3 L·min⁻¹·m⁻²) receiving either low-dose dopamine or dobutamine, who remained hypotensive despite fluid administration (mean arterial pressure 57 mm Hg), phenylephrine was begun at 0.5 µg·kg⁻¹·min⁻¹ and was titrated to maintain a mean arterial pressure >70 mm Hg. Patients required phenylephrine for an average of 65 hrs, and the maximum dosage in each patient averaged 3.7 µg·kg⁻¹·min⁻¹ (range 0.4–9.1 µg·kg⁻¹·min⁻¹). Phenylephrine resulted in an increase in mean arterial pressure, systemic vascular resistance, cardiac index, and stroke index. There was no change in heart rate. A significant increase in urine output without a change in serum creatinine was observed during phenylephrine therapy.

The limited information available with phenylephrine suggests that this drug can increase blood pressure modestly in fluid-resuscitated septic shock patients. In addition, phenylephrine therapy does not impair cardiac or renal function. Phenylephrine may be a good choice when tachyarrhythmias limit therapy with other vasopressors. An increase in oxygen consumption and delivery may occur during therapy.

**Epinephrine.** In patients unresponsive to volume expansion or other catecholamine infusions, epinephrine can increase mean arterial pressure, primarily by increasing cardiac index and stroke volume with more modest increases in systemic vascular resistance and heart rate (90, 133–135). The dose–response relationship is more predictable in some studies (134) than others (90, 133). In patients with right ventricular failure, epinephrine increases right ventricular function by improving contractility (136). Epinephrine can increase oxygen delivery, but oxygen consumption may be increased as well (133–137).

Epinephrine decreases splanchnic blood flow, with transient increases in arterial, splanchnic, and hepatic venous lactate concentrations, decreases in pH, and increases in PCO₂ gap (100, 121, 138). These effects may be due to a reduction in splanchnic oxygen delivery to a level that impairs nutrient blood flow and results in a reduction in global tissue oxygenation, (100, 121) and may potentially be reversed by the concomitant administration of dobutamine (121). Alternatively, CO₂ production secondary to the thermogenic effect of epinephrine may play a role. These studies have been limited by the concurrent use of other catecholamines. Two more recent studies, however, found increased gastric mucosal perfusion with epinephrine compared with norepinephrine alone, to an extent similar to that of norepinephrine in combination with dobutamine (139, 140). In a recent study of 20 patients with septic shock, dopamine was replaced by either norepinephrine or epinephrine. In ten patients with severe shock (mean arterial pressure <65 mm Hg despite high-dose dopamine), epinephrine increased global oxygen delivery and consumption but caused a lower absolute and fractional splanchnic blood flow and lower indocyanine green clearance, thus validating the adverse effects of epinephrine alone on the splanchnic circulation (127).

Epinephrine administration has been associated with increases in systemic and regional lactate concentrations (121, 133, 137). Despite respiratory compensation and decreased arterial PCO₂, the increase in plasma lactate was associated with decreases in arterial pH and base excess (137). The monitoring periods were short, and so it is unclear if these increases are transient; in the one longer study, arterial lactate and pH returned to normal values within 24 hrs (121). Other adverse effects of epinephrine include increases in heart rate, but electrocardiographic changes indicating ischemia or arrhythmias have not been reported in septic patients (133, 134). Epinephrine has had minimal effects on pulmonary artery pressures and pulmonary vascular resistance in sepsis (133, 134).

In summary, epinephrine clearly increases blood pressure in patients unresponsive to traditional agents. However, because of its effects on gastric blood flow and its propensity to increase lactate concentrations, its use should be limited to patients who fail to respond to traditional therapies for increasing or maintaining blood pressure.

**Corticosteroids.** Corticosteroids exert important actions on various elements of the cardiovascular system including the capillaries, the arterioles, and the myocardium. Topical glucocorticoids constrict the dermal vessels, provoking blanching (141), although the mechanisms of this vasoconstriction remain poorly understood. Corticosteroids may up-regulate the sympathetic nervous system and the renin-angiotensin system (142, 143) and also enhance vascular responses to norepinephrine and angiotensin II, possibly through stimulation of the phosphoinositide signaling system in smooth muscle cells (144). Glucocorticoids also inhibit nitric oxide production by inducible nitric oxide synthase (145). Corticosteroids may potentiate catecholamine activity by several mechanisms: increasing phenylethanolamine N-methyltransferase activity and epinephrine synthesis (146), inhibiting catecholamine reuptake in neuromuscular junctions and decreasing their metabolism (147), increasing binding capacity and affinity of β-adrenergic receptors in arterial smooth muscle cells (148), and potentiating receptor G coupling and catecholamine-induced cyclic adenosine monophosphate synthesis (149). Corticosteroids also increase angiotensin II type I receptor expression in vascular smooth muscles (150) and significantly enhance central pressor effects of exogenous angiotensin II (151).

Numerous studies in various animal models, in healthy volunteers challenged with lipopolysaccharide, and in patients...
consistently show that corticosteroids enhance vascular responsiveness to vasoactive agents. In a rodent endotoxemia model, pretreatment with dexamethasone prevented endotoxin-induced vascular hyporesponsiveness to norepinephrine (152), probably by inhibiting extracellular release of lipocortin-1 (153). In a rodent model of hypotensive and hypokineti...
documented in several types of shock during hypovolemia (169) and seems to restore impaired hemodynamic mechanisms in physiologic conditions (166), but vasopressin constrains vascular smooth muscle directly via V1 receptors and also increases responsiveness of the vasculature to catecholamines (166). Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle NO production (167) and K⁺-ATP channels (168).

Normal concentrations of vasopressin have little effect on blood pressure in physiologic conditions (166), but vasopressin helps maintain blood pressure during hypovolemia, (169) and seems to restore impaired hemodynamic mechanisms and also inhibit pathologic vascular responses in shock. Increased concentrations of vasopressin have been documented in several types of shock (170, 171), but a growing body of evidence indicates that this response is abnormal or blunted in septic shock. One study found markedly increased concentrations of circulating vasopressin in 12 patients with cardiogenic shock but much lower concentrations in 19 patients with septic shock, concentrations that were hypothesized to be inappropriately low (172). One potential mechanism for this relative vasopressin deficiency would be depletion of pituitary stores, possibly in conjunction with impaired synthesis. Depletion of vasopressin stores in the neurohypophysis evaluated by magnetic resonance imaging has in fact been described in a small group of septic shock patients (173). A recent prospective cohort study of patients with septic shock found that vasopressin concentrations were almost always elevated in the initial hours of septic shock and decreased afterward; one third of patients developed relative vasopressin deficiency as defined by the investigators (174).

Given this theoretical rationale, several small observational studies have examined the effects of addition of vasopressin to catecholamines in patients with pressor-refractory septic shock. The first report showed that with infusion of low dose of vasopressin (0.04 units/min) in five patients with septic shock, vasopressin plasma concentrations reached 100 pg/ml (a concentration commensurate with those in patients with normal stress responses), and blood pressure increased significantly (172). Discontinuation of vasopressin was followed by a marked decrease in the arterial pressure. Similar findings were noted by the same group with low-dose vasopressin administration in the 19 patients with sepsis and low vasopressin concentrations in the study cited previously (172). Other studies have tested longer infusions. One report examined the effects of infusion of 0.04 units/min of vasopressin for 16 hrs in 16 patients with catecholamine-refractory septic shock and found an increase in mean arterial pressure in 14–16, with stable cardiac output, and increased urine output in the ten patients who were not anuric on study entry (175). In another report, in 50 patients with severe septic shock who had received continuous vasopressin infusion for 48 hrs, mean arterial pressure increased by 18% in the 4 hrs after the beginning of the infusion and then stabilized at 24 and 48 hrs; catecholamine doses were reduced by 33% at the 4th hour (p = .01) and by 50% at the 48th hour (166). Of note, five of the six patients with cardiac arrest during the study had received vasopressin doses >0.05 units/min (166).

Randomized studies of vasopressin infusion have been small. In one, ten patients with hyperdynamic septic shock on catecholamines were randomized to a low dose of vasopressin (0.04 units/min) or placebo (176). The patients who received vasopressin had a significant increase in systolic arterial pressure (from 98 to 125 mm Hg, p < .05) with successful weaning of catecholamines. No variation in arterial pressure was noted in the placebo group. The cardiac index did not differ in the two groups. Before termination of the study at 24 hrs, two of the five patients in the placebo group died of refractory hypotension; there were no deaths during the study in vasopressin-treated patients. Another group randomized 24 patients with septic shock on high-dose vasopressors to a 4-hr infusion of either norepinephrine or vasopressin, with open-label titration of vasopressors to maintain mean arterial pressure (177). In the vasopressin group, norepinephrine doses were significantly reduced at the 4th hour (25 to 5 μg/min, p < .001). Vasopressin doses varied between 0.01 and 0.08 units/min. In the norepinephrine group, doses were not significantly modified. Mean arterial pressure and cardiac index were maintained in both groups, and the gastric CO₂ gradient was unchanged as well. Urine output and creatinine clearance increased significantly in the vasopressin group but did not vary in the norepinephrine group (177).

All of the previously cited studies infused arginine-vasopressin, the vasopressin that is naturally present in humans. Lysine-vasopressin or terlipressin, the vasopressin present in the pig, has been evaluated in patients with septic shock in one reported study (178). Terlipressin administered as a single bolus of 1 mg to eight patients with septic shock refractory to catecholamines, hydrocortisone, and methylene blue improved blood pressure during the first 5 hrs and enabled partial or total weaning of catecholamines (178).

In summary, vasopressin plays an important role in normalizing blood pressure in states of shock. There is evidence that in septic shock, a relative deficiency of vasopressin may contribute to persis-
tent hypotension. Current evidence demonstrates that in catecholamine-resistant septic shock, the addition of low-dose vasopressin (0.01–0.04 units/min) by continuous infusion to catecholamines can be used to increase blood pressure and decrease catecholamine doses. There is concern, however, that vasopressin infusion in septic patients may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa (179, 180). Data examining outcomes and clinical side effects are limited.

Complications of Vasopressor Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. Tachyarrhythmias can occur as well. In patients with significant coronary atherosclerosis, vasopressor-induced coronary artery constriction may precipitate myocardial ischemia and infarction; this is of particular concern in patients treated with vasopressin. In the presence of myocardial dysfunction, excessive vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. Should this occur, the dose of vasopressor should be lowered, or the addition of an inotropic agent such as dobutamine should be considered (91). Vasopressors can also cause limb ischemia and necrosis.

Administration of vasopressors may impair blood flow to the splanchnic system, and this can be manifested by stress ulceration, ileus, malabsorption, and even bowel infarction (121, 137). Gut mucosal integrity occupies a key position in the pathogenesis of multiple organ failure, and countercurrent flow in splanchnic microcirculation gives the gut a higher critical threshold for oxygen delivery than other organs. If possible, episodes of intramucosal acidosis, which might be detected either by a decrease in gastric mucosal pH or an increase in gastric mucosal PCO₂, should be avoided, although no prospective randomized controlled trial has demonstrated a decrease in mortality rate with pHi or gastric PCO₂-directed care in the management of patients with septic shock.

INOTROPIC THERAPY IN SEPSIS

Overview

Sepsis is characterized by a hyperdynamic state with normal to low blood pressure, normal to high cardiac index, and a low systemic vascular resistance (1, 29). Although cardiac output is usually maintained in the volume-resuscitated septic patient, a number of investigations have demonstrated that cardiac function is impaired (97, 181, 182). This myocardial dysfunction is characterized by a decreased ejection fraction, ventricular dilation, impaired contractile response to volume loading, and a low peak systolic pressure/end-systolic volume ratio (a relatively load-independent measure of ventricular function) (183–185). The mechanism of this cardiac dysfunction is complex. Myocardial ischemia is unlikely, as coronary blood flow is normal and there is no net lactate production across the coronary vascular bed (186, 187). Animal studies of endotoxemia or bacterial infection have suggested that myocardial edema (188), alterations in sarcosomal or intracellular calcium homeostasis (189), and uncoupling or disruption of β-adrenergic signal transduction may contribute to the cardiac contractile dysfunction (190). A variety of inflammatory mediators, including prostanoids (191), platelet-activating factor (65), tumor necrosis factor-α, interleukin-1 and interleukin-2, (192), and nitric oxide (193, 194) have been shown to cause myocardial depression in a number of animal models, possibly through the sphinomyelinase pathway (195). Although it is clear that myocardial performance is altered during sepsis and septic shock, end points for cardiac resuscitation are uncertain.

Inotropic therapy in septic shock is complex, because different approaches endeavor to achieve different goals. In patients with decreased cardiac output, the goals of therapy are straightforward and are aimed at restoring normal physiology. Because of the complexity of assessment of clinical variables in septic patients, measurement of cardiac output is advisable. Such measurements need to be interpreted in the clinical context; a patient with preexisting cardiac disease may have a limited ability to increase cardiac output, and thus values within the normal range or even slightly below normal may actually represent a hyperdynamic response for that particular patient. Thus, other end points of global perfusion should be followed as well. When global hyperperfusion is manifested by decreased mixed venous oxygen saturation, this measure may be followed as an index of the efficacy of inotropic therapy. Similarly, although lactate production in sepsis is complex, a decrease in blood lactate concentrations concomitant with increased cardiac output is a good prognostic sign. To further complicate matters, the pharmacokinetics and pharmacodynamics of inotropic agents in septic patients can be quite complex and variable (196, 197).

Some critically ill septic patients are hypermetabolic and may require high levels of oxygen delivery to maintain oxidative metabolism. Data from the 1980s and early 1990s suggested that a linear relationship between oxygen delivery and oxygen consumption (“pathologic supply dependency”) was common in septic patients, (33, 198) with the inference that oxygen delivery was insufficient to meet the metabolic needs of the patient. These observations led to the hypothesis that resuscitation to predetermined elevated end points of cardiac index and oxygen delivery and consumption (“hyperresuscitation”) might improve patient outcome. Retrospective analyses showed that achievement of cardiac index >4.5 L-min⁻¹-m⁻², oxygen delivery >600 mL-min⁻¹-m⁻², and oxygen consumption >170 mL-min⁻¹-m⁻² correlated with improved survival (39). Other investigations, however, have challenged the concept of pathologic supply-dependency and hyperresuscitation (199–202). Although cardiac index and oxygen delivery are correlated with outcome (39), it is unclear if increases in these variables are the cause of increased survival or represent the underlying physiologic reserve of the patient. Randomized studies to test the practice of routinely increasing oxygen delivery to these predefined levels in all critically ill patients have produced conflicting results (199–201, 203, 204), and it is unclear if increases in cardiac index and oxygen delivery are the cause of increased survival or represent underlying physiologic reserve of the patient. Thus, a strategy of routinely increasing oxygen delivery to predetermined elevated end points of cardiac index and oxygen delivery cannot be recommended on the basis of current data (205). Nonetheless, some clinicians believe that this issue has not been settled definitively in
those patients with septic shock and argue that a subset of these patients may benefit from therapy aimed at supranormal oxygen delivery.

Uncertainty exists in regard to other end points for inotropic therapy. Deficits in oxygen delivery can clearly cause a lactic acidosis, but the converse is not true: elevated lactate concentrations in patients with sepsis or septic shock do not necessarily reflect deficits in oxygen delivery (206). In adequately resuscitated septic patients, mixed venous oxygen saturation is usually normal or high, this value correlates poorly with cardiac output, and several studies have questioned the value of SvO₂ as the end point for inotropic therapy in critically ill patients (207, 208). Low mixed venous oxygen saturation may indicate decreased global oxygen delivery, however (207).

Despite seemingly adequate resuscitation, some septic shock patients develop multiple organ failure, resulting in death. It has been argued that even after hypotension has been corrected and global oxygen delivery is adequate in patients with septic shock, blood flow and tissue perfusion can remain suboptimal. Gastric tonometry and sublingual capnometry monitor gastric and sublingual PCO₂ as a proxy for determining the adequacy of gut perfusion. Although these monitors serve as good predictors for the ultimate outcome of critically ill patients (22–25), their utility to guide therapy in patients with sepsis and septic shock has not been proven. In dysoxic states with normal or elevated blood flow, these monitors generally fail to detect an elevated intramucosal-arterial PCO₂ gap (209). No current evidence supports improved outcome with empirical therapy to raise cardiac output in patients with normal blood pressure, but a subpopulation of patients might have regional hypoperfusion that would respond to additional therapy. One would want to titrate such therapy to an index of regional perfusion, although the precise end points are uncertain. In this context, it is important to realize that different interventions to increase oxygen delivery, such as fluid resuscitation, blood transfusion, or infusion of vasoactive agents, can have different effects on regional perfusion (101, 112, 121). Different vasoactive agents have been shown to have divergent effects on gastric intramucosal pH.

An inotropic agent should be considered to maintain an adequate cardiac index, mean arterial pressure, SwO₂, and urine output. Cardiac output can be measured using a pulmonary artery catheter, by echocardiography, with an esophageal Doppler probe, or by pulse contour analysis. Regardless of the measurement method chosen, clinicians should define specific goals and desired end points of inotropic therapy in septic patients and titrate therapy to those end points. These goals and end points should be refined at frequent intervals as patients’ clinical status changes.

Therapies and Efficacy

Most investigations evaluating inotropic agents have been observational and have used the baseline hemodynamic characteristics of the patient as the controls. The majority of these studies have used heart rate, cardiac index or output, and/or stroke volume or stroke volume index as the outcome variables. Only a few studies have assessed ventricular function by reporting left (or right) ventricular stroke work index. The results are summarized in Table 1.

Individual Inotropic Agents

Isoproterenol. Isoproterenol is a β₁- and β₂-adrenergic agonist. Few studies have evaluated isoproterenol in sepsis and septic shock. In septic shock patients with a low cardiac index (mean <2.0 L-min⁻¹·m⁻²), isoproterenol (2–8 µg/min) will significantly increase cardiac index without decreasing blood pressure but at the expense of increasing heart rate (29, 210). In patients with a normal cardiac index, however, isoproterenol can decrease blood pressure through its β₂-adrenergic effects. In addition, the chronotropic effects of β₁-adrenergic stimulation may precipitate myocardial ischemia.

Dopamine. Dopamine is an adrenergic agonist with predominant dopaminergic properties at doses <5 µg·kg⁻¹·min⁻¹ and increased β and α activity at doses >5 µg·kg⁻¹·min⁻¹. However, even at low doses, significant α and β agonism may occur since the pharmacokinetics of dopamine in critically ill patients is highly variable (197).

In patients with severe sepsis and/or septic shock, most studies have shown that dopamine will increase cardiac index with a range from 4% to 44%, left ventricular stroke work index by 5–91%, and right ventricular stroke work index by a modest 5–10% (101, 103, 104, 106, 108, 109, 111–113, 137, 210–213). These improvements in cardiac performance come at the expense of an increase in the heart rate of approximately 15% (range up to 23%). The greatest increase in these variables occurs at doses ranging from 3 to 12 µg·kg⁻¹·min⁻¹. At higher doses, the rate of improvement in cardiac function decreases. Although dopamine may increase mesenteric blood flow, it may also decrease mesenteric oxygen consumption (113). It is not clear whether effects of dopamine are superior to any other adrenergic agent.

Dobutamine. Dobutamine is a racemic mixture of two isomers, a D isomer with β₁- and β₂-adrenergic effects, and an L isomer with β₁- and α₁-adrenergic ef-

| Table 1. Summary of cardiac effects of inotropes used in sepsis and septic shock: Physiologic values are reported as percent change from baseline |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range, µg·kg⁻¹·m⁻¹</th>
<th>Heart Rate</th>
<th>Cardiac Index</th>
<th>Stroke Volume Index</th>
<th>SVRI</th>
<th>LVSWI</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.06 to 0.47</td>
<td>–6 to 27</td>
<td>24 to 54</td>
<td>12</td>
<td>–7 to 34</td>
<td>32 to 95</td>
<td>(135, 138)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.03 to 3.3</td>
<td>–6 to 8</td>
<td>–3 to 21</td>
<td>5 to 15</td>
<td>13 to 111</td>
<td>42 to 142</td>
<td>(135, 138)</td>
</tr>
<tr>
<td>Milrinone</td>
<td>2 to 28</td>
<td>9 to 23</td>
<td>12 to 61</td>
<td>15</td>
<td>–6 to –21</td>
<td>23 to 58</td>
<td>(16, 92, 203, 215–218)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0.5</td>
<td>1</td>
<td>41 to 49</td>
<td>47</td>
<td>–30 to –35</td>
<td>51 to 56</td>
<td>(228, 229)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>1.5 to 18</td>
<td>11 to 20</td>
<td>47 to 119</td>
<td>22 to 89</td>
<td>–24 to –44</td>
<td>74 to 157</td>
<td>(29, 230)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2 to 55</td>
<td>1 to 23</td>
<td>4 to 44</td>
<td>7 to 32</td>
<td>–6 to 18</td>
<td>5 to 91</td>
<td>(102, 104, 105, 107, 109, 110, 112–114, 138, 211–214)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.06 to 0.47</td>
<td>–6 to 27</td>
<td>24 to 54</td>
<td>12</td>
<td>–7 to 34</td>
<td>32 to 95</td>
<td>(135, 138)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.03 to 3.3</td>
<td>–6 to 8</td>
<td>–3 to 21</td>
<td>5 to 15</td>
<td>13 to 111</td>
<td>42 to 142</td>
<td>(135, 138)</td>
</tr>
<tr>
<td>Milrinone</td>
<td>2 to 28</td>
<td>9 to 23</td>
<td>12 to 61</td>
<td>15</td>
<td>–6 to –21</td>
<td>23 to 58</td>
<td>(16, 92, 203, 215–218)</td>
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<td>Milrinone</td>
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<td>(16, 92, 203, 215–218)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0.5</td>
<td>1</td>
<td>41 to 49</td>
<td>47</td>
<td>–30 to –35</td>
<td>51 to 56</td>
<td>(228, 229)</td>
</tr>
</tbody>
</table>

SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index.

*With other inotropes including dopamine, dobutamine, norepinephrine and/or epinephrine.
ects; its predominant effect is inotropic via stimulation of \( \beta_1 \) receptors, with a variable effect on blood pressure.

A number of studies have investigated the effect of dobutamine on cardiac function during sepsis or septic shock at doses ranging from 2 to 28 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (91, 202, 214–218). In these studies, increases in cardiac index ranged from 12% to 61%. However, heart rate increases, often significantly (9–23%). Two studies reported that left ventricular stroke work index increased by 23–58% at mean dobutamine doses of 5–12 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (214, 215). Similar increases in right ventricular stroke work were also observed in these studies.

Although dobutamine does not influence the distribution of blood flow, therapy is often aimed at increasing blood flow to organs such as the gut or the kidneys.

**Epinephrine.** Epinephrine stimulates both \( \alpha \) and \( \beta \) receptors. At low doses, the \( \beta \)-adrenergic effects predominate. A few recent studies have examined the hemodynamic effects of epinephrine in septic shock at doses ranging from 0.1 to 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (134, 135, 137). The increase in cardiac index varied from 24% to 54%, and the heart rate response was variable. Increases in left ventricular stroke work index as high as 95% have been noted (135). Other studies indicated that lactic acidosis is increased and perfusion to the gut is altered with the use of epinephrine (121, 127, 137).

**Norepinephrine.** Like epinephrine, norepinephrine stimulates both \( \alpha \) and \( \beta \) receptors; however, the \( \alpha \)-adrenergic response is the predominant effect. The effect of norepinephrine on cardiac index is modest, with the majority of studies showing no change or increases of up to 21% while heart rate is unaffected or even decreases by up to 8% (91, 93, 101, 103, 106, 112, 119). However, several studies have shown a marked increase in left and right ventricular stroke work index due to increased blood pressure (93, 101, 112, 119).

**Combination and Comparative Studies.** A number of studies have investigated catecholamine combinations (86, 94, 121, 126, 219–222). The majority of these studies did not study the catecholamine combination in a standardized fashion, thus limiting the conclusions that can be drawn about the effects of these catecholamine combinations on cardiac function. Patients who do not respond to dopamine with an increase in cardiac index may reach the desired end point with a dopamine/norepinephrine combination (106). Dobutamine and norepinephrine appear to be an effective combination to improve cardiac index and blood pressure (91). In addition, some (223) but not all (224, 225) studies have shown that dobutamine or a dobutamine/norepinephrine combination will also enhance mesenteric perfusion.

A few investigations have been performed comparing different inotropic regimens (87–90, 101, 112, 121, 137). Epinephrine appears to be as good if not better at improving cardiac performance than dopamine or a dobutamine/norepinephrine combination (121, 137). However, with one exception (140), studies have shown that when epinephrine is compared with other adrenergic agents or their combinations, there are increases in arterial lactate and decreases in gastric intramucosal pH, suggesting that perfusion to regional vascular beds may be impaired (121, 127, 137, 139, 226). In several studies, dopamine increased cardiac index and stroke volume index to a greater extent than norepinephrine, but increases in left and right ventricular stroke volume index were about the same with the two agents (101, 112). There was less prominent tachycardia with norepinephrine, and one unconfirmed pilot study suggested that mesenteric perfusion is impaired with dopamine compared with norepinephrine (101, 112).

**Phosphodiesterase Inhibitors.** Phosphodiesterase inhibitors are vasodilators with long half-lives, raising the potential for prolonged decreases in blood pressure when used in septic patients. There are a few small studies of these agents in patients with sepsis, but meaningful conclusions cannot be made because of the size of the studies and the concomitant use of disparate adrenergic agents (227–230).

**Complications**

In the septic patient who has been inadequately volume resuscitated, all of the inotropic agents can cause significant tachycardia and other cardiac arrhythmias (77). In patients with coexisting coronary disease, the change in myocardial oxygen consumption may precipitate myocardial ischemia and infarction (199). Excessive doses of catecholamines can also result in myocardial band necrosis independent of the presence of coronary disease.

**RECOMMENDATIONS FOR HEMODYNAMIC SUPPORT OF SEPTIC PATIENTS**

**Basic Principles**

1. Resuscitation of patients with sepsis should be initiated expeditiously and pursued vigorously. Measures to improve tissue and organ perfusion are most effective when applied early.

2. Patients with septic shock should be treated in an intensive care unit, with continuous electrocardiographic monitoring and monitoring of arterial oxygenation.

3. Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intra-arterial pressure and to allow beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.

4. Resuscitation should be titrated to clinical end points of arterial pressure, heart rate, urine output, skin perfusion, and mental status, and indexes of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation.

5. Assessment of cardiac filling pressures may require central venous or pulmonary artery catheterization. Pulmonary artery catheterization also allows for assessment of pulmonary artery pressures, cardiac output measurement, and measurement of mixed venous oxygen saturation. Echocardiography may also be useful to assess ventricular volumes and cardiac performance.
The fundamental principle is that clinicians using hemodynamic therapies should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis by monitoring a combination of variables of global and regional perfusion.

Fluid Resuscitation

Recommendation 1—Level B. Fluid infusion should be the initial step in hemodynamic support of patients with septic shock. Initial fluid resuscitation should be titrated to clinical end points.

Recommendation 2—Level B. Isotonic crystalloids or iso-oncotic colloids are equally effective when titrated to the same hemodynamic end points.

Recommendation 3—Level D. Invasive hemodynamic monitoring should be considered in those patients not responding promptly to initial resuscitative efforts. Pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation. Fluid infusion should be titrated to a level of filling pressure associated with the greatest increase in cardiac output and stroke volume. For most patients, this will be a pulmonary artery occlusion pressure in the range of 12–15 mm Hg. An increase in the variation of arterial pressure with respiration may also be used to identify patients likely to respond to additional fluid administration.

Recommendation 4—Level C. Hemoglobin concentrations should be maintained between 8 and 10 gm/dL. In patients with low cardiac output, mixed venous oxygen desaturation, lactic acidosis, widened gastric-arterial PCO₂ gradients, or significant cardiac or pulmonary disease, transfusion to a higher concentration of hemoglobin may be desirable.

Vasopressor Therapy

Recommendation 1—Level C. Dopamine and norepinephrine are both effective for increasing arterial blood pressure. It is imperative to ensure that patients are adequately resuscitated. Dopamine raises cardiac output more than norepinephrine, but its use may be limited by tachycardia. Norepinephrine may be a more effective vasopressor in some patients.

Recommendation 2—Level D. Phenylephrine is an alternative to increase blood pressure, especially in the setting of tachyarrhythmias. Epinephrine can be considered for refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion.

Recommendation 3—Level B. Administration of low doses of dopamine to maintain renal function is not recommended.

Recommendation 4—Level C. Patients with hypotension refractory to catecholamine vasopressors may benefit from addition of replacement dose steroids.

Recommendation 5—Level D. Low doses of vasopressin given after 24 hrs as hormone replacement may be effective in raising blood pressure in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome.

Inotropic Therapy

Recommendation 1—Level C. Dobutamine is the first choice for patients with low cardiac index and/or low mixed venous oxygen saturation and an adequate mean arterial pressure following fluid resuscitation. Dobutamine may cause hypotension and/or tachycardia in some patients, especially those with decreased filling pressures.

Recommendation 2—Level B. In patients with evidence of tissue hypoperfusion, addition of dobutamine may be helpful to increase cardiac output and improve organ perfusion. A strategy of routinely increasing cardiac index to predefined “supranormal” levels (>4.5 L/min·1·m⁻²) has not been shown to improve outcome.

Recommendation 3—Level C. A vasopressor such as norepinephrine and an inotrope such as dobutamine can be titrated separately to maintain both mean arterial pressure and cardiac output.

REFERENCES

15. (V) Friedman G, Berlot G, Kahn RJ: Com-
42. (III) Shoemaker WC: Comparisons of the relative effectiveness of whole blood transfusions and various types of fluid therapy in resuscitation. Crit Care Med 1976; 4:71–78


106. (II) Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treat-


134. (III) Moran JL, M O


Regul Integr Comp Physiol 2001; 280: R171–R1726


169. (V) Juste RN, Moran L, Hooper J, et al: Dopamine clearance in critically ill pa-


Checking the carotid pulse check: diagnostic accuracy of first responders in patients with and without a pulse

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Abstract

International guidelines for cardiopulmonary resuscitation (CPR) in adults advocate that cardiac arrest be recognized, within 5–10 s, by the absence of a pulse in the carotid arteries. However, validation of first responders’ assessment of the carotid pulse has begun only recently. We aimed (1) to develop a methodology to study diagnostic accuracy in detecting the presence or absence of the carotid pulse in unresponsive patients, and (2) to evaluate diagnostic accuracy and time required by first responders to assess the carotid pulse.

In 16 patients undergoing coronary artery bypass grafting, four groups of first responders (EMT-1: 107 laypersons with basic life support (BLS) training; EMT-2: 16 emergency medical technicians (EMTs) in training; PM-1: 74 paramedics in training; PM-2: 9 certified paramedics) performed, single-blinded and randomly allocated, carotid pulse assessment either during spontaneous circulation, or during non-pulsatile cardiopulmonary bypass. Time to diagnosis of carotid pulse status, concurrent haemodynamics and diagnostic accuracy were recorded.

In 10% (6/59), an absent carotid pulse was not recognized as pulselessness. In 45% (66/147), a pulse was not identified despite a carotid pulse with a systolic pressure ≥80 mmHg. Thus, although sensitivity of all participants for central pulselessness approached 90%, specificity was only 55%. Both sensitivity and, to a lesser degree, specificity improved with increasing training; blood pressure or heart rate had no significant effect. The median diagnostic delay was 24 s (minimum 3 s). When no carotid pulse was found, delays were significantly longer (30 s; minimum 13 s), than when a carotid pulse was identified (15 s; minimum 3 s) (P < 0.0001). Of all participants, only 15% (31/206) produced correct diagnoses within 10 s. Only 1/59 (2%) identified pulselessness correctly within 10 s.

Our cardiopulmonary bypass model of carotid pulse assessment proved to be feasible and realistic. We conclude that recognition of pulselessness by rescuers with basic CPR training is time-consuming and inaccurate. Both intensive retraining of professional rescuers and reconsideration of guidelines about carotid pulse assessment are warranted. Copyright © 1996 Elsevier Science Ireland Ltd

Keywords: Cardiopulmonary resuscitation; Cardiopulmonary bypass; Carotid artery; Emergency medical services; Pulselessness; Quality assurance; Resuscitation training

Abbreviations: CPR, cardiopulmonary resuscitation; BLS, basic life support; CP, carotid pulse; EMT, emergency medical technician; ROSC, restoration of spontaneous circulation.

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1. Introduction

The first responder’s correct recognition of cardiocirculatory arrest is the crucial factor in initiating cardiopulmonary resuscitation (CPR). In the majority of prehospital sudden cardiac arrests (SCA), the diagnosis is based on clinical signs and symptoms. According to current American Heart Association (AHA) and European Resuscitation Council (ERC) guidelines, central
pulselessness, to be verified within 5–10 s, remains the diagnostic trigger to start CPR [1–3].

Missing or delaying the diagnosis of cardiocirculatory arrest will reduce a patient’s chance of survival to zero within about 10 min [4]: basic life support (BLS) is not instituted, and the opportunity of rapid defibrillation is lost. On the other hand, failure to recognize vital signs reliably may expose patients to unwarranted attempts at artificial ventilation and chest compressions. This may, at the very least, cause discomfort but may also lead to life-threatening complications, e.g. regurgitation and aspiration of gastric contents, fractures of sternum and ribs, or laceration of intrathoracic and intraabdominal organs [5].

Recently, the ability of lay responders, paramedical and medical personnel to assess a carotid pulse reliably has come under scrutiny: retention of knowledge about carotid pulse checking has been described as modest. Flesche et al. demonstrated that in CPR manikins, only 50% of BLS-trained medical students [6], 17% of experienced ambulance crew members [6] and 3% of BLS-trained lay persons [7] were able to assess unresponsiveness and carotid pulse correctly within 30 s. Only about 10% of paramedical professionals and medical students from three centres in Norway, the United States and Germany were able to detect a mock carotid pulse in manikins [8]. In healthy volunteers, the same test persons needed, on average, 6 s to identify carotid pulsations. In unconscious patients, a BLS-trained medical student subgroup required more than 18 s to detect carotid pulsation; 8% could not verify an existing pulse at all within 120 s [8]. These authors concluded that intensified training is required and questioned the usefulness of teaching CPR to the lay public. These and other investigators’ results were discussed intensely at the 1995 meetings of the International Liaison Committee in Stavanger, Norway, and Atlanta, Georgia.

In the Flesche study, even the subgroup with the best performance in manikins did not meet current guidelines in unconscious patients with pulsatile circulation [8]. It was hypothesized that the experimental setup itself may influence to a large degree the probands’ performance and the results. Therefore, the aims of the following investigation were: (1) to develop a methodology to study the ability of first responders at various stages of CPR training and experience to detect in unresponsive but live patients with variable arterial pressure, rate and rhythm, the presence as well as the absence of a carotid pulse; and (2) to evaluate the accuracy and delay of the diagnostic assessment of a left carotid pulse by first-responder groups who were blinded to the conditions.

2. Patients and methods

2.1. Patients

With preanaesthetic informed patient consent, 16 patients undergoing coronary artery bypass surgery were selected for intraoperative examination by four study groups. All patients had preoperative sonographic evaluation of the supraaortic arterial vessels, and carotid arterial pulses palpable bilaterally. Instrumentation included monitoring of ECG leads II and V5, cannulation of a radial artery, general anaesthesia with endotracheal intubation, and placement of right external or internal jugular vein catheters. Surgery consisted of left internal mammary artery mobilization and saphenous vein graft harvesting, institution of non-pulsatile cardiopulmonary bypass, temporary aortic cross clamping with cardioplegic cardiac arrest, and construction of aortocoronary bypass grafts thereafter.

2.2. Exclusion criteria

Patients with previous surgery or cannulation attempts in the left neck area, thyroid enlargement, sonographic evidence of carotid plaques or stenoses, history or clinical signs of cerebrovascular insufficiency, and hypersensitive carotid sinus reflexes were excluded from the study.

2.3. Study periods

Two periods were selected for carotid pulse assessment:

(1) A period of spontaneous circulation during mobilization of the internal mammary artery, when the systolic arterial pressures were > 80 mmHg. This period lasts about 30 min and is characterized by stability of nociceptive input, anaesthetic level and haemodynamics.

(2) A period of non-pulsatile cardiopulmonary bypass with the aorta cross-clamped. This period also lasts about 30 min, and is characterized by arterial and venous pulselessness at mean arterial pressures of 50–80 mmHg.

2.4. Participants

We tested four groups of first responders with different levels of CPR training.

1 The International Liaison Committee consists of representatives of the American Heart Association (AHA), the Australian Resuscitation Council, the European Resuscitation Council (ERC), the Resuscitation Council of Southern Africa and the Heart and Stroke Foundation of Canada.

2 EMT, substituted in the following for the German Rettungssanitäter, paramedic, for the German Rettungsaufgabenträger.
EMT-1 \((n = 107)\): Laypersons, i.e. emergency medical technician (EMT) students prior to the beginning of a training course; they had, however, already passed an 8-h first aid course, including 4 h BLS.

EMT-2 \((n = 16)\): EMTs in training, i.e. after 4 weeks of theoretical and 6 weeks of practical instruction, including BLS.

PM-1 \((n = 74)\): Paramedics (PM) in training, i.e. after 1 year of theoretical and practical training (BLS, advanced life support).

PM-2 \((n = 9)\): Certified PMs after completion of their 2-year curriculum.

Persons with prior exposure to cardiac surgical operating theatres or cardiopulmonary bypass techniques were excluded from the study. Participants within each group were randomly allocated to either an assessment period during spontaneous circulation or during non-pulsatile cardiopulmonary bypass, and remained blinded to their assignment. They were instructed to identify the presence or absence of a central pulse as quickly as possible, preferably within a time interval of 5–10 s after arrival at the patient’s side, as required by current AHA and ERC guidelines [1–3].

In obtaining informed consent and in preparation for the study, all participants were given the following standardized information:

1. They were to perform carotid pulse checks in anaesthetized patients in the operating theatre.
2. All monitors, the ventilator and the entire operative environment would be shielded from their view by drapes.
3. They would have access to the left carotid only, due to dressings on the right side of the neck.
4. They were free to use their hand as well as their technique of choice for carotid palpation.
5. They should count out the beats loudly as soon as they felt a pulse or, alternatively.
6. They were to state their diagnosis of central pulselessness as soon as possible.
7. The patients could be either with or without a pulse; no further information about the techniques involved was disclosed.
8. In searching for a pulse, they should try to imagine being pressed for time, just as during a real emergency; their diagnostic delay would be measured by stopwatch.
9. They would enter and leave the operating and anaesthesia area without contact with anyone except the investigators.

All participants were treated accordingly during the conduct of the study. They gathered and changed in a separate locker room prior to the study, where they were briefed once more not to communicate their results to colleagues. One of the investigators led them swiftly, one by one, to and from the patient through different doors of the operating theatre. Their entrance and exit from the operating facilities were also kept separate in order to prevent contact between pre- and post-assessment participants. In the operating theatre, haemodynamic monitor screens, the ventilator (Cicero®, Draeger, Luebeck, Germany) and all other components showing respiratory or pulsatile movements, as well as the entire operative, nursing and perfusionist’s environment were barred from the assessors’ view by drapes. Also, acoustic pulse and ventilator signals and alarms were shut off. The surgical staff was instructed, and very cooperative in doing so, not to communicate anything about the stage of the procedure during the assessment periods.

### 2.5. Measurements

The patients’ age, gender, height and weight, neck circumference at the cricoid cartilage, and the distance

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Morphometric patient data (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Pulsatile</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>11/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>42.5 ± 3.2</td>
</tr>
<tr>
<td>Palpable neck length (cm)</td>
<td>7.3 ± 1.1</td>
</tr>
</tbody>
</table>
between left mandibular angle and supraclavicular border of the surgical drapes were recorded. Time from the participant’s arrival at the patient’s side until diagnosis of pulse status was measured in seconds using a stopwatch. During each assessment, a hard copy of concurrent haemodynamic data (ECG rate and rhythm, invasively measured arterial and central venous pressures) was recorded (Sirecust® 1281, Siredoc 200; Siemens, Erlangen, Germany). The diagnosis made by the participant was compared with the objective pulse status of the patient at the time of assessment.

During study periods, each patient was fully monitored by an independent anaesthesiologist using the surgeons’ and perfusionists’ monitor screens.

2.6. Statistical analysis

Diagnostic delay: the percentiles of participants reaching a decision were determined for each second of diagnostic delay up to 1 min. Comparison of time intervals between groups (given as medians and range) were made using non-parametric analysis (Mann-Whitney, Kruskall-Wallis).

Diagnostic accuracy: the ability of the pulse check by the participants to diagnose the patient’s pulse status correctly was assessed by calculation of the sensitivity and specificity of the carotid pulse check for central pulselessness (as the time-critical decision) (Table 1). In this context, sensitivity is the ability to recognize patients on cardiopulmonary bypass with closed aortic cross-clamp as pulseless; specificity is the ability to recognize patients with spontaneous circulation as pulsatile prior to bypass. Diagnostic accuracy denotes the percentage of correct diagnoses among all assessments.

Effect of haemodynamics: Student’s t-test was used to compare blood pressure and heart rate data between different groups.

Significance levels were set at $P < 0.05$ (two-tailed).

3. Results

A total of 206 participants performed pulse checks in 16 patients. There were 147 assessments with, and 59 without, a pulse present. Age, height and weight, neck circumference, or distance between left mandibular angle and supraclavicular border of the surgical drapes (palpable neck length) were not different between pulseless and pulsatile patients (Table 2). There were no perioperative complications related to the assessments, nor any prolongation of, or interference with, anaesthetic or surgical procedures.

Table 3
Diagnostic accuracy for central pulselessness at various training levels

<table>
<thead>
<tr>
<th>Training level</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Diagnostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMT-1</td>
<td>107</td>
<td>32/38 [84%]</td>
<td>25/69 [36%]</td>
<td>57/107 [53%]</td>
</tr>
<tr>
<td>EMT-2</td>
<td>16</td>
<td>6/6 [100%]</td>
<td>3/10 [30%]</td>
<td>9/16 [56%]</td>
</tr>
<tr>
<td>PM-1</td>
<td>74</td>
<td>15/15 [100%]</td>
<td>45/59 [76%]</td>
<td>60/74 [81%]</td>
</tr>
<tr>
<td>PM-2</td>
<td>9</td>
<td>0/0 [n/a]</td>
<td>8/9 [89%]</td>
<td>8/9 [89%]</td>
</tr>
<tr>
<td>All</td>
<td>206</td>
<td>53/59 [90%]</td>
<td>81/147 [55%]</td>
<td>134/206 [65%]</td>
</tr>
</tbody>
</table>

n/a, Not applicable. Other abbreviations as in Section 2 and Table 1.
In 10% (6/59) of assessments, pulselessness was not recognized within 60 s. Three of these six participants erroneously announced a pulse as present, three others could not reach any decision within the allotted time.

In contrast, 45% (66/147) declared the patient pulseless, when a carotid pulse was actually present with a radial arterial systolic pressure of more than 80 mmHg (Fig. 1).

Therefore, the sensitivity of all participants for central pulselessness approached almost 90%, but the specificity was only 55%.

When the results were analyzed between the participating groups, both sensitivity and specificity increased with increasing levels of training. Specificity, i.e. avoidance of false assumptions of pulselessness, did not, however, improve as well as sensitivity, and never
reached 90%, even with full paramedic training (Table 3).

The median delay until a decision about pulse status was communicated to the observer, was 24 s (range 3–60 s) (Fig. 2). The time to decision was longer (32 s; range 12–60 s), if no pulse was present, than in cases with a pulse (22 s; range 3–55 s) \( (P < 0.001) \) (Fig. 3). Also, when participants assumed that they could not find a pulse, they communicated this conclusion significantly later (30 s; range 13–60 s) than when they were sure that they had identified a pulse (15 s; range 3–48 s) \( (P < 0.0001) \) (Fig. 4). Overall training level had a

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**Fig. 4.** Cumulative frequency plot: time intervals from first responders' access to the carotid area until decision about pulsatility, separated according to assumed pulse status. Search for a pulse in apparently pulseless patients delays candidates' decisions considerably. AHA and ERC recommendations are marked as horizontal at 10 s.

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**Fig. 5.** Box plot: time intervals from first responders' access to the carotid area until decision about pulsatility, grouped according to first responders' training. EMT-1: BLS-trained layperson; EMT-2: EMT-in-training; PM-1: paramedic-in-training; PM-2: certified paramedic. Post hoc testing describes largest difference between PM-1 and EMT-1 \( (P < 0.02) \). AHA and ERC recommendations are marked as horizontal at 10 s.
significant effect upon shortening the delay to decision ($P < 0.005$); in particular, group PM-1 was faster in reaching a diagnosis than group EMT-1 ($P < 0.02$ after Bonferroni correction for multiple testing) (Fig. 5).

Altogether, only 16.5% (34/206) participants managed to reach their diagnosis within the time window of 10 s proposed by current international guidelines. Diagnostic accuracy within the first 10 s is listed for all training levels in Table 4. Of these 34, 30 correctly recorded an existing pulse. One correctly identified a pulseless patient, whereas three erroneously recorded pulselessness in pulsatile patients. Thus, only 15% of all participants (31/206) produced correct diagnoses within the recommended 10 s. Moreover, only one of 59 (1.7%) test persons correctly identified pulselessness within 10 s. The assessments in which a present pulse was diagnosed correctly and those in which pulse was erroneously rated as absent did not significantly differ with respect to systolic blood pressure or heart rate during the period of assessment (Fig. 6(a) and (b)).

Neck dimensions had no significant impact on diagnostic accuracy in pulsatile patients. Pulselessness was actually missed more often in patients with smaller neck circumferences and a longer paracervical area accessible to palpation.

4. Discussion

The main findings of our study are as follows: testing the skill of carotid pulse checking in a single-blinded fashion on patients prior to and during non-pulsatile cardiopulmonary bypass appears to be a feasible, safe, reproducible and objective technique. Short of real resuscitation situations, our scenario is as close to prehospital clinical reality as possible, but without time constraints or risks to the patient. With this methodology, we found that neither lay persons nor responders with advanced prehospital training were able to diagnose central pulselessness reliably within the time frame required in the current international guidelines.

Table 4

<table>
<thead>
<tr>
<th>Training level</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Diagnostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMT-1</td>
<td>7/107</td>
<td>n/a</td>
<td>5/7 [71%]</td>
<td>5/7 [71%]</td>
</tr>
<tr>
<td>EMT-2</td>
<td>0/16</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>PM-1</td>
<td>25/74</td>
<td>1/1 [100%]</td>
<td>23/24 [96%]</td>
<td>24/25 [96%]</td>
</tr>
<tr>
<td>PM-2</td>
<td>2/9</td>
<td>n/a</td>
<td>2/2 [100%]</td>
<td>2/2 [100%]</td>
</tr>
<tr>
<td>All</td>
<td>34/206</td>
<td>1/1 [100%]</td>
<td>30/33 [91%]</td>
<td>31/34 [91%]</td>
</tr>
</tbody>
</table>

n, Number of participants in each level reaching a decision within 10 s from access to patient. n/a, Not applicable. Other abbreviations as in Section 2 and Table 1.

These results are in good accordance with the surprisingly poor performance of healthcare providers in manikins, healthy volunteers and ventilated patients described by Flesche [6–8]. Necessarily, in his series, only the manikin trials were blinded, whereas all alive volunteers and ventilated patients obviously had to have pulses. However, even with this bias toward finding pulses, a specially trained subgroup of medical students needed more than 18 s to identify pulses in unconscious ventilated patients [8]. This delay is quite comparable to the median 15 s which our participants needed to identify a pulse, right or wrong.

Our model, however, appears one step closer to reality, since our participants were allocated randomly to either pulsatile or non-pulsatile patients, reducing their bias to detect a pulse in every patient. It nevertheless also has methodological limitations: when testing scores of EMT students, we could not completely exclude that information was exchanged between participants about the technique of achieving 'pulselessness'. The anaesthetist observers could not be blinded to the pulse status since they were familiar with the progress of the surgical procedure. We were not able to randomize pulseless with pulsatile assessments fully, since in an individual patient, pulselessness always followed pulsatility. Also, the higher number of assessments with pulse was due to the technical fact that the time window for pulse assessments during internal mammary artery preparation was usually longer than that during aortic cross-clamping. In this context, we did not consider using the pulsatile post-bypass period, because during this time the anaesthetist needed continuous and unimpeded access to the patient, as well as an unobstructed view at the surgical site.

With regard to diagnostic accuracy, the correct pulse detection rate of 55% in our study contrasts with the respective rate of less than 10% in the manikin series of Flesche et al. [8]. It appears that carotid pulse assessment, even in 'well-developed' manikins, still remains quite unrealistic and much more difficult than in patients. In fact, overemphasis on manikin training might well be counterproductive in the acquisition of clinical skills, which could be honed much easier and better in patients. This may be one mechanism which could account for poor training results reported from several international BLS training programs [8,9]. Again, a live model of 'a pulseless patient' may offer additional opportunities for clinical teaching in BLS.

One major factor of pulse assessment quality in our study is the level of first-responder training. Sensitivity and, to a lesser degree, specificity for pulselessness did improve with advanced training. It is, however, well known that retention of BLS skills is limited to the first 5–6 months after training [10]. Thus it is no surprise that mid-training paramedics performed best in our survey, combining shorter decision intervals, compared
Fig. 6. Diagnostic accuracy in identifying an existing carotid pulse was independent of the patients’ systolic arterial pressure (a) and heart rate (b). Displayed blood pressures of pulseless patients (a) are their mean arterial pressures generated by non-pulsatile cardiopulmonary bypass.

with certified colleagues, with similar diagnostic accuracy. This again supports the findings of Flesche et al., whose paramedic ambulance staff with an average clinical experience of 8 years after qualification were consistently outperformed in basic CPR skills by junior medical students trained recently in BLS [6].

Apart from the problem of diagnostic inaccuracy, the median half-minute delay to the vital ‘no pulse’ decision recorded in our study will, in practice, increase significantly the collapse–defibrillation interval of an emergency medical response (EMS) system in the field. Until now, there are no precise data available on the magnitude of this problem in the preclinical setting.
Furthermore, our results demonstrate clearly that identifying an existing pulse is much easier and shorter than reaching a positive decision of pulselessness in a cardiac arrest victim. This simple problem has not yet been discussed in the literature base for international guidelines, nor in publications on the educational aspects of CPR. Palpating one’s own carotid pulse, or that of another trainee or a ventilated patient, does not indicate a reliable estimate of the diagnostic lag time in a pulseless patient.

Accordingly, our findings put into question the recommendation for a carotid pulse check as part of the initial survey, at least when the first responder is a layperson or has had only occasional exposure to cardiac arrest victims.

Our data also give rise to second thoughts about recommendations for carotid pulse checks later in the course of a resuscitation; according to current guidelines, the effectiveness of compressions has to be evaluated via carotid pulse check by the ventilating rescuer. If the low accuracy and considerable lag time to decision in our series are valid estimates of real performance in national EMS systems, then there is reason to believe that pulse control during BLS by first responders is virtually worthless as a monitoring tool for effectiveness of chest compressions.

In accordance with contemporary teaching, another 5-s pulse check is required, during a prolonged resuscitation, at the end of each CPR sequence and after defibrillation [1–3]. It is, however, well known from invasively monitored defibrillation threshold testing during implantation of internal cardioverter-defibrillator devices, that the first series of beats after a successful countershock produce initially low, but gradually increasing, arterial pulsation. Therefore, according to our results, a real possibility exists that SCA victims who convert into a perfusing rhythm after countershock may frequently be misclassified as post-countershock electromechanical dissociation. It follows that the low specificity for pulselessness of 55% found in our study predicts that there may be more than 40% of cases with ‘pseudo’-post-countershock electromechanical dissociation who will undergo renewed attempts at mechanical CPR. At the very least, this may curtail these patients’ chances of return of a spontaneous circulation [11]. Although the negative impact of inaccurate carotid pulse checks on survival rates after circulatory arrest and CPR is not known, it is potentially not insignificant.

As a perspective for the future, the low sensitivity and specificity of a pulse check by our first responders is in contrast to the diagnostic accuracy of automated external defibrillators’ algorithms for recognition of ventricular fibrillation. Their sensitivity is currently over 96%, and their specificity over 98% [12–17]. Replacing the inaccurate, time-consuming, merely diagnostic instrument of pulse checking by the highly accurate, rapid rhythm analysis of an automated external defibrillator might benefit a large subgroup of SCA victims with good survival chances, especially since immediate defibrillation is the most effective treatment of this condition. After prehospital SCA, only patients in ventricular fibrillation have ultimate survival chances of more than 5%, whereas pulseless electrical activity and asystole have an extremely poor outcome even with aggressive therapy.

In summary, diagnostic inaccuracy and delay in first-responder carotid pulse checks are unacceptably high. Low sensitivity for pulselessness will, at the very least, increase collapse-to-BLS and collapse-to-defibrillation intervals. Low specificity for pulselessness will expose patients with marginal spontaneous circulation, e.g. immediately following restoration of spontaneous circulation, to mechanical and pharmacological irritation of their jeopardized myocardium.

We conclude that current training of first responders, as performed in basic and advanced cardiac life support courses on manikins and during field exposure, is indeed deficient in teaching very basic clinical skills. In particular, training of patient assessment on manikins may not be as effective as it is hoped to be. These deficits appear amenable, but to a limited degree only, to improved and intensified training and retraining in controlled clinical settings of pulselessness. With more studies on this subject, however, we may also be forced to conclude that the guideline of the AHA and ERC to perform a valid carotid pulse check within 5–10 s may be a time-honoured but unrealistic postulate, whose feasibility has just never been corroborated.

References


Challenges in the care of the acutely ill

J F Bion, J E Heffner

Health care providers, hospital administrators, and politicians face competing challenges to reduce clinical errors, control expenditure, increase access and throughput, and improve quality of care. The safe management of the acutely ill inpatients presents particular difficulties. In the first of five *Lancet* articles on this topic we discuss patients’ safety in the acute hospital. We also present a framework in which responsibility for improvement and better integration of care can be considered at the level of patient, local environment, hospital, and health care system; and the other four papers in the series will examine in greater detail methods for measuring, monitoring, and improving inpatient safety.

“It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm.” Florence Nightingale.

Notes on hospitals (London, 1859)

Patients’ safety has come to characterise the first decade of the third millennium just as managed care and cost-containment did the 1990s. According to the much-quoted Institute of Medicine (IOM) report *To err is human,* between 44 000 and 98 000 patients die every year in the USA as a result of clinical errors; the lower estimate makes clinical error the seventh most common cause of death. Health care expenditure incurred as a result of clinical errors is thought to be US$17–29 billion in the USA,1 Au$4–7 billion in Australia,2 and £6 billion in the UK.3,4 Those countries, and also Canada and Denmark, are implementing systems for improving patients’ safety,5 and evidence-based recommendations to improve safety are emerging.6–8

Medical trainees quickly learn—and soon come to accept—that some background rate of clinical error is an unfortunate yet seemingly ineradicable feature of patient care. What is new is the characterisation of clinical error as an epidemic, the recognition that most errors go undetected and unreported, and the realisation that the perceived clinical errors as neither acceptable nor inevitable. In the USA, more than 40% of people report personal or family experiences with clinical errors, and 62% favour public disclosure of serious hospital errors.9

Causation, taxonomy, and detection

Causation

The term medical error has served as a convenient half-truth by which adverse clinical events arising from a presumed chain of causation are attributed to the last link of that chain, usually a doctor or nurse. Health-care institutions have failed to scrutinise the primary elements in a causation pathway10 or search for root causes,11 even though other industries have been implementing error analysis for decades. Error-reduction efforts in health care have focused on the doctor-patient interface that might seem to casual observers to be the most obvious cause of medical accidents. Although failures by clinicians do contribute to unsafe acts, efforts to correct the performance of individual health-care providers seldom contribute to a general improvement in patients’ safety throughout a health-care system.

Studies of human error in industrial and transportation accidents have refocused our understanding of clinical errors as a systems problem that requires systems-oriented solutions. Latent failures embedded in organisational design set the stage for unsafe practices. Failures such as poorly designed equipment and monitoring alarms, paper records with illegible physician orders, and work conditions that promote fatigue and inattention lie dormant within organisations’ structures until a fatigued clinician with poor handwriting, for example, or a high patient turnover triggers error. Heinrich surveyed12,13 industrial accidents in the 1940s and estimated that for every major adverse event there were 29 minor ones and 300 non-injury accidents (near-misses). If similar proportions relate to health care, latent failures represent a tremendous opportunity to improve patient safety.

Even though errors of omission outnumber errors of commission by two to one,1 organisations respond more readily to errors of commission—for example, by addressing the risk of administering highly concentrated potassium solutions intravenously while overlooking failure to correct hypokalaemia, which affects 20% of inpatients and promotes life-threatening cardiac

Search strategy

We focused our review on patients’ safety and the management of the acutely ill hospital patient. To retrieve information about the health care environment, we also searched for publications about health care organisation and emergency services. We used MEDLINE, EMBASE, and Google, to access government publications and “grey” literature, using singly and in paired combination the terms safety, medical error, postoperative complications, emergency medical services, critical care, and intensive care. We discussed the themes extracted from this process with other authors in the series and with professional colleagues worldwide.
arrhythmias.\textsuperscript{15} Health services need to find novel ways of avoiding errors of omission. Routine necropsy provides one opportunity for identifying diagnostic and therapeutic errors but they are less common than they used to be.\textsuperscript{16} Although a systems approach has improved safety in the aerospace and airline industries by identifying and correcting latent errors, systems engineering remains largely untested in health care.\textsuperscript{17}

\textbf{Definitions}

Disagreement exists not only about the precise scale of medical error,\textsuperscript{14,15} the degree of public disclosure required to stimulate safer medical practices,\textsuperscript{10} and the extent to which errors can be eliminated in complex systems,\textsuperscript{22} but also about the terminology.\textsuperscript{17,23} The IOM used an outcomes-based definition: “the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.”\textsuperscript{21} Others define error as latent failures at the systems level that include human, organisational, and technical constraints on performance,\textsuperscript{24} whether there are adverse consequences or not. “Lumpers” include any instance of underuse, overuse, or misuse of medical care\textsuperscript{23} whereas “splitters” confine the definition to failed processes that have been proved to cause adverse outcomes.\textsuperscript{17,23}

These competing taxonomies mesh poorly with the definitions of health care quality on which efforts to improve organisational performance are based.\textsuperscript{25–29} Definitions of quality incorporate concepts of causation, attribution, preventability, and near-misses, which are absent from definitions of medical error. Communication is hampered too; so is research; and the identification and correction of unsafe practices before an adverse event occurs are delayed. The medical errors movement has yet to take full advantage of the principles of outcomes research. For instance, no investigators have comprehensively and prospectively looked at the frequency of clinical errors using a priori definitions to establish causative links between errors and outcomes.\textsuperscript{30}

Most of the studies used for the IOM report were not designed primarily to detect errors; assessors were not masked to outcomes, and the reliability of the measures were not provided. Because trained investigators have poor interobserver agreement in identifying clinical errors from medical record reviews,\textsuperscript{21,30} clinicians justifiably expect prospective, masked, outcome-based studies to determine the dimensions of the problem, identify methods for correcting it, and describe the quality of acute care.\textsuperscript{31}

\textbf{Cultural context}

The causes of error are diverse, often complex, and rarely attributable to single actions, events, or individuals. The causes are usually rooted in unsafe systems rather than individual caregivers. The final common pathway, however, is the interaction between practitioner and patient. This relation has undergone a profound change in the past 50 years. Previously paternalistic, personal, trusting, limited in therapeutic potency and low in expectation of results, patient-clinician interactions have become more equal, transparent, team-based, and contractual. Patients want doctors to communicate more effectively and devote more time to them. Treatments have become more effective and have a correspondingly greater capacity to harm if misused.\textsuperscript{18,19} Increasingly, the public expects medical services to deliver the anticipated results, and on time, and if the outcome is not as anticipated, a culprit must be sought and retribution exacted. In a telephone survey of members of the public in the USA, 50% believed that suspension of licences to practise would be an effective way to prevent clinical error.\textsuperscript{16} Substantial cultural differences also seem to exist between medical disciplines\textsuperscript{33} and between countries\textsuperscript{34,35} in attitudes to error. A reduction in professional authority might have contributed to a lessening of physicians’ sense of personal responsibility for the duration of their patients’ care. Methods for reducing error need to take into account changing doctor-patient relationships and cultural differences.

\textbf{Comparisons with industry}

The safety and error-prevention record for health care services is often compared unfavourably with that of aviation, banking, chemicals, manufacturing, and military services in peacetime, the best of which have highly developed strategies to protect workers and clients. These strategies include a safety culture that emphasises the importance of safe practices, commitment of management to safety, and non-punitive and simplified reporting of errors with feedback of error analyses. Aviation has focused on the importance of working in teams, and lessons learned from crew resource management are starting to be applied to health care.\textsuperscript{16,24} Industries with successful safety records emphasise standardisation of practices combined with flexibility to address unique circumstances. They also invest in safety training and research. This strategy has resulted in substantial reductions in errors and adverse outcomes, with some industries reporting no serious workforce injuries for many years. The IOM has adopted the viewpoint of groups that study “high reliability organisations” (nuclear aircraft carriers, nuclear power plants, and air-traffic control) that successful systems engineering for high levels of safety is achievable.\textsuperscript{27,36}

Health services have, therefore, been encouraged to align their safety efforts with those of industry\textsuperscript{45} and aim for an error rate of less than 3·4 per million events.\textsuperscript{41,42} This is known as “six sigma quality” because it lies outside six SDs of a normal distribution. Anaesthesia has made substantial contributions to patients’ safety through concerted efforts by practitioners and equipment manufacturers to standardise processes. The IOM report\textsuperscript{1} states that deaths attributable to anaesthesia have fallen to 5·4 per million, which approaches five sigma, although the validity of the data that support this observation has been questioned.\textsuperscript{46} The persistence of a steady rate of fatalities in aviation\textsuperscript{22} or road transport\textsuperscript{43} despite increased traffic volume suggests that benefits of safety efforts could be counterbalanced by competing risk factors, such as high throughput, seriously ill patients, and complex interventions. Although industrial experience provides valuable insight into potential solutions for clinical errors, the extent to which it applies to health care remains uncertain. Health care is characterised by highly complex processes, unique problems and needs of individual patients, loosely knit teams, multiple outcome measures, incomplete evidence for many health care decisions, and varying layers of responsibility. In hospitals, unpredictable workloads and uncertainty about individual patients’ outcomes are additional factors. A more appropriate industrial analogy for safe care of the acutely ill patient would be the armed forces contending with the uncertainties of warfare, friendly fire, and “collateral damage”, a distinction which governments seem willing to apply to safety of military personnel.\textsuperscript{14} Health services should learn from other industries but they need models that address the unique challenges of the acute hospital setting.

\textsuperscript{\textit{INPATIENT SAFETY I}}
Error and environment

Although most large safety studies have been in acute care settings, few distinguish between elective admissions and emergency admissions or emergencies during planned treatment. Elective admissions and procedures have well-defined care pathways which facilitate analysis of deviations; emergencies tend to be less predictable. In our view emergency care needs to be seen as a separate entity with a focus on patients’ safety that cuts across disciplines and departments. In view of the pressures to accelerate patient throughput, improved safety will also require better integration of community health care with discharge planning, especially since preventable adverse events might affect 6% of patients after hospital discharge.41

Error in acute care

The risk of adverse events is higher for patients admitted to emergency departments46–48 and general medical wards than for those admitted for elective surgery.49 Clinical errors most commonly affect the elderly,50 who account for most emergency admissions51 and have the highest risk from emergency surgery.52 The risk of error increases when such care is provided, as it often is, by inexperienced clinicians and unsupervised trainees.52–54 The risk of an adverse event increases by about 6% per day for patients admitted as emergencies,55 and is especially high for those needing lifesaving invasive interventions.56

Critical illness increases the opportunity for clinical error57–59 because of the complexity of patients’ problems and the frequency of invasive interventions. The intensity of monitoring in critical care units means that errors are more likely to be detected. Iatrogenic complications are a common cause of admission to intensive care,60 and previously suboptimal care is associated with an increased mortality in the intensive care unit.61 Cardiopulmonary arrest in hospital is frequently preceded by warning signs62 and can be prevented by interventions to identify and manage patients earlier.63 Premature discharge from intensive care is associated with increased in-hospital mortality.64 These factors confirm the need for a systems approach to error prevention.

Effect of case-mix

The greater risk of clinical errors in emergency admissions is especially alarming because of the increasing demand for emergency care.65,66 In the USA, emergency admissions constitute more than a third of all hospital admissions, 41% of admissions of children, and 55% of admissions of patients older than 80 years. 54% have at least one comorbid condition and a third have two or more.67 Age and comorbid disease add to the risk of adverse events68 either from limited physiological reserve or because of exposure to more interventions. In the UK, about 60% of hospital admissions are emergencies, and the proportion has been increasing yearly by 2-1% since 1989, when data were first collated. For patients older than 65 years, the annual increase is 3-3%.69

Changes in service provision

In many developed countries the need for emergency services has been growing in parallel with pressures to reduce length of stay and numbers of beds.70 For example, day-cases account for an increasing proportion of elective admissions. In the UK, the number of National Health Service beds fell from 480,000 in 1948 to 190,000 in 1998, throughput and occupancy have increased, and length of stay has shortened.71 Many regions in the USA have shortages of beds and face the need to replace old hospitals, and increasingly crowded emergency depart-

ments have a statutory obligation to provide care for the 46 million Americans who carry no health insurance. These pressures can represent a substantial hindrance to efforts to improve safety.

Poor integration of acute hospital services can also contribute to error. Market forces in the USA promote competition between neighbouring facilities, often resulting in redundant services. In the UK, however, a desire for convenient local access causes acute hospitals to proliferate, preventing economies of scale when nearby hospitals replicate specialist services, a tension reflected in abrupt changes in governmental planning.72 This lack of integration dilutes professional experience, including operative procedures, and lowers competency and quality of outcomes.

Working hours

To provide safe acute care means employing adequate numbers of trained staff, which is increasingly difficult in the European Union because the Working Time Directive, from August, 2004, limits the working hours for trainee doctors to 56 per week and to an average of 48 for all employees by 2009. “Work” is defined as “required to be present at the health centre” regardless of the activities being undertaken. This ruling has important implications for out-of-hours and emergency care39 since being asleep in an on-call bedroom will still count as work. In the USA, resident physicians in training have, since July, 2003, been limited to an average of 80 h a week.73 Comparison of the effects of the European and American regulations should prove useful, in view of evidence that fatigue from long hours of work impairs patient safety.74

Concerns have been expressed that these constraints may adversely affect training and acquisition of skills.75 They will certainly strain services in countries that have a physician shortage. It will not be possible to train enough extra doctors in the UK to fill the gap created by the European directive before 2015. Reliance on non-physician care-givers may improve the delivery of preventive medicine and enhance performance of specific tasks but does not seem to improve acute care.76 Moreover, the worldwide shortage of nurses77 restricts the large-scale transfer of traditional physician duties. A more constructive approach for maintenance of patients’ safety in acute care would be to focus on models of team-working rather than transferring work to other groups.

Discontinuities in patient care

Hospital medicine has become increasingly compartmentalised, with blurred borders of responsibility and multiple transitions (“hand offs”) between different health care providers and teams.78 The benefits of reduced fatigue from restricted hours of work for medical staff may be offset by the discontinuities in care and personal isolation caused by shift-working, the greater risk of communication failures, and constraints on the delivery of clinical education. A clinical vignette illustrates the problems (panel).

This patient did not have just one illness and nor did she have a distinct medical error that resulted in a well-defined adverse event. She had several comorbidities, was exposed to high-risk interventions with known side-effects, and was treated in an acute care environment with insufficient safeguards against clinical error. Potentially avoidable adverse events were caused by faulty actions and inactions, suboptimal training, poor supervision, and inadequate service provision at local and national levels. However, establishing a root-cause would be difficult because of the varied, diffuse, and overlapping failures.
A 56-year-old woman was admitted on a Saturday evening to a university teaching hospital with progressive malaise, diffuse abdominal pain, and diarrhoea 1 week after chemotherapy for breast cancer. 10 years previously she had had cancer in the other breast and had undergone mastectomy with radiotherapy. She was on warfarin for an auxiliary vein thrombosis caused by a Hickman catheter and had a history of penicillin allergy. She was apyrexial, tachypnoeic, hypotensive, and oliguric; total leucocyte count of less than 0·1 x 10^9/L, platelets 70 x 10^9/L, serum creatinine 170 μmol/L, and international normalised ratio 6·2. Blood culture produced gram-negative rods within 12 h.

She was treated by the resident medical staff in the emergency unit with piperacillin and gentamicin, inadequate intravenous fluids, parental non-steroidal anti-inflammatory analgesics, and diuretics. She had a head injury after falling unobserved from the commode where she had been placed by the nursing assistants, who then sat her in a chair despite a documented systolic blood pressure of 70 mm Hg. There were only two trained nurses on duty for this 28-bed ward. She was eventually seen by a consultant 24 h after admission, and was referred to intensive care in neutropenic septic shock with multiple organ failure.

Because no bed was immediately available in the intensive care unit, mechanical ventilation and cardiovascular support were started in the ward. Preparations for transfer to another hospital were cancelled when an appropriate bed did become free. Shortly after admission she developed a transient rash that was attributed to piperacillin, already discontinued. A CT scan showed a small subdural haematoma that did not need intervention other than correction of the coagulopathy. Renal replacement treatment was needed. During her 4 weeks in intensive care, she developed a ventilator-associated pneumonia and became colonised with meticillin-resistant Staphylococcus aureus. After being discharged to the ward, she developed bacteraemia from a central venous catheter that had been left in place several days longer than intended and needed a brief re-admission to intensive care.

She returned home 2 months later, weak but able to look after herself. Her husband confided that he was surprised by the contrast between the quality of care in the intensive care unit compared with that on the ward.

Vincent and colleagues have developed a structured approach for analysis of such episodes, combining the factors that affect clinical practice with Reason’s organisational model of error. We have adapted this model, bringing in elements from the quality literature (table), as a method for assessment safe care of the acutely ill patient.

Responding to the challenge

Our perspective is that safety and reliability are the most important components of quality in health care and that services need extensive restructuring to achieve an acceptable level of these characteristics of high quality care. The restructuring demands a systems approach. In the panel, we identify deficiencies in resources and organisation, processes and delivery of care, monitoring, clinical competence, communication, continuity of care, therapeutic interventions including prescribing, leadership and governance, and patient empowerment. We classify these deficiencies as occurring at the four levels of patient, microsystem, organisation, and environment, a classification that allows consideration of quality and safety issues from different perspectives. What follows is a summary of some of these issues. The next four articles in this Lancet series will go into more detail, looking at the monitoring of and improvements in safety for the acute inpatient, both from a local and a systems standpoint.

Resources and organisation

Emergency departments

Safe emergency care needs prompt access to initial treatment for life-threatening emergencies, and hospitals cannot provide that if their emergency departments are overloaded by medical problems that could have been managed by a family practitioner or a pharmacist. Patients cannot obtain prompt treatment without either adequate local facilities or an efficient ambulance service. In large hospitals, parallel provision of primary and secondary care within the emergency department improves efficiency and focuses resources on sicker patients. Small and rural acute hospitals will need local solutions to professional staffing that include shared management of the emergency department by community practitioners, consultation available via telemedicine links, and appropriately staffed rapid transport to take more seriously ill patients to better-equipped centres. This hub-and-spoke integration is well-accepted for paediatric emergency care.

Models for delivering acute care

Future clinicians who provide core services in the acute-hospital setting will need new skill sets, which will be transdisciplinary and especially suited to the range of health care needs of hospital patients. Physicians, nurses, pharmacists, and other health-care providers will develop team-based models of care that avoid gaps in knowledge and services. These gaps constitute an important risk for patient safety. Essential skill sets will draw on anaesthesia, internal medicine, surgery, accident and emergency medicine, basic sciences, and ethics whereas behavioural competencies will learn from aviation and crew resource management. Critical care medicine illustrates this development. Intensivists (ie, intensive care specialists) have become the general practitioners of acute care. They have adopted multidisciplinary collaboration, contributed to systems management within intensive care, and emphasised intervention at the first signs of clinical instability. Integrative models with well-organised systems within intensive care units have reduced mortality, and the appointment of intensivists is a key recommendation of the Leapfrog Group in the USA for improving hospital safety.

In the USA, acute hospital care has been developed into a professional track termed hospital medicine practised by the “hospitalist”. Australian hospitals have extended intensive care services and personnel into hospital wards by creating medical emergency teams. The UK has outreach care provided by critical-care-trained nurses for patients admitted to the wards. Such outreach detects early signs of clinical deterioration and improves communication between ward admitting teams and staff in intensive care units. Although there are no comparative data to favour one model over another, studies suggest that early intervention might reduce cardiac arrest rates, though there is a risk that the point of death could merely be shifted to the ICU. Better integration should also extend into post-hospital recovery. We are only just beginning to identify the safety limits of this approach, and patient outcomes will determine how far we move beyond the limit of feasibility.
issues of post-discharge care, though we know that the physical consequences of critical illness persist.

**Processes and delivery of care**
Providing evidence-based interventions in a coordinated and prompt manner to patients with complex health problems defy the human abilities of inpatient practitioners. With over 30 000 new publications entering the MEDLINE database each month, clinicians need knowledge pathfinders to assist their decision-making. Safe care of patients will need greater reliance on clinical pathways, clinical practice guidelines, and decision support tools. No longer “physician-centric”, transdisciplinary teams will undertake their clinical responsibilities in an integrated manner using guidelines and protocols. A team approach using treatment algorithms has achieved more rapid weaning of ventilator-dependent patients compared to traditional monitoring in the acute hospital often identifies adverse events only after they occur. Reactive systems, based on instructions to call a doctor if there are major changes in vital signs, should be replaced by proactive monitoring to identify early changes and empower ward staff to call for help and initiate further investigation to prevent or limit the magnitude of adverse events.

**Information management and communication**
Failures of communication between health-care providers and between clinicians and patients are common causes of error and litigation. Training in communication skills will be especially important for multidisciplinary teams functioning in rapid-paced inpatient settings. The electronic medical record and computerised physician order entry (prescription system) offer opportunities to provide clinicians with an electronic platform that embeds decision support and knowledge resources to promote best practice. Computerised prescribing should improve patient safety by reducing documentation and by warning of potential drug interactions, contraindications, dosing adjustments, and allergies. Evidence is emerging for benefits from error reduction and improved decision making, and computer-assisted record keeping and prescribing are among the interventions recommended by the Leapfrog Group.

Information technology does need staged “bottom-up” development, pilot testing, and appropriate implementation into existing hospital cultures. Greater dependency on computerised systems creates new safety issues when the system fails. However, health services for the most part still depend on the oral transmission of information supported by handwritten records. It does seem logical to build on the progress with computerised prescribing, and develop an electronic patient record with modules for investigations, diagnosis, interventions, and outcomes.

**Monitoring and analysis**
Early warning systems
Traditional monitoring in the acute hospital often identifies adverse events only after they occur. Reactive systems, based on instructions to call a doctor if there are major changes in vital signs, should be replaced by proactive monitoring to identify early changes and empower ward staff to call for help and initiate further investigation to prevent or limit the magnitude of adverse events.

**Adverse event and error monitoring**
Adverse event reporting is essential for improving patient safety but current methods are unsatisfactory. Major events may be more reliably reported, but near-misses are likely to be ignored, deferred, or forgotten in the pressured environment of clinical work. Barriers include cumbersome and non-standardised paper formats; a litigious culture that deters open reporting and discussion; difficulty with identifying and reporting errors of omission; a long interval between intervention and adverse outcome (for example, nosocomial infection); deficiencies in information synthesis, analysis, and feedback; and failure of institutions to address improvements in processes of care. Whether incident reporting should be process or outcomes based remains unclear.
Hospitals need data collection systems that allow providers to enter information anonymously and easily. Intranet-based online systems with automated analysis and reporting to directors of patient safety and hospital executives should improve institutional responsiveness.\(9\)\(10\)\ Collation of institutional data by regulatory or governmental agencies should make it easier to detect patterns and recommend improvements. The US University Health System Consortium has an internet-based reporting system; the Joint Committee on Accreditation of Healthcare Organisations encourages voluntary reporting of sentinel events; and four agencies within the US Department of Health and Human Services are integrating their data systems on clinical errors or adverse events. These developments will increase the pressure for public disclosure of patient safety records but such data must accurately reflect the quality of care and the hospital’s case-mix. So far, no such data collection systems exist.

**Competency-based training**

Many of our proposals need investment in new ways of training health care personnel. Traditional teaching has been specialty-based. Evidence of the trainee’s success in making the transition to independent practitioner has rested on the completion of training of the required duration followed by a formal examination. This model has not facilitated horizontal integration of trainees across disciplines, and it has inhibited the sharing of knowledge and skills, and impeded collaboration and team building. The focus on knowledge assessment also produces a barrier between the curriculum and desirable educational outcomes. This is now starting to change with the development of competency-based training.

Competency-based training replaces time-based training. The process of defining areas of competence and mapping it to the core curriculum promotes integration of common elements across specialties. Patients’ safety will become one such core competency. The UK has a competency-based training programme for multidisciplinary intensive-care medicine,\(10\)\(11\) and proposals are being developed for a similar approach across Europe. The US Accreditation Council for Graduate Medical Education has also restructured postgraduate medical education around competency-based “outcomes”.

The same educational principles must be applied in the undergraduate setting but undergraduate curricula remain largely silent on patients’ safety.\(12\)\(13\) One method by which undergraduates can learn the basic principles of patients’ safety and team-working in acute care is by provision of transdisciplinary peer-led tuition in resuscitation and emergency care, training senior students to act as tutors and role models in multidisciplinary groups.\(14\)\(15\)

**Governance: taking responsibility for change**

To achieve improvements in acute patient safety in the current climate and across different health care systems will take many years, but the process has started. Classen\(16\) proposes four evolutionary stages: building awareness; development of organisational learning; proactive management of risk; and establishment and maintenance of high reliability organisations.\(17\) Progress through these stages will need a multiplicity of approaches, from step-change at a local level to strategic planning at national and international levels. It will also need the establishment of common goals and shared responsibilities as we build partnerships between the public, practitioners, politicians, administrators, insurers, and educators.

Health care providers cannot be passive in this process but must lead it, if they are to show patients that they are worthy of public trust, and they must lead by example and from the front. This in turn requires commitment from the public, from politicians and from administrators to provide an infrastructure that facilitates safe care and to support those responsible for delivering it.

**Conflict of interest statement**

None declared.

**References**


85 pizza L, Goldfarb NI, Nash DB. Crew resource management and its


Volume expansion is frequently used in critically ill patients to improve hemodynamics. Because of the positive relationship between ventricular end-diastolic volume and stroke volume, the expected hemodynamic response to volume expansion is an increase in right ventricular end-diastolic volume (RVEDV), left ventricular end-diastolic volume, stroke volume, and cardiac output. The increase in end-diastolic volume as a result of fluid therapy depends on the partitioning of the fluid into the different cardiovascular compliances organized in...
series. The increase in stroke volume as a result of end-diastolic volume increase depends on ventricular function since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume. Therefore, only 40 to 72% of critically ill patients have been shown to respond to volume expansion by a significant increase in stroke volume or cardiac output in studies designed to examine fluid responsiveness. This finding emphasizes the need for predictive factors of fluid responsiveness in order to select patients who might benefit from volume expansion and to avoid ineffective or even deleterious volume expansion (worsening in gas exchange, hemodilution) in nonresponder patients, in whom inotropic and/or vasopressor support should preferably be used.

Bedside indicators of ventricular preload have been proposed as predictors of fluid responsiveness. In this regard, a postal survey in Germany showed that right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) are used by a majority of ICU physicians when deciding to administer fluid, and several recommendations support the use of cardiac filling pressures in order to guide fluid therapy in critically ill patients. Other bedside indicators of ventricular preload, namely RVEDV and left ventricular end-diastolic area (LVEDA), have also been tested as predictors of the hemodynamic effects of volume expansion in critically ill patients.

The respiratory changes in RAP, arterial pressure, and aortic blood velocity, assumed to be dynamic indicators of the sensitivity of the heart to changes in preload induced by changes in pleural pressure, have also been proposed to predict fluid responsiveness in critically ill patients. Therefore, the aim of the present study was to analyze the clinical studies investigating predictive factors of fluid responsiveness in critically ill patients in order to assess the value of each parameter tested.

Materials and Methods

Selection of Studies To Be Evaluated

We collected studies investigating the predictive factors of fluid responsiveness in critically ill patients by doing a search in MEDLINE (from 1966). Studies were selected according to the following criteria: volume expansion performed in critically ill patients, patients classified in two groups (responders and non-responders) according to the effects of volume expansion on stroke volume or on cardiac output, and comparison of responder and nonresponder patients characteristics before volume expansion. The reference lists of the selected articles were scanned for additional studies. Of the 12 included studies, 11 studies were identified from the electronic database and 1 study was identified from reference tracing. The main characteristics of these studies are presented in Table 1.

Parameters Tested as Predictors of Fluid Responsiveness

Ten studies have investigated the value of ventricular preload indicators in predicting fluid responsiveness. The parameters tested were RAP in five studies, PAOP in nine studies, and RVEDV in six studies, and

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Fluid Infused</th>
<th>Volume Infused, mL</th>
<th>Speed of FC, min</th>
<th>Definition of Response</th>
<th>Rate of Response, %</th>
<th>Parameters Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvin et al</td>
<td>28 28</td>
<td>5% Alb</td>
<td>250</td>
<td>20–30</td>
<td>ΔSV &gt; 0%</td>
<td>71</td>
<td>RAP, PAOP, RVEDV</td>
</tr>
<tr>
<td>Schneider et al</td>
<td>18 18</td>
<td>FFP</td>
<td>500</td>
<td>30</td>
<td>ΔSV &gt; 0%</td>
<td>70</td>
<td>RAP, PAOP, RVEDV</td>
</tr>
<tr>
<td>Reuse et al</td>
<td>33 33</td>
<td>9% NaCl</td>
<td>100–950</td>
<td>30</td>
<td>ΔCO &gt; 250</td>
<td>32</td>
<td>ΔRAP</td>
</tr>
<tr>
<td>Diebel et al</td>
<td>15 22</td>
<td>R. lactate Colloids</td>
<td>300–500</td>
<td></td>
<td>ΔCO &gt; 10%</td>
<td>59</td>
<td>PAOP, RVEDV</td>
</tr>
<tr>
<td>Diebel et al</td>
<td>32 36</td>
<td>R. lactate Colloids</td>
<td>300–500</td>
<td></td>
<td>ΔCO &gt; 250</td>
<td>52</td>
<td>PAOP, RVEDV</td>
</tr>
<tr>
<td>Wagner and Leatherman</td>
<td>25 57</td>
<td>9% NaCl</td>
<td>938 ± 48</td>
<td>7–12</td>
<td>ΔSV &gt; 10%</td>
<td>40</td>
<td>PAOP, RVEDV</td>
</tr>
<tr>
<td>Tavernier et al</td>
<td>65 65</td>
<td>5% Alb, FFP</td>
<td>574 ± 157</td>
<td></td>
<td>ΔSV &gt; 10%</td>
<td>56</td>
<td>PAOP, RVEDV</td>
</tr>
<tr>
<td>Magder and Lagonidis</td>
<td>15 29</td>
<td>25% Alb</td>
<td>100–150</td>
<td></td>
<td>ΔCO &gt; 15%</td>
<td>45</td>
<td>ΔRAP</td>
</tr>
<tr>
<td>Tousignant et al</td>
<td>36 36</td>
<td>9% NaCl</td>
<td>150–400</td>
<td></td>
<td>ΔSV &gt; 20%</td>
<td>40</td>
<td>PAOP, RVEDA</td>
</tr>
<tr>
<td>Michaud et al</td>
<td>40 40</td>
<td>HES</td>
<td>500</td>
<td>30</td>
<td>ΔCO &gt; 15%</td>
<td>40</td>
<td>PAOP, ΔPP</td>
</tr>
<tr>
<td>Feissel et al</td>
<td>19 19</td>
<td>HES</td>
<td>8 mL/kg</td>
<td>30</td>
<td>ΔCO &gt; 15%</td>
<td>53</td>
<td>ΔLVEDA, ΔVpeak</td>
</tr>
<tr>
<td>Total</td>
<td>334 406</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

*FC = fluid challenge; Alb = serum albumin; FFP = fresh frozen plasma; NaCl = serum saline solution; R. lactate = Ringer’s lactate; HES = hydroxyethylstarch; ΔSV = volume expansion-induced changes in stroke volume; ΔCO = volume expansion-induced changes in cardiac output.*
LVEDV in three studies (Table 1). In all studies, the RAP and PAOP were measured at end-expiration without ventilator disconnection or removal of positive end-expiratory pressure (PEEP). In four studies, RVEDV was calculated from the measurement of right ventricular ejection fraction and cardiac output by using a fast-response thermistor pulmonary artery catheter as follows: RVEDV = (cardiac output/heart rate)/right ventricular ejection fraction. In two other studies, RVEDV was evaluated by cardiac scintigraphy. LVEDA was measured by transesophageal echocardiography using the transgastric short-axis view of the left ventricle.

Five studies have investigated the value of dynamic parameters in predicting fluid responsiveness. These parameters were the inspiratory decrease in RAP (ΔRAP) in two studies, the expiratory decrease in arterial systolic pressure (Δdown) in one study, the respiratory changes in arterial pulse pressure (ΔPP) in one study, and the respiratory changes in aortic blood velocity (ΔVpeak) in one study (Table 1). The ΔRAP was calculated as the difference between the expiratory and the inspiratory RAP. The Δdown was calculated as the difference between the maximal and minimal value of systolic pressure over a single respiratory cycle. The ΔPP was calculated as the difference between the maximal and minimal value of pulse pressure over a single respiratory cycle, divided by the mean of the two values, and expressed as a percentage. The ΔVpeak was calculated as the difference between the maximal and minimal peak velocity of aortic blood flow over a single respiratory cycle, divided by the mean of the two values, and expressed as a percentage.

Aortic blood flow was measured by a pulsed-wave Doppler echocardiographic beam at the level of the aortic valve.

### Results

There were 406 fluid challenges in 334 patients (Table 1). Most of the patients were septic (55%) and receiving mechanical ventilation (84%). The decision of volume expansion was based on criteria listed in Table 2. Fluid administration was performed using colloid solutions (albumin, fresh frozen plasma, or hydroxyethylstarch) in 253 instances, and crystalloid solutions (serum saline solution or Ringer’s lactate) in 153 instances (Table 1). In nine studies, the volume infused was predetermined and ranged from 250 to 500 mL for colloids and from 300 to 500 mL for crystalloids (Table 1). In two studies, volume infusion was performed until a rise in RAP ≥ 2 mm Hg was obtained; hence, the volume of serum saline solution infused varied from 100 to 950 mL. In another study, fluid was administered until a rise in PAOP ≥ 3 mm Hg was obtained. In this case, the volume infused was 938 ± 480 mL for serum saline solution and 574 ± 187 mL for 5% albumin or fresh frozen plasma. The speeds of fluid infusion are reported in Table 1. In all studies but one, hemodynamic measurements were performed just before and immediately at the end of fluid infusion.

The hemodynamic response to volume expansion was defined by an increase in stroke volume in five studies and in cardiac output in seven studies (Fig 1). The values of stroke volume or cardiac output increase used to define responder and nonresponder patients are presented in Table 1.

### RAP

Before volume expansion, RAP was not significantly lower in responders than in nonresponders in three of five studies (Fig 1). The two remaining studies reported a lower value of baseline RAP in

### Table 2—Criteria Used to Decide Volume Expansion

<table>
<thead>
<tr>
<th>Source</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvin et al12</td>
<td>Cardiac index &lt; 3.5 L/min/m² and PAOP &lt; 12 mm Hg in septic and trauma patients</td>
</tr>
<tr>
<td>Schneider et al13</td>
<td>Cardiac index &lt; 2.5 L/min/m² and PAOP &lt; 20 mm Hg in acutely ill patients with a defined cardiac cause</td>
</tr>
<tr>
<td>Reuse et al4</td>
<td>Systemic infusion in patients with septic shock</td>
</tr>
<tr>
<td>Magder et al5</td>
<td>Systolic BP &lt; 90 mm Hg or cardiac index &lt; 2.5 L/min/m² or heart rate &gt; 120/min or decreased urine output (&lt; 25 mL/h)</td>
</tr>
<tr>
<td>Diebel et al6</td>
<td>Clinical impression that the cardiac output was inadequate for tissue needs and would respond to volume loading</td>
</tr>
<tr>
<td>Diebel et al6</td>
<td>Oliguria (urine output &lt; 30 mL/h) or hypotension or in an attempt to optimize oxygen delivery</td>
</tr>
<tr>
<td>Wagner and Leatherman8</td>
<td>In an attempt to increase oxygen delivery to &gt; 600 mL/min/m² or to reach a plateau in the oxygen consumption-delivery relationship</td>
</tr>
<tr>
<td>Tavernier et al9</td>
<td>Sepsis-induced hypotension (systolic BP &lt; 90 mm Hg or its reduction by ≥ 40 mm Hg from usual values)</td>
</tr>
<tr>
<td>Magder and Lagonidt10</td>
<td>As part of routine testing to assess cardiac filling status if PAOP ≤ 18 mm Hg</td>
</tr>
<tr>
<td>Tousignant et al11</td>
<td>PAOP &lt; 20 mm Hg or inotropic support or low urine output and adequate gas exchange</td>
</tr>
<tr>
<td>Michaud et al12</td>
<td>Systolic BP &lt; 90 mm Hg or the need of vasoactive drugs (dopamine &gt; 5 µg/kg/min or norepinephrine)</td>
</tr>
<tr>
<td>Feissel et al13</td>
<td>Systemic infusion in septic shock patients with preserved left ventricular systolic function and PaO2/Fio2 &gt; 100 mm Hg</td>
</tr>
</tbody>
</table>

*Fio2 = fraction of inspired oxygen.
responders than in nonresponders (Fig 1), and a significant relationship between the baseline RAP ($r^2 = 0.20$), and the increase in stroke volume in response to volume expansion was reported by Wagner and Leatherman. However, the marked overlap of individual RAP values did not allow the identification of a RAP threshold value discriminating responders and nonresponders before fluid was administered.

**PAOP**

Before volume expansion, PAOP was not significantly lower in responders than in nonresponders in seven of nine studies$^{2–4,6,7,9,12}$ (Table 3). Three studies$^{6,8,11}$ reported a significant difference between the baseline value of PAOP in responders and nonresponders (Table 3). In the first study,$^6$ the mean value of PAOP was significantly higher in responder patients ($14 \pm 7$ mm Hg vs $7 \pm 2$ mm Hg, $p < 0.01$). In contrast, the two other studies$^{8,11}$ reported a significantly lower value of PAOP at baseline in responders than in nonresponders (Table 3), and a significant relationship between the baseline PAOP ($r^2 = 0.33$) and the increase in stroke volume in response to volume expansion was reported by Wagner and Leatherman. However, in none of these studies, a PAOP cutoff value was proposed to predict the hemodynamic response to volume expansion before fluid was administered.

**RVEDV**

Before volume expansion, RVEDV index was not significantly lower in responders than in nonresponders in four of six studies$^{2–4,8}$ (Fig 2). In the two remaining studies of Diebel et al,$^6,7$ RVEDV index was significantly lower at baseline in responders than in nonresponders (Fig 2), RVEDV index $< 90$ mL/m$^2$ was associated with a high rate of response (100% and 64%, respectively), and RVEDV index $> 138$ mL/m$^2$ was associated with the lack of response to volume expansion. However, when the RVEDV index ranged from 90 to 138 mL/m$^2$, no threshold value was proposed to discriminate responder and nonresponder patients before volume expansion. Moreover, another study$^8$ reported a positive response to volume expansion in four of nine patients with a RVEDV index $> 138$ mL/m$^2$, a lack of response in three of nine patients despite a RVEDV $< 90$ mL/m$^2$, and a significant but weak relationship between the baseline RVEDV index

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**Table 3—PAOP Before Volume Expansion in Responders and Nonresponders**

<table>
<thead>
<tr>
<th>Source</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvin et al$^2$</td>
<td>$8 \pm 1$</td>
<td>$7 \pm 2$</td>
</tr>
<tr>
<td>Schneider et al$^3$</td>
<td>$10 \pm 1$</td>
<td>$10 \pm 1$</td>
</tr>
<tr>
<td>Reuse et al$^4$</td>
<td>$10 \pm 4$</td>
<td>$10 \pm 3$</td>
</tr>
<tr>
<td>Diebel et al$^6$</td>
<td>$14 \pm 7$</td>
<td>$7 \pm 2$</td>
</tr>
<tr>
<td>Diebel et al$^7$</td>
<td>$16 \pm 6$</td>
<td>$15 \pm 5$</td>
</tr>
<tr>
<td>Wagner and Leatherman$^6$</td>
<td>$10 \pm 3$</td>
<td>$14 \pm 4$</td>
</tr>
<tr>
<td>Tavernier et al$^8$</td>
<td>$10 \pm 4$</td>
<td>$12 \pm 3$</td>
</tr>
<tr>
<td>Tousignant et al$^{11}$</td>
<td>$12 \pm 3$</td>
<td>$16 \pm 3$</td>
</tr>
<tr>
<td>Michaud et al$^{12}$</td>
<td>$10 \pm 3$</td>
<td>$11 \pm 2$</td>
</tr>
</tbody>
</table>

$^*$Values are expressed as mean $\pm$ SD, except for the study of Schneider et al$^3$ (mean $\pm$ SEM).

$^1p < 0.05$ responders vs nonresponders.
(r^2 = 0.19) and the increase in stroke volume in response to volume expansion.

**LVEDA**

In two studies,^9,11^ the LVEDA before volume expansion was significantly lower in responders than in nonresponders (Table 4). In the study of Tavernier et al.^9^ a significant and negative relationship (r^2 = 0.4, p = 0.01) was also reported between the baseline value of LVEDA index and the percentage of increase in stroke volume in response to volume expansion. However, using receiver operating characteristic curve analysis, Tavernier et al.^9^ demonstrated minimal value of LVEDA index to discriminate responder and nonresponder patients. In the study of Tousignant et al.,^11^ a marked overlap of baseline individual LVEDA values was observed so that a given value of LVEDA could not be used to predict the hemodynamic response to fluid infusion. Moreover, in another study,^13^ responder and nonresponder patients were not different with regard to the baseline value of LVEDA index (10 ± 4 cm^2/m^2 vs 10 ± 2 cm^2/m^2), and no significant relationship (r^2 = 0.11, p = 0.17) was observed between the baseline value of LVEDA index and the percentage of increase in cardiac index in response to volume expansion.

**ΔRAP**

In patients with spontaneous breathing activity, two studies from Magder et al.^5,10^ demonstrated that an inspiratory decrease in RAP ≥ 1 mm Hg predicted a positive response to volume expansion, with positive predictive values of 77% and 84% and negative predictive values of 81% and 93% (Table 5).

**Δdown**

In sedated patients receiving mechanical ventilation with sepsis-induced hypotension, one study^8^ demonstrated that the Δdown was significantly greater (11 ± 4 mm Hg vs 4 ± 2 mm Hg, p = 0.0001) in responders than in nonresponders, and that the Δdown threshold value of 5 mm Hg was able to discriminate responders and nonresponders with a positive predictive value of 95% and a negative predictive value of 93% (Table 5). Moreover, this study^9^ reported a positive and good relationship (r^2 = 0.58, p = 0.001) between the baseline value of Δdown and the percentage of increase in stroke volume in response to volume expansion.

### Table 4—LVEDA Before Volume Expansion in Responders and Nonresponders*

<table>
<thead>
<tr>
<th>Source</th>
<th>LVEDA, cm^2/m^2</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tavernier et al^9^</td>
<td>9 ± 3</td>
<td>12 ± 4‡</td>
<td></td>
</tr>
<tr>
<td>Tousignant et al^11^</td>
<td>15 ± 5†</td>
<td>20 ± 5‡</td>
<td></td>
</tr>
<tr>
<td>Feissel et al^13^</td>
<td>10 ± 4</td>
<td>10 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†p < 0.05 responders vs nonresponders.
‡Area expressed in centimeters squared.
Table 5—Positive and Negative Predictive Values of Dynamic Parameters

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Parameters Tested</th>
<th>Best Threshold Value</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
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</thead>
<tbody>
<tr>
<td>Magder et al</td>
<td>33</td>
<td>ΔRAP</td>
<td>1 mm Hg</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>Tavernier et al</td>
<td>35</td>
<td>Δdown</td>
<td>5 mm Hg</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>Magder and Lagonidis</td>
<td>29</td>
<td>ΔRAP</td>
<td>1 mm Hg</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>Michal et al</td>
<td>40</td>
<td>ΔPP</td>
<td>13%</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Feissel et al</td>
<td>19</td>
<td>ΔVpeak</td>
<td>12%</td>
<td>91</td>
<td>100</td>
</tr>
</tbody>
</table>

**ΔPP**

In sedated patients receiving mechanical ventilation with acute circulatory failure related to sepsis, one study demonstrated that ΔPP was significantly greater (24 ± 9% vs 7 ± 3%, p < 0.001) in responders than in nonresponders, and that a ΔPP threshold value of 13% allowed discrimination between responder and nonresponder patients with a positive predictive value of 94% and a negative predictive value of 96% (Table 5). Moreover, in this study, the value of ΔPP before fluid administration was significantly and closely correlated ($r^2 = 0.85$, $p < 0.001$) with the volume expansion-induced changes in cardiac output, such that the higher ΔPP at baseline, the greater was the increase in cardiac output in response to fluid infusion.

**ΔVpeak**

In sedated patients receiving mechanical ventilation with septic shock, one study demonstrated that ΔVpeak was significantly greater (20 ± 6% vs 10 ± 3%, $p < 0.01$) in responder patients than in nonresponder patients, and that a ΔVpeak threshold value of 12% allowed discrimination between responder and nonresponder patients with a positive predictive value of 91% and a negative predictive value of 100% (Table 5). Moreover, a positive and tight linear correlation ($r^2 = 0.83$, $p < 0.001$) was found between the ΔVpeak before volume expansion and the volume expansion-induced changes in cardiac output.

**Discussion**

The present analysis emphasizes the minimal clinical value of ventricular preload indicators and the higher value of dynamic parameters (testing the cardiovascular response to respiratory changes in pleural pressure) in predicting fluid responsiveness in critically ill patients. It has been suggested that a beneficial hemodynamic effect of volume expansion cannot be expected in critically ill patients with a RAP > 12 mm Hg and/or a PAOP > 12 mm Hg or > 15 mm Hg. In this regard, RAP and PAOP have been reported to be lower in responders than in nonresponder patients in two studies (Fig 1, Table 3). Moreover, a significant relationship between the increase in stroke volume in response to volume expansion and the baseline RAP ($r^2 = 0.20$) or the baseline PAOP ($r^2 = 0.33$) was reported by Wagner and Leatherman, suggesting that the lower RAP or PAOP before volume expansion, the greater the increase in stroke volume in response to fluid infusion. However, although statistically significant, these relationships were weak because a given value of RAP or of PAOP could not be used to discriminate responders and nonresponders before fluid was administered. Moreover, in all other clinical studies (Fig 1, Table 3), no difference between responder and nonresponder patients was observed with regard to the baseline value of RAP and of PAOP, and no relationship was reported between cardiac filling pressures before volume expansion and the hemodynamic response to volume expansion. Finally, it must be noted that fluid infusion has been shown to significantly increase cardiac output in some critically ill patients with central venous pressures > 15 mm Hg.

Two studies of Diebel et al reported a lower value of RVEDV index in responder than in nonresponder patients, and suggested that a beneficial hemodynamic effect of volume expansion was likely (rate of response 100% and 64%) when the RVEDV index was below 90 mL/m$^2$ and very unlikely (rate of response 0%) when the RVEDV index was > 138 mL/m$^2$. However, when the RVEDV index ranged from 90 to 138 mL/m$^2$, no cutoff value could be proposed to discriminate responder and nonresponder patients. Moreover, Wagner and Leatherman reported positive responses to volume expansion in patients with a RVEDV index > 138 mL/m$^2$, and the lack of response in patients with a RVEDV index < 90 mL/m$^2$. Finally, in four of six studies investigating whether RVEDV could predict fluid responsiveness, no significant difference was observed between re-
sponders and nonresponders with regard to the baseline value of RVEDV index (Fig 2).

The echocardiographic measurement of LVEDA has been shown to reflect more accurately the left ventricular preload when compared with PAOP, and to improve the ability to detect changes in left ventricular function caused by acute blood loss. In nine anesthetized mongrel dogs, Swenson et al reported a significant relationship between baseline LVEDA and changes in cardiac output induced by IV fluid therapy, suggesting that LVEDA could be an indicator of fluid responsiveness. In this regard, LVEDA was found to be significantly lower in responders than in nonresponders in two clinical studies, and a significant relationship between the baseline LVEDA index and the changes in stroke volume induced by volume expansion has also been reported. However, using receiver operating characteristic curve analysis, Tavernier et al demonstrated in patients with sepsis-induced hypotension the minimal value of a given LVEDA index value to discriminate responders and nonresponders before fluid was administered. Moreover, in the study of Tousignant et al, including medical-surgical ICU patients, considerable overlap of baseline individual values of LVEDA was observed between responders and nonresponders, supporting the interpretation that a specific LVEDA value cannot reliably predict fluid responsiveness in an individual patient. Recently, in patients with septic shock, Feisel et al did not observe any difference between the mean baseline value of LVEDA index in responders and nonresponders, neither any relationship between the baseline value of LVEDA index and the percentage of change in cardiac index in response to volume expansion.

Therefore, all clinical studies have emphasized the lack of value of ventricular preload indicators as predictors of fluid responsiveness in critically ill patients. Methodologic and physiologic reasons could be advanced to explain these findings. First, RAP, PAOP, RVEDV, and LVEDA are not always accurate indicators of ventricular preload. Indeed, RAP and PAOP have been shown to overestimate transmural pressures in patients with external or intrinsic PEEP. The PAOP is highly dependent on left ventricular compliance, which is frequently decreased in ICU patients (sepsis, ischemic, or hypertrophic cardiopathy). Because it is the transmural pressures and not intracavitary pressures such as RAP and PAOP that are related to end-diastolic volumes via the chamber compliance, it is not surprising that those surrogates bear little relationship to fluid responsiveness. The evaluation of RVEDV by thermodilution has been shown influenced by tricuspid regurgitation, which is frequently encountered in patients with pulmonary hypertension (ARDS, mechanical ventilation with PEEP). The estimation of the LVEDA by echocardiography does not always accurately reflect left ventricular end-diastolic volume and hence LV preload. Second, in case of right ventricular dysfunction, a beneficial hemodynamic effect of volume expansion cannot be expected, even in the case of low left ventricular preload. Third, knowing the preinfusion end-diastolic volume tells little about the diastolic chamber compliance. In this regard, hypovolemia can be associated with a normal or high LVEDA value in patients with dilated cardiopathy. Finally, two matters must be stressed: (1) the increase in end-diastolic volume as a result of fluid therapy depends on the partitioning of the fluid into the different cardiovascular compliances organized in series, and (2) the rise in stroke volume as a result of end-diastolic volume increase depends on ventricular function since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume. Therefore, a patient can be nonresponder to a fluid challenge because of high venous compliance, low ventricular compliance and/or ventricular dysfunction. In this regard, it is not so surprising that bedside indicators of cardiac chambers dimensions are not accurate predictors of fluid responsiveness in ICU patients in whom venous capacitance, ventricular compliance, and contractility are frequently altered.

Assuming that respiratory changes in pleural pressure induce greater changes in RAP when the right ventricle is highly compliant than when it is poorly compliant, Magler et al investigated whether the inspiratory decrease in RAP could be used to predict fluid responsiveness. Two studies demonstrated that a positive response to volume expansion was very likely in patients with an inspiratory decrease in RAP ≥ 1 mm Hg, while it was unlikely if the inspiratory decrease in RAP was < 1 mm Hg. Unfortunately, most of ICU patients with acute circulatory failure are sedated and receiving mechanical ventilation, thus are unable to produce an inspiratory decrease in pleural pressure sufficient to decrease the RAP. In this condition, analysis of the respiratory changes in left ventricular stroke volume has been proposed to predict fluid responsiveness. Indeed, by decreasing the venous return pressure gradient, mechanical insufflation may decrease the right ventricular filling and consequently the right ventricular output if the right ventricle is sensitive to changes in preload. In this condition, the following decrease in left ventricular filling may also induce a significant decrease in left ventricular output if the left ventricle is sensitive to changes in preload. Therefore, the magnitude of the respiratory changes...
in left ventricular stroke volume, which reflects the sensitivity of the heart to changes in preload induced by mechanical insufflation, has been proposed as a predictor of fluid responsiveness. Because the arterial pulse pressure (systolic minus diastolic pressure) is directly proportional to left ventricular stroke volume, the respiratory changes in left ventricular stroke volume have been shown reflected by changes in pulse pressure. Accordingly, the respiratory changes in pulse pressure have been shown to accurately predict fluid responsiveness in patients receiving mechanical ventilation with acute circulatory failure related to sepsis. The analysis of the respiratory changes in systolic pressure has also been proposed to assess fluid responsiveness. However, the systolic pressure variation induced by mechanical ventilation results not only from changes in aortic transmural pressure (mainly related to changes in left ventricular stroke volume), but also from changes in extramural pressure (ie, from changes in pleural pressure). Therefore, the systolic pressure variation is a less specific indicator of changes in left ventricular stroke volume and hence a less accurate predictor of fluid responsiveness than the pulse pressure variation. In this regard, it has been proposed to discriminate the inspiratory increase in systolic pressure (not necessarily due to a change in left ventricular stroke volume) from the $\Delta$down, which in contrast necessarily reflects a change in left ventricular stroke volume. Experimental and clinical studies have emphasized the influence of volume status on $\Delta$down (hemorrhage increases $\Delta$down, while volume expansion decreases $\Delta$down), and Tavernier et al demonstrated that $\Delta$down is an accurate predictor of fluid responsiveness in septic patients with hypotension.

The analysis of the arterial pressure waveform is not possible in patients with cardiac arrhythmias. Indeed, in this condition, the changes in arterial pressure do not reflect the effects of mechanical insufflation on left ventricular stroke volume. It must be emphasized that the evaluation of $\Delta$down and of $\Delta$PP requires invasive arterial pressure catheterization. However, in shock states, estimation of BP using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure. Interestingly, Feissel et al have recently demonstrated that Doppler echocardiographic imaging of aortic blood velocity could be used to assess noninvasively the respiratory changes in aortic blood velocity and to predict fluid responsiveness in patients with septic shock. It must be noted that $\Delta$down, $\Delta$PP, and $\Delta$Vpeak have been shown to be accurate predictors of fluid responsiveness in sedated patients receiving mechanical ventilation with sepsis. Whether they also predict fluid responsiveness in nonsedated, spontaneously breathing patients without sepsis remains to be determined.

It must be emphasized that various types and volumes of fluid, speeds of fluid infusion, and definitions of responders to volume expansion have been used in the studies analyzed (Table 1). This may have a significant influence on the results and conclusions of the studies. Indeed, the hemodynamic effects of an hypertonic colloid infusion are expected to be more dramatic than those of an equal volume of isotonic crystalloid infusion. Because of intravascular-extravascular equilibration, the speed of volume infusion should also greatly influence the hemodynamic response, particularly in septic patients with systemic capillary leakiness. Moreover, because of different definitions of responders from one study to another, some patients considered as responders in some studies, would have been considered as nonresponders in other studies. Unfortunately, because individual data were not available in all but one study, a comparison of the predictive value of each parameter using the same definition of responders was not possible. Finally, the predictive value of dynamic parameters has been tested by only few studies. Therefore, further studies are required to confirm the high value of dynamic parameters in discriminating responder and nonresponder patients before fluid inclusion. However, our analysis emphasizes the minimal value of static ventricular preload parameters as predictors of fluid responsiveness and strongly supports the use of the dynamic parameters in the decision-making process concerning volume expansion in critically ill patients.

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REFERENCES

8 Wagner JC, Leatherman JW. Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. Chest 1998; 113:1048–1054
34 Perel A, Pizov R, Cotev S. Systolic BP: variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 1987; 67:498–502