Hemodynamic Monitoring

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Hemodynamic Evaluation and Monitoring in the ICU*

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Hemodynamic monitoring, a cornerstone in the management of the critically ill patient, is used to identify cardiovascular insufficiency, its probable cause, and response to therapy. Still it is difficult to document the efficacy of monitoring because no device improves outcome unless coupled to a treatment that improves outcome. Several clinical trials have consistently documented that preoptimization for high-risk surgery patients treated in the operating room and early (< 12 h) goal-directed resuscitation in septic patients treated in the emergency department reduce morbidity, mortality, and resource use (costs) when the end points of resuscitation were focused on surrogate measures of adequacy of global oxygen delivery (Do_2). The closer the resuscitation is to the insult, the greater the benefit. When resuscitation was started after ICU admission in high-risk surgical patients, reduced length of stay was also seen. The focus of these monitoring protocols is to establish a mean arterial pressure > 65 mm Hg and then to increase Do_2 to 600 mL/min/m^2 within the first few minutes to hours of presentation. To accomplish these goals, hemodynamic monitoring focuses more on measures of cardiac output and mixed venous oxygen saturation to access adequacy of resuscitation efforts than on filling pressures. Although these protocols reduce mortality and morbidity in selected high-risk patient groups, the widespread use of monitoring-driven treatment protocols has not yet happened, presumably because all studies have been single-center trials using a single, proprietary blood flow-monitoring device. Multicenter trials are needed of early goal-directed therapies for all patients presenting in shock of various etiologies and when the protocol and not the monitoring device is the primary variable. *(CHEST 2007; 132:2020–2029)*

Key words: blood-flow monitoring; goal-directed therapy; hemodynamic monitoring; ICU

Abbreviations: Do_2 = oxygen delivery; HR = heart rate; LV = left ventricular; MAP = mean arterial pressure; PLR = passive leg raising; P_{PAO} = pulmonary artery occlusion pressure; PPV = pulse pressure variation; P_{RA} = right atrial pressure; RV = right ventricular; SpO_2 = oxygen saturation by pulse oximetry; SPV = systolic pressure variation; SvO_2 = mixed venous oxygen saturation; SVV = stroke volume variation; Vo_2 = oxygen consumption.

Hemodynamic monitoring is a cornerstone in the care of the critically ill patient in the ICU. The ICU provides a place for monitoring and care of patients with potentially severe physiologic instability requiring advanced artificial life support. Within this context, hemodynamic monitoring is used to identify hemodynamic instability and its cause and to monitor the response to therapy. We have witnessed an impressive number of medical technological advances, allowing monitoring, display, and assessment of physiologic variables not even imagined before,[1] yet the utility of most hemodynamic monitoring is unproven. It is the commonly available technologies for which clinical studies have demonstrated relevance. Physiologic measures available from commonly available monitoring devices are given in Table 1. Despite the many options available, most ICUs monitor and display only BP, heart rate (HR)

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This work was supported in part by National Institutes of Health grants HL67181, HL07820, and HL073198.
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Manuscript received January 9, 2007; revision accepted April 30, 2007.

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DOI: 10.1378/chest.07-0073

Table 1—*Hemodynamic Monitoring-Defined Primary Hemodynamic Variables

Noninvasive monitoring
ECG
HR, dysrhythmias, HR variability
Pulse oximetry
Sp_{O_2}, HR
Arterial pressure
Sphygmomanometry
Systolic and diastolic BP, HR, pulse paradoxus
Central venous pressure
Jugular venous distention, hepatojugular reflex, cannon waves (A-V dissociation), tricuspid regurgitation
Invasive monitoring
Arterial catheterization
Systolic BP, diastolic BP, MAP, HR, and pulse pressure
Arterial blood gas analysis
pH, Pa_{O_2}, Sa_{O_2}, Pa_{CO_2}, hemoglobin
Arterial pressure waveform analysis
Stroke volume, cardiac output, PPV and SVV
Central venous catheterization
Central venous pressure, venous pressure waveform ("v" waves), respiratory variations
Central venous blood gas analysis
pH, Pcv_{O_2}, Scv_{O_2}, Pcv_{CO_2}, hemoglobin
Thermodilution indices (when coupled to an arterial thermal sensor)
Stroke volume, cardiac output, intrathoracic blood volume, global end-diastolic volume, and Do_2
Pulmonary artery catheter
Systolic BP, diastolic BP, MAP, pressure waveform ("v" waves), and Ppao
Mixed venous blood gas analysis
pH, Pv_{O_2}, Sv_{O_2}, Pv_{CO_2}, hemoglobin
Thermodilution cardiac output (by thermodilution either intermittent or continuous)
Stroke volume, cardiac output, RV ejection fraction, and RV end-diastolic volume
Esophageal Doppler echocardiographic monitoring
Stroke volume, cardiac output, and SVV

*Sa_{O_2} = arterial oxygen saturation; Pcv_{O_2} = central venous O_2 partial pressure; Scv_{O_2} = central venous oxygen saturation; Pcv_{CO_2} = central venous CO_2 partial pressure; Pv_{O_2} = mixed venous O_2 partial pressure; Pv_{CO_2} = mixed venous CO_2 pressure.

and oxygen saturation by pulse oximetry (Sp_{O_2}), as they have done for the last 20 years. Furthermore, with few exceptions, such monitoring does not drive treatment protocols but rather serves as an automated vital signs record to trigger further attention. It is hard to validate the utility of monitoring when it is used in this fashion because no hemodynamic monitoring device will improve outcome useless coupled to a treatment that itself improves outcome. Thus, the effectiveness of hemodynamic monitoring to improve outcome is limited to specific patient groups and disease processes for which proven effective treatments exist. Although, like most of medicine, the utility of hemodynamic monitoring is not well documented, a primary rationale for the use of hemodynamic monitoring is to identify cardiovascular instability and its specific etiology, and to guide therapy.

Interestingly, physicians have developed a psychological dependence on feedback from continuous hemodynamic monitoring tools, independent of their utility. Sp_{O_2} monitoring in low-risk patients is an example. One would presume that continual measure of Sp_{O_2} should improve patient outcomes by identifying hypoxemia and brady/tachyarrhythmias, thus allowing for effective and rapid correction before the development of global tissue ischemia. However, Moller et al[2] examined the benefit of intraoperative Sp_{O_2} monitoring in low-risk surgery patients. They monitored 20,802 patients: 10,312 patients assigned to an oximetry group, and 10,490 patients assigned to a control group without oximetry. They found no numerical differences in cardiovascular, respiratory, neurologic, or infectious complications, duration of hospital stay, or number of in-hospital deaths between the two groups. When shown these results, 80% of the anesthesiologists replied by questionnaire that they still felt more secure in their practice when they used a pulse oximeter in these patients.[3] In this article, I shall discuss the rationale for commonly available monitoring, the usefulness of static measured variables to assess specific disease states (hemodynamic profile analysis), and interactive monitoring to predict response to therapy (applied physiology), and monitoring-driven treatment protocols (functional hemodynamic monitoring) that improve outcomes.

Rationale for Hemodynamic Monitoring

Three progressive arguments can be made for using specific monitoring. At the basic level, one cites its common use. Here, prior experience has shown that such monitoring can identify disease states and/or known complications, even though the link between the monitoring and disease may not be known or even postulated. The second level of defense rests with an understanding of shock pathophysiology, the etiologies of which are usually categorized into four broad groups: hypovolemic, cardiogenic, obstructive, or distributive, all of which may have different causes and treatments.[4] Since the primary goal of the cardiovascular system is to supply adequate amounts of oxygen to meet the metabolic demands of the body, calculation of systemic oxygen delivery (Do_2) and oxygen consumption (Vo_2), identifying tissue ischemia (usually monitored by mixed venous oxygen saturation [Sv_{O_2}]) as well as measures of ventricular performance (stroke work) are often calculated from such primary variables. At this level,

hemodynamic monitoring is used to define cardiovascular status, not response to treatments based on assumed pathophysiology, and predict outcome. Most of the rationale for hemodynamic monitoring resides at this pathophysiology level. The implied assumption here is that restoration of normal hemodynamic values will prevent further organ injury and reduce mortality. Unfortunately, this argument may not be valid, primarily because hemodynamic monitoring usually only assesses global circulatory status, not organ function or microcirculation, and does not address the mechanisms by which disease occurs.[5-7] The highest level of defense comes from documentation of improved outcomes based on hemodynamic monitoring-driven treatments that may alter therapy in otherwise unexpected ways. These treatment protocols often have a mechanistic rationale, but such scientific rationale is not mandatory. This final defense is supported by clinical trials adding weight to the applied physiologic approach to hemodynamic monitoring and can form the basis for evidence-based medicine recommendations. Such validation has only recently been shown for hemodynamic monitoring-driven protocolized resuscitation in selected high-risk patient groups as described below.

Hemodynamic Profile Analysis

Circulatory shock causes tissue hypoperfusion. Cellular dysfunction, organ injury, and death may occur proportional to the degree and duration of tissue hypoperfusion as quantified by oxygen debt.[8] The four pathophysiologic categories of shock are usually characterized by different specific hemodynamic variables, induced by the associated primary hemodynamic event and the autonomic response to it. These variables can be measured by a variety of noninvasive and invasive means (Table 1) and derived hemodynamic parameters calculated that reflect global cardiovascular status (Table 2).

The relation between specific hemodynamic variables is complex is health, and even more complex is disease. However, a solid understanding of the cardiovascular underpinnings of blood flow homeostasis is required to interpret hemodynamic variables effectively. If disease causes cardiac output and DO_2 to decrease, mean arterial pressure (MAP) decreases as well. Baroreceptors in the aortic arch and carotid body alter vasomotor tone through modulation of sympathetic tone to maintain cerebral perfusion pressure (eg, MAP > 65 mm Hg).[9] The hemodynamic effects of this increased sympathetic tone are tachycardia and restoration of MAP toward normal values by reducing unstressed circulatory blood volume and increased arterial vasomotor tone. Thus, hypotension reflects failure of the sympathetic nervous system to compensate for circulatory shock, while normotension does not insure hemodynamic stability.[10] Since regulation of blood flow distribution occurs by regional vasodilation of arterial resistance vessels, hypotension impairs autoregulated blood flow distribution.[11,12] Except in conditions of severe hypoxemia and anemia, the primary means by which DO_2 is varied to match metabolic requirements is by varying cardiac output and tissue oxygen extraction. Since metabolic demands can vary widely, there is no normal cardiac output or DO_2 value, but rather minimal thresholds for resting conditions and potentially adequate higher levels during stress. Operationally, it is better to access cardiac output as being either adequate or inadequate to meet the metabolic demands of the body. Inadequate DO_2 is presumed to occur if tissue oxygen extraction is markedly increased, as manifest by a decrease in SvO_2 < 70%.[13]

Table 2—*Derived Hemodynamic Parameters From Hemodynamic Monitoring

Primary hemodynamic variables
HR, beats/min
MAP, mm Hg
P_{RA}, mm Hg
MPAP, mm Hg
P_{PAC}, mm Hg
CO, L/min
SaO_2, %
SpO_2, as an estimate of SaO_2, %
SvO_2, %
Hb, g/dL
Height and weight needed to calculate BSA, m^2
Calculated hemodynamic parameters
CI = CO/BSA, L/min/m^2
Stroke volume = CO/HR × 1,000, mL/min
Stroke index = stroke volume/BSA, mL/m^2
LV stroke work = stroke volume × (MAP − P_{PAC}), mL · mm Hg
LV stroke work index = LV stroke work/BSA, mL · mm Hg/m^2
Total peripheral resistance = (MAP/CO) × 80, dyne · s/cm^5
Systemic vascular resistance = ([MAP − P_{RA}]/CO × 80, dyne · s/cm^5
RV stroke work = stroke volume × (MPAP − P_{RA}), mL · mm Hg
RV stroke work index = RV stroke work/BSA, mL · mm Hg/m^2
Pulmonary vascular resistance = ([MPAP − P_{PAC}]/CO) × 80, dyne · s/cm^5
Global DO_2†= CO × (SaO_2 − SvO_2) × Hb × 1.36 × 1,000, mL oxygen/min
Global DO_2 index† = CI × (SaO_2 − SvO_2) Hb × 1.36, mL oxygen/min
Global VO_2† = CO × SaO_2 × Hb × 1.36 × 1,000, mL oxygen/min
Global VO_2 index† = CI × SaO_2 × Hb × 1.36 × 1,000, mL oxygen/min

*CO = cardiac output, CI = cardiac index, BSA = body surface area, SaO_2 = arterial oxygen saturation, MPAP = mean pulmonary artery pressure, Hb = hemoglobin.
†SpO_2 can be substituted for arterial oxygen saturation in these calculations.

Of the four categories of shock, only distributive shock states following intravascular volume resuscitation are associated with an increased cardiac output but decreased vasomotor tone.[4] Thus, cardiac output, stroke work, DO_2, and $S\bar{v}O_2$ are decreased in cardiogenic, hypovolemic, and obstructive shock but may be normal or even increased in distributive shock. However, in all conditions, HR increases associated with an increased sympathetic tone. Cardiogenic shock represents primary cardiac failure. It can be due to impaired contractility (myocardial ischemia/infarction, electrolyte imbalance, hypoxemia, hypothermia, endocrinologic diseases, metabolic poisoning, β-blockers), pump function (valvulopathy, ventriculoseptal defect, dysrhythmias), or diastolic compliance (fibrosis, infiltrative cardiomyopathies, hypertrophy). The specific cardinal findings of cardiogenic shock are increased back pressure to cardiac filling (right atrial pressure [Pra] and pulmonary artery occlusion pressure [Ppao]) and upstream edema (peripheral and pulmonary). Hypovolemic shock represents a decrease in effective circulating blood volume and venous return. It can be due to primary intravascular volume loss (hemorrhage, capillary leak), secondary intravascular volume loss (third-space loss, insensible loss through skin with burns, diarrhea, vomiting), and increased unstressed vascular volume (loss of sympathetic tone, spinal cord injury, vasodilating drugs). The specific findings of hypovolemic shock are decreased filling pressures. Obstructive shock represents a blockage of blood flow. It may be due to right ventricular (RV) outflow obstruction (pulmonary embolism, hyperinflation), tamponade (pericardial effusion, hyperinflation), or left ventricular (LV) outflow obstruction (aortic stenosis, dissecting aortic aneurysm). The specific findings of obstructive shock are often more subtle but include decreased LV diastolic compliance (small LV volume with increased Ppao) and signs of cor pulmonale (Pra greater than Ppao, tricuspid regurgitation). Distributive shock represents loss of normal sympathetic responsiveness resulting in decreased vasomotor tone. In the nonresuscitated subject, this presents as hypovolemic shock,[14] but with fluid resuscitation BP does not increase despite an increase in cardiac output. It can be due to loss of vascular responsiveness (sepsis, spinal shock, vasodilating drugs, metabolic poisons). The specific findings of distributive shock are an increased cardiac output, DO_2, and $S\bar{v}O_2$ despite persistent hypotension. Hemodynamic monitoring can aid in determining circulatory shock etiology.

Since most forms of circulatory shock reflect inadequate tissue DO_2, a primary goal of resuscitation is to increase DO_2. Three important functional questions are usually asked of the hemodynamically unstable patient. First, will cardiac output increase with fluid resuscitation and, if so, by how much? Physiologically speaking, this equates to preload responsiveness. Second, in the hypotensive patient is arterial vasomotor tone increased, decreased, or normal? Finally, is the heart capable of sustaining an effective cardiac output once arterial pressure is restored without going into failure? Clearly, patient-specific hemodynamic questions are also asked but, in general, these are the fundamental questions addressed by most effective treatment algorithms. Unfortunately, although specific patterns of hemodynamic values, as described above, reflect specific types of disease, they do not predict individual patient response to therapy.

Applied Physiology Applied to Hemodynamic Monitoring

To address the question of preload responsiveness, physicians usually attempt to measure intravascular volume status, either by indirect measures (skin turgor, mucus membrane wetness and venous congestion, or vascular pedicle diameter of the chest radiograph)[15] or by attempting to estimate RV and LV end-diastolic volumes. Importantly, the published clinical literature does not support the use of direct or indirect measures of end-diastolic volume as a means to predict preload responsiveness. Readers are referred to the metaanalysis by Michard and Teboul[16] published in *CHEST* for further discussion. Although general trends in filling pressures and volumes define patient populations, their use in clinical decision making is poor. Specifically neither absolute values for Pra, Ppao, RV end-diastolic volume, or LV end-diastolic area predict preload responsiveness. Furthermore, the changes in either Pra or Ppao do not reflect changes in either cardiac output or stroke volume in hemodynamically unstable patients.[17] Although increases in either RV or LV end-diastolic volumes do increase stroke volume, knowing ventricular pressures or volumes at a single point in time is not useful in making this prediction. Although the reasons for such inaccuracies of using Pra or Ppao to estimate preload may reflect inaccuracies in measures,[18] or in understanding what Ppao reflects even when these values are measured accurately,[19] even when measured accurately they do not predict preload responsiveness.[20] Thus, the lack of the ability of measures of Pra or Ppao to predict preload responsiveness may explain the lack of difference in outcome from Pra- vs Ppao-guided fluid resuscitation therapies in the two published articles on the ARDS Clinical Trials Network Fluid and

Catheter Treatment Trial comparing central venous catheters (Pra guided) to pulmonary arterial catheters (Ppao guided)[21] and liberal vs restricted fluid resuscitation (high Pra or Ppao vs low Pra or Ppao), other than length of stay being slightly shorter in the conservative fluids arm[22] because neither measure correlates with DO_2, although both tend to parallel changes in effective circulating blood volume. Furthermore, the Surviving Sepsis Campaign recommendations[23] for targeted values of Pra and Ppao are not supported by the existing evidence. Fluid responsiveness was documented to be unrelated to the recommended Pra and Ppao values.[24] Such negative findings based on a treatment protocol targeting specific Pra or Ppao values are not surprising. In essence, preload is not preload responsiveness. Clearly, as numerous previous studies[25–28] have underscored, just inserting a catheter to make measurements without a defined and effective treatment protocol requiring such information is unlikely to result in improved patient outcomes. What clinicians need to know is the latter, and what static measurers estimate is the former. Clearly, as intravascular volume increases, Pra may also increase, especially in patients with impaired RV function. Still, one can have an expanded intravascular volume and a low Pra, as is the case in hyperdynamic hepatic cirrhosis patients. Similarly, Ppao also tends to be higher with hypervolemia and tends to tract intrathoracic blood volume especially in heart failure patients. However, as was shown previously by Michard and Teboul,[16] absolute Pra or Ppao values are no better than a random chance at predicting preload responsiveness. There are few relative truths in the assessment of single, fixed hemodynamic variables, but Table 3 lists those I have come to realize when considering acute resuscitation of the critically ill.

In the assessment of preload responsiveness, one needs to measure other parameters than filling pressures and ventricular volumes. The time-honored method of assessing preload responsiveness is the intravascular fluid challenge, whereby a bolus of fluid is rapidly infused and the subsequent changes in specific flow-dependent variables (cardiac output, MAP, HR, SvO_2, Pra, Ppao) are measured. The problems with performing a fluid challenge for clinical decision making are multiple. First, only half the hemodynamically unstable patients administered a volume challenge will have increased cardiac output.[16] Thus, the correct management may have been delayed in half the patients. Second, in the half of those patients who are not preload responsive, volume loading may be directly injurious. For example, both acute cor pulmonale (pulmonary embolism, COPD) or LV failure may deteriorate further with volume loading. Two alternative methods of performing a reversible fluid challenge have recently gained interest in the acute care setting. These include the use of positive pressure ventilation-induced changes in arterial pressure and LV stroke volume to cyclically varying venous return, and by performing a passive leg raising (PLR) maneuver to transiently increase venous return and noting the change in mean blood flow.

Positive pressure ventilation when applied to a patient at rest and with no spontaneous respiratory effort is associated with a cyclic increase in Pra in phase with inspiration. Since Pra is the back-pressure to venous return, if upstream venous pressures do not simultaneously increase[29] then RV filling will also decrease in a cyclic fashion. This cyclic variation in RV filling will induce a cyclic variation in LV filling if both RV and LV are preload responsive.[30] This cyclic variation in LV filling will induce a cyclic variation in LV stroke volume and arterial pulse pressure if the patient is preload responsive. Several studies[31–33] have documented that the associated variations in LV stroke volume, referred to as *stroke volume variation* (SVV) and quantified as the maximal to minimal stroke volume values over their mean over three breaths or a defined time interval (*eg*, 20 to 30 s), is highly predictive of preload responsiveness. For a tidal volume of 6 mL/kg, a SVV ≥ 10% predicts a ≥ 15% increase in cardiac output for a 500-mL fluid bolus.[34–36] Since the primary determinant of arterial pulse pressure is stroke volume, pulse pressure variation (PPV), calculated in the same manner as SVV, has also been shown to predict preload responsiveness well. Here however, a ≥ 13% PPV predicts a ≥ 15% increase in cardiac output for a 500-mL volume bolus. Presently, PPV is easier to measure than SVV because it only requires inspection of the arterial pressure waveform over time,[37] whereas SVV can be assessed by either esophageal Doppler echocardiography[38] or echocardiographic measures of aortic velocity.[39] Several commercially available technologies have evolved based on arterial waveform analysis that can estimate stroke volume from the pulse pressure waveform. Furthermore, only quantifying systolic pressure variation (SPV) over the ventilatory cycle has been proposed.[40] This measured, also known as *pulse paradoxus*, has the advantage of being easier to monitor but also has de-

Table 3—*Hemodynamic Monitoring Truths*

Tachycardia is never a good thing.
Hypotension is always pathologic.
There is no such thing as normal cardiac output.
Central venous pressure is only elevated in diseases.
Peripheral edema is of cosmetic concern.

creased sensitivity because it does not quantify the varying diastolic arterial pressure component of the PPV.[41] Finally, studies suggest that the SpO_2 plethysmographic waveform amplitude co-varies with arterial pulse pressure.[42], and this plethysmographic signal variation predicts fluid responsiveness in hypotensive patients.[43] If validated to predict preload responsiveness in the broader group of hemodynamically unstable patients, then such noninvasive techniques could expand the application of this applied physiologic approach at the bedside.

Like all hemodynamic monitoring approaches, the use of SVV, PPV, or SPV to assess preload responsiveness requires an understanding of its physiologic underpinnings. SVV, PPV, and SPV are created by tidal volume-induced changes in venous return. They presume a constant R-R interval and are measured from diastole to systole, not *vice versa*, such that SVV, PPV, and SPV reflect only changes in venous return and not diastolic filling time. Thus, these parameters will lose their predictive value under conditions of varying R-R intervals (atrial fibrillation), and they may also lose accuracy if tidal volume varies from breath to breath as may occur with assisted and spontaneous ventilation.[44–46] Thus, these approaches are limited to only a small percentage of critically ill patients. Furthermore, since the ratio of PPV to SVV reflects central arterial compliance, if arterial tone varies, PPV and SVV may vary in disproportional ways. However, potentially one can monitor the PPV/SVV ratio to identify changing central arterial vasomotor tone. Finally, preload responsiveness does not mean that the patient requires volume resuscitation because normal subjects are also preload responsive.[47]

More advanced monitoring using transthoracic[48,49] and transesophageal[50,51] ultrasound (echo) imaging of the vena caval collapse during positive pressure ventilation has also been shown to predict Pra > 10 mm Hg. If venal caval diameter is decreased below a threshold value, the Pra is < 10 mm Hg; otherwise, it is > 10 mm Hg. This Pra threshold value is important in a limited way because patients with a Pra < 10 mm Hg invariably have decreased cardiac output if additional positive end-expiratory pressure is applied during positive pressure ventilation.[52] However, if Pra is > 10 mm Hg, no predictions can be made as to the change in cardiac output in response to increasing levels of positive end-expiratory pressure.

To simplify these approaches, the clinically validated PLR method can be used as a transient and reversible increase in venous return.[53] The PLR method requires that the legs be raised 30° above the chest and held there for 1 min. PLR causes an approximate 300-mL blood bolus in a 70-kg man that persists for about 2 to 3 min before resulting in intravascular volume redistribution. The immediate hemodynamic response from before to during the PLR is taken to reflect preload response.[54] To minimize the need for a constant HR and tidal volume, measures of mean aortic flow averaged over 20 to 30 s can be measured and are actually superior to SVV and PPV measures in the same subjects.[46] There are two important implications of these findings. First, since measures of changing mean blood flow during PLR accurately predict preload responsiveness during both spontaneous and positive pressure ventilation and with or without arrhythmias, this approach can be applied in all hemodynamically unstable patients. Second, since measures of mean blood flow can be ascertained at the bedside using many commercially available devices, including esophageal Doppler flow-measuring devices[55–57] and arterial pressure waveform estimates of flow,[20,58,59,60] most ICUs are capable of making these measures today.

Unfortunately, although SVV, PPV, and SPV have been described for several years, and recently the change in mean blood flow with PLR, none of these techniques has been used to drive treatment protocols. Clearly, this application of these simple monitoring approaches is the next step in the evolution of functional hemodynamic monitoring.

Functional Hemodynamic Monitoring: Goal-Directed Therapy

Numerous clinical trials have attempted to document improved patient outcome when resuscitation strategies were driven by measured hemodynamic variables. Early on, the results were either mixed or negative. However, with increased understanding of the pathophysiology of shock and a heightened awareness of the need to prevent tissue ischemia, clinical trials in the emergency department by Rivers et al[30] and the operating room[61–65] have clearly documented improved outcome. Clearly, intraoperative volume expansion improves organ perfusion and reduces gastric ischemia[64] as assessed by tonometric measures of gastric PCO_2.[65] Importantly, in the study by Rivers et al,[30] the total amount of resuscitation fluids administered was similar in the treatment and control groups, but the treatment group received more additional early fluid when the control group protocol did not require it because traditional hemodynamic measures such as Pra and MAP were at their target levels. The benefits realized from these studies have recently filtered into the ICU environment, where two prospective clinical trials[66,67] have shown that goal-directed therapy improves outcome. All these studies follow the same

theme: the earlier treatment is begun and tissue ischemia resolved, the better the outcome.

For example, the greatest outcome benefit of goal-directed therapy appears to exist in the field of high-risk surgery or, speaking from a physiologic perspective, scheduled trauma. This form of resuscitation has been termed *preoptimization* because the resuscitation starts prior to the cardiovascular stress and surgical trauma. In essence, resuscitation occurs before tissue injury. Shoemaker et al[66] documented improved outcome and reduced cost when high-risk surgery patients were resuscitated to high DO_2 values (> 600 mL/min/m^2) prior to surgery. These findings were duplicated by Boyd et al[69] and Lobo et al.[70] Importantly, Lobo et al[70] showed that the improved patient outcomes were realized across the entire treatment group of elderly patients, even in those patients who did not achieve the target DO_2 levels. One need not target DO_2 to see improved outcome. Goepfert et al[71] measured the sum end-diastolic volume of the heart (eg, right and left atrial and ventricular volumes at end diastole) and targeted global end-diastolic volume in cardiac surgery patients and documented reduced need for catecholamines and less time on the ventilator but an increase in net fluid balance of approximately 800 mL.

Studies[72] in critically ill ICU patients using goal-directed therapy presumed that if DO_2 were increased to supranormal levels (as references to resting DO_2 values), as was done in the preoptimization studies above, patients would have improved survival. This approach is referred to as *postoptimization* in distinction to the intraoperative preoptimization protocols because it is started after the patient presents in shock. However, neither Tuchschmidt et al[73] nor Gattinoni et al[74] were able to document any improved outcome when critically ill patients were enrolled 12 to 36 h after presenting with shock.[75] In fact, Hayes et al[76] saw increased mortality in their treatment group presumably because of overly aggressive attempts to reach target DO_2 values. However, Rivers et al[66] underscored the importance of immediate (emergency department at presentation) and appropriate (adequate level of DO_2 as defined by the central venous oxygen saturation as a surrogate of SvO_2)[77] resuscitation of critically ill patients to improve outcome.[78] These authors[79] also reported that proinflammatory cytokine levels were reduced in treatment patients, suggesting that early goal-directed therapy also reduces the systemic inflammatory response. Their study[78] validated the principal of immediate restoration of cardiovascular stability as the primary treatment for circulatory shock and focused the issue on rapid triage and management. Clearly, allowing patients to remain in shock for hours before starting aggressive resuscitation is a major cause of increased morbidity and mortality. One prior study[66] documented improved outcome and reduced cost when resuscitation was targeted to a minimal SvO_2; however, these studies were not followed up using defined treatment protocols until recently. If one delays resuscitation further, the benefits of that activity diminish. For example, McKendry et al[80] used esophageal Doppler monitoring of mean blood flow to maximize preload in the immediate postoperative resuscitation of cardiac surgery patients. Their nurse-driven protocol targeted DO_2 values for only the first 6 postoperative hours. They observed a reduced length of hospital stay and a markedly reduced incidence of complications, most notably postoperative wound infections. Similarly, Pearse et al[67] followed that up with a similar study design in postoperative high-risk patients. They targeted a postoperative DO_2 of 600 mL/kg/min using arterial pressure-derived estimates of cardiac output. Importantly, the treatment group received more colloid and dopexamine infusions but had similar stroke volumes, Pra, and blood lactate levels with the control groups. They found similar reductions in hospital length of stay primarily because of a reduced incidence of postoperative complications.

These data demonstrate two important things. First, that in high-risk surgical populations, preoptimization applied prior to surgery and postoptimization therapies applied in the ICU in a protocolized fashion improves outcomes and reduce cost. Second, the longer one delays aggressive metabolic targeted resuscitation, the less the observed benefit. It is not clear how long the therapeutic window remains open before such aggressive therapies worsen outcome, as exemplified by Hayes et al.[76] Furthermore, it is not clear that similar metabolically targeted therapies will also be beneficial in other ICU patient populations, such as those with septic shock or single-organ failures such as primary ARDS and trauma. Furthermore, none of the above-mentioned clinical trials used the newly established SVV, PPV, or SPV methods of assessing preload responsiveness for clinical decision making. Clearly, prospective clinical trials of these proven treatment strategies and novel robust decision-support parameters used in different patient populations are needed. Still, the results of studies that have been completed using functional measures in targeted high-risk populations early in their disease have all been positive, whereas those studies using more traditional measures or using similar functional measures but applied later in the course of shock have been unsuccessful. The theme therefore appears to be clear: target patients at risk for tissue ischemia prior to severe organ injury using titrated therapies that monitoring circulatory sufficiency, and administer that therapy as soon as possible.

However, these consistent findings across studies, although promising, still reflect single-center trials using one proprietary blood flow-monitoring device (eg, esophageal Doppler, arterial pulse contour) in highly selected high-risk patient groups. What is needed is a large multicenter clinical trial aimed at early goal-directed treatment of all patients in shock from various etiologies for which the goals of therapy and the rapidity of treatment rather than the means to access treatment are the primary operative variables, while any within study comparison of monitoring device differences would be of secondary importance. If such studies documented improved patient outcomes, then the choice of which monitoring devices one uses would be subject more to issues of cost, convenience, and complications.

Future Monitoring Approaches

The future of hemodynamic monitoring is already here and can be summarized as focusing on measuring tissue wellness using continuous, noninvasive, and metabolic markers. Examples of these devices include sublingual PCO_2,[51,52] tissue oxygen saturation,[53] and capillary blood flow measured under the tongue.[54] The above continuous noninvasive measures describe metabolic effects of circulatory function. Potentially, they may be used to identify compensated shock and to define functional end points of resuscitation. When applied using the above-mentioned titration of resuscitation to restore and sustain tissue blood flow, such novel monitoring devices may add an extra dimension to our monitoring options by allowing real-time assessment of response to therapy and potentially when to stop. Since no prospective outcomes clinical trials have been done, the use of these novel monitoring approaches is speculative.

Conclusion

Enough clinical data have accumulated over the past 30 years to defend abolishing the use of static hemodynamic values, such as Pra and Ppao, as markers of preload responsiveness. Dynamic responses, to either a volume challenge or a physiologic reversible volume challenge using either positive pressure ventilation or PLR are highly sensitive and specific for preload responsiveness. Numerous prospective clinical trials[60–72] have documented improved outcome and reduced cost when early goal-directed therapies are applied in a protocolized fashion in high-risk patients, whereas no benefit and even harm may occur when aggressive resuscitation is applied late (> 12 h) in the course of circulatory shock.

References

1 Pinsky MR, Payen D. Functional hemodynamic monitoring. Crit Care 2005; 9:566–572

2 Moller JT, Pedersen T, Rasmussen LS, et al. Randomized evaluation of pulse oximetry in 20,802 patients: i. Design, demography, pulse oximetry failure rate, and overall complication rate. Anesthesiology 1993; 78:436–444

3 Moller JT, Johannessen NW, Espersen K, et al. Randomized evaluation of pulse oximetry in 20,802 patients: ii. perioperative events and postoperative complications. Anesthesiology 1993; 78:445–453

4 Weil MH, Shubin H. Shock following acute myocardium infarction: current understanding of hemodynamic mechanisms. Prog Cardiovasc Dis 1968; 11:1–17

5 Schmidt-Nielsen K. Circulation. In: Animal physiology. 4th ed. Cambridge, UK: Cambridge University Press; 1983; 97–133

6 Lush CW, Kvietys PR. Microvascular dysfunction in sepsis. Microcirculation 2000; 7:83–101

7 Buwalda M, Ince C. Opening the microcirculation: can vasodilators be useful in sepsis? Intensive Care Med 2002; 28:1208–1217

8 Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and non-lethal postoperative organ failure. Crit Care Med 1988; 16:1117–1120

9 LeDoux D, Astiz ME, Carpati C, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000; 28:2729–2732

10 Partrick DA, Bensard DD, Janik JS, et al. Is hypotension a reliable indicator of blood loss from traumatic injury in children? Am J Surg 2002; 184:555–559

11 Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. Crit Care Med 1991; 19:1365–1369

12 Bellomo R, Kellum JA, Wisniewski SR, et al. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. Am J Respir Crit Care Med 1999; 159:1186–1192

13 Pinsky MR, Vincent JL. Let us use the pulmonary artery catheter correctly and only when we need it. Crit Care Med 2005; 33:1119–1122

14 Carroll CC, Snyder JV. Hyperdynamic severe intravascular sepsis depends on fluid administration in cynomolgus monkey. Am J Physiol 1982; 243:R151–R161

15 Passos RH, Ricardo JS, Pereira AJ, et al. Radiologic assessment of volemic status: vascular pedicle width. Crit Care 2005; 9(suppl 2):P110–P112

16 Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002; 121:2000–2008

17 Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med 2004; 32:691–699

18 Papadakos PJ, Vender JS. Training requirements for pulmonary artery catheter utilization in adult patients. New Horiz 1997; 5:287–291

19 Pinsky MR. Clinical significance of pulmonary artery occlusion pressure. Intensive Care Med 2003; 29:175–178

20 Michard F, Chemla D, Richard C, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. Am J Respir Crit Care Med 1999; 159:935–939

21 The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network.

Pulmonary artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354: 2213–2224
22 The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354:2564–2575
23 Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32:858–873
24 Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med 2007; 35:64–68
25 Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276:889–897
26 Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003; 348:5–14
27 Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2003; 290:2713–2720
28 Yu DT, Platt R, Lanken PN, et al. Relationship of pulmonary artery catheter use to mortality and resource utilization in patients with severe sepsis. Crit Care Med 2003; 31:2734–2741
29 Van den Berg P, Jansen JRC, Pinsky MR. The effect of positive-pressure inspiration on venous return in volume-loaded post-operative cardiac surgical patients. J Appl Physiol 2002; 92:1223–1231
30 Vieillard-Baron A, Chergui K, Augarde R, et al. Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. Am J Respir Crit Care Med 2003; 168:671–676
31 Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 2001; 119:867–873
32 Berkenstadt H, Margalit N, Hadani M, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. Anesth Analg 2001; 92:984–989
33 Slama M, Masson H, Teboul JL, et al. Respiratory variations of aortic VTI: a new index of hypovolemia and fluid responsiveness. Am J Physiol Heart Circ Physiol 2002; 283:H1729–H1733
34 Monnet X, Rienzo M, Osman D, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. Intensive Care Med 2005; 31:1195–1201
35 Reuter D, Felbinger TW, Schmidt C, et al. Stroke volume variation for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. Intensive Care Med 2002; 28:392–398
36 Berkenstadt H, Margalit N, Hadani M, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. Anesth Analg 2001; 92:984–989
37 Wesseling KH, Jansen JRC, Settels JJ, et al. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 1993; 74:2566–2573
38 Slama M, Masson H, Teboul JL, et al. Monitoring of respiratory variations of aortic blood flow velocity using esophageal Doppler. Intensive Care Med 2004; 30:1182–1187
39 Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood flow velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 2001; 119:867–873
40 Perel A. Assessing fluid responsiveness by the systolic pressure variation in mechanically ventilated patients: systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. Anesthesiology 1998; 89:1309–1310
41 Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000; 162:134–138
42 Cannesson M, Besnard C, Durand PG, et al. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients. Crit Care 2005; 9:R562–R568
43 Natalini C, Rosano A, Taranto M, et al. Arterial versus plethysmographic dynamic indices to test responsiveness for testing fluid administration in hypotensive patients: a clinical trial. Anesth Analg 2006; 103:1478–1484
44 Reuter DA, Bayerlein J, Goepfert MS, et al. Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. Intensive Care Med 2003; 29:476–480
45 De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med 2005; 31:517–523
46 Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness during spontaneous breathing or with arrhythmia. Crit Care Med 2006; 34:1402–1407
47 Pinsky MR. Using ventilation-induced aortic pressure and flow variation to diagnose preload responsiveness. Intensive Care Med 2004; 30:1008–1010
48 Barbier C, Loubières Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 2004; 30:1740–1746
49 Feissel M, Michard F, Faller JP, et al. The respiratory variation in the inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 2004; 30:1834–1837
50 Vieillard-Baron A, Augarde R, Prin S, et al. Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 2001; 95:1083–1088
51 Vieillard-Baron A, Chergui K, Rabiller A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 2004; 2004; 30:1734–1739
52 Jellinek H, Krafft P, Fitzgerald RD, et al. Right atrial pressure predicts hemodynamic response to apnoic positive airway pressure. Crit Care Med 2000; 28:672–678
53 Thomas M, Shillingford J. The circulatory response to a standard postural change in ischaemic heart disease. Br Heart J 1965; 27:17–27
54 Boulain T, Achard JM, Teboul JL, et al. Changes in blood pressure induced by passive leg raising predict response to fluid loading in critically ill patients. Chest 2002; 121:1245–1252
55 Singer M, Clarke J, Bennett D. Continuous hemodynamic monitoring by esophageal Doppler. Crit Care Med 1989; 17:447–452
56 Valtier B, Cholley BP, Belot JP, et al. Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. Am J Respir Crit Care Med 1998; 158:77–83
57 Carlon A, Menchi M, Joly LM, et al. Noninvasive cardiac output monitoring by aortic blood flow determination: evaluation of the Sometec Dynemo-3000 system. Crit Care Med 1998; 1998; 26:2066–2072
58 Linton R, Band D, O'Brien T, et al. Lithium dilution cardiac output measurement: a comparison with thermodilution. Crit Care Med 1997; 25:1716–1800
59 Pittman J, Bar-Yosef S, SumPing J, et al. Continuous cardiac

output monitoring with pulse contour analysis: a comparison with lithium indicator dilution cardiac output measurement. Crit Care Med 2005; 33:2015–2021
60 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368–1377
61 Can TJ, Soppitt A, Marcoof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97:820–826
62 Fenwick E, Wilson J, Scrimgeor M, et al. Pre-operative optimisation employing dopexamine or adrenaline for patients undergoing major elective surgery: a cost-effectiveness analysis. Intensive Care Med 2002; 28:590–608
63 Venn R, Steele A, Richardson P, et al. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002; 88:65–71
64 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995; 130:423–429
65 Tang W, Weil MH, Sun S, et al. Gastric intramural PCO_2 as a monitor of perfusion failure during hemorrhagic and anaphylactic shock. J Appl Physiol 1994; 76:572–577
66 McKendry M, McClein H, Sabert D, et al. Randomized controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimization of circulatory status after cardiac surgery. BMJ 2004; 329:438–444
67 Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay: a randomized, controlled trial. Crit Care 2005; 9:R687–R693
68 Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94:1176–1186
69 Boyd O, Grounds M, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993; 270:2699–2707
70 Lobo S, Salgado P, Castillo VGT, et al. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000; 28:3396–3404
71 Coopfert MS, Reuter DA, Akyol D, et al. Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 2007; 33:96–103
72 Bland RD, Shoemaker WC, Abraham E, et al. Hemodynamic and oxygen transport patterns in surviving and nonsurviving postoperative patients. Crit Care Med 1985; 13:85–90
73 Tuchschmidt J, Fried J, Astiz M, et al. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992; 102:216–220
74 Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients: SvO_2 Collaborative Group. N Engl J Med 1995; 333:1025–1032
75 Hayland DK, Cook DJ, King D, et al. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996; 1996; 24:517–524
76 Hayes MA, Timmins AC, Yau EH, et al. Evaluation of systemic oxygen delivery in the treatment of the critically ill. N Engl J Med 1994; 330:1717–1722
77 Rathbart K, Kuhn HJ, Hartog C, et al. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 2004; 30:1572–1578
78 Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002; 30:1686–1692
79 Vincent JL, de Carvalho FB, Dollacker D. Management of septic shock. Ann Med 2002; 34:606–613
80 Jastremski MS, Chelburt L, Bonny KM. Analysis of the effects of continuous on-line monitoring of mixed venous oxygen saturation on patient outcome and cost-effectiveness. Crit Care Med 1989; 17:148–153
81 Nakagawa Y, Weil MH, Tang W, et al. Sublingual capnometry for diagnosis and quantification of circulatory shock. Am J Respir Crit Care Med 1998; 157:1838–1843
82 Marik PE, Bankov A. Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 2003; 31:818–822
83 Clavijo-Alvarez JA, Sims CA, Sollar B, et al. Monitoring skeletal muscle and subcutaneous tissue acid-base status and oxygenation during hemorrhagic shock and resuscitation. Shock 2005; 24:270–276
84 Dollacker D, Creteur J, Preiser JC, et al. Microcirculatory blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 2002; 166:98–104

Perfusion monitoring and hemodynamic interventions at five represenative levels — HISTORY

Year	Perfusion Monitor	Hemodynamic Intervention
1950	Auscultatory BP	Fluid administration, pressors: Norepinephrine Phenylephrine Epinephrine
1965	Direct arterial BP	Fluid adminstration, pressors: Norepinephrine Phenylephrine Epinephrine
1970	Indocyanine green dye cardiac output	Fluid administration, pressors: Norepinephrine Phenylephrine Epinephrine
1975	Thermodilution cardiac output plus PLWP	Fluid administration, pressors, intra-aortic balloon pump, inotropic agents, vasodilators: Norepinephrine Phenylephrine Epinephrine Dopamine Sodium nitroprusside
1980	SvO_2	Fluid administration, pressors, intra-aortic balloon pump, inotropic agents, vasodilators
1990	Continuous CO monitoring	

Monitor characteristics

- Accuracy of Measurement
  - Bias
  - Precision
- Incorporation into Clinical Reasoning
  - Sensitivity
  - Positive predictive value
  - Specificity
  - Negative predicitive value
  - Cutoff point definition
  - Speed
  - Utility in clinical reasoning process
    - Diagnosis
    - Surveillance
    - Patient management

Systemic Perfusion	Systemic Oxygenation	Cerebral Oxygenation
Auscultatory BP	Cyanosis	Neurologic examination
Direct arteral BP	Arterial blood gases	systemic BP
Indocyanine green dye cardiac output	Ear oximetry Pulse oximetry	ICP
Thermodilution cardiac output	$Ptco_2$	CBF
Svo_2	Pulse oximetry	Niroscopy
Lactic acidosis	Oxygen delivery & consumption	

Modified from D. Prough, Critical Care Vol 11, 1990

Monitoring cardiac output

Method	Sensitivity	Specificity	Speed	Utility: Surveillance	Utility: Patient Management
BP	1+	2+	4+	3+	3+
TEB	2+	2+	4+	2+	2+
Esophageal Doppler	3+	3+	4+	2+	2+
Thermodilution PA catheter	3+	3+	3+	3+	4+
Continuous Svo_2	3+	3+	4+	3+	4+

Modified from D. Prough, Critical Care Vol 11, 1990

Oxygenation monitoring in ICU

Method	Sensitivity	Specificity	Speed	Utility: Surveillance	Utility: Patient Management
Pulse oximetry	3+	3+	4+	4+	4+
$Ptco_2$	2+	2+	3+	2+	2+
In-line oxygen analyzer	2+	4+	4+	3+	1+
Capnography	1+	1+	3+	3+	1+
Qsp/Qt calculation	4+	4+	2+	2=	2+
Continuous Svo_2	3+	3+	4+	3+	3+
Dual oximetry	3+	2+	4+	4+	4+

Modified from D. Prough, Critical Care Vol 11, 1990

Regional Vo_2 and distribution of oxygen transport

Tissue	Vo_2 (% of total)*	Oxygen Transport (% of total)*	Fractional Oxygen Extraction
Heart	11	4	.60
Skeletal muscle	30	21	.44
Brain	20	13	.33
Splanchnic circulation	25	24	.22
Kedney	7	19	.07
Skin	2	9	.05

*Note that column does not toal 100% because all organs are not included

G. Lister, Vol. 12, Critical Care, 1991

Pulse Oximetry

Conditions Adversely affecting Accuracy of oximetry

I. **Conditions resulting in poor signal:**

* probe malposition, * motion, * hypothermia
* no pulse, * vasoconstriction, * hypotension

II. **Falsely lowers $Sp0_2$**

Nail polish, Dark skin, infrared heating lamp
Elevated serum lipid, Methylene blue, Indocyanine dye
Indigo carmine, Presence of significant venous pulsation,
Severe Rt. Heart failure, Obsruction to venous return,

III. **Falsely raises SpO_2**

Elevated carboxyhemoglobin, Elevated methehemoglobin
Ambient light, hypothermia

TABLE 1. INDICATIONS FOR PULMONARY ARTERY CATHETERIZATION

I. Assessment and Management of shock
* Differentiation of shock (preload, output, afterload failure)
* Cardiogenic,
* Septic,
* Hypovolemic

II. Monitoring : Hemodynamic instability due to any cause

III. Management of complicated myocardial infarction:
* Severe LV failure
* Low cardiac output syndrome
* Evaluation of ventricular function
* Rt Ventricular infarction
* Ventricular septal defect

IV. Diagnostic Indications (along with monitoring)
* Valvular lesions such as acute mitral regulation
* Right ventricular dysfunction
* Chronic congestive heart failure (constrictive pericarditis, cardiomyopathy, etc.)
* Pericardial tamponade

V. Differentiation of pulmonary edema (cardiogenic versus permeability)
Pulmonary hypertension
Pulmonary embolism

VI. Assessment of oxygen transport:
Optimizing oxygen transport and consuption

VII. Monitoring Indications
* Shock or hemodynamic instability
* Trending response to titrated hemodynamic therapy:
* Intravascular volume and LVEDVassessment and manipulations.
* Inotropic therapy

VIII. Peri-operative monitoring
* Cardiothoracic, Vascular or major abdominal procedures
* Patient with significant cardio-pulmonary disease undergoing major surgery
* Aspiration of air emboli in neurosurgical patients during operation in sitting position
* Severe trauma

IX. * Ventricular pacing via paceport PA catheter

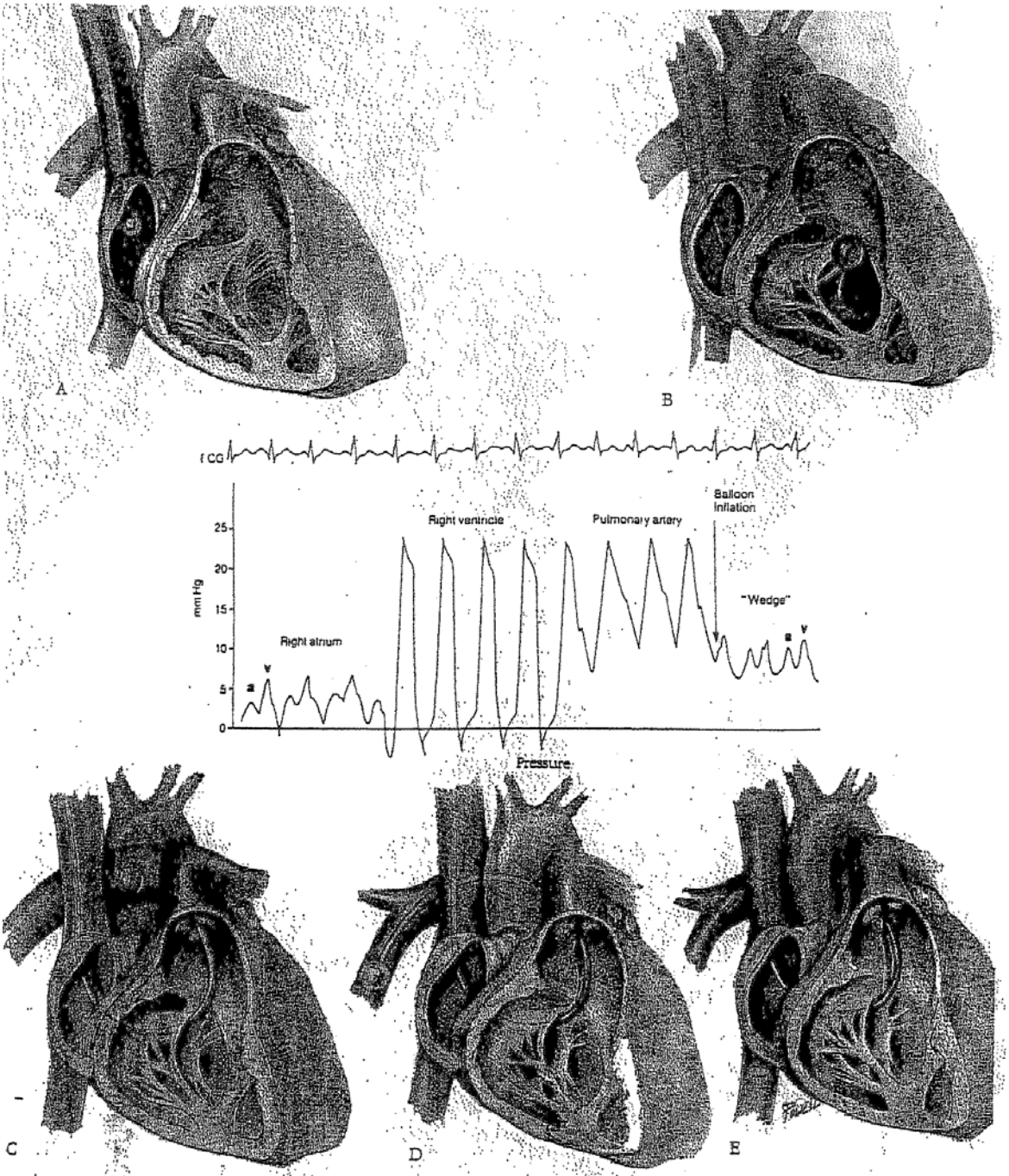


Fig. 1 Center. Waveform tracings generated as the balloon-tipped catheter is advanced through the right heart chambers into the pulmonary artery. RA = right atrium; RV = right ventricle; PA = pulmonary artery; PAWP = pulmonary artery wedge pressure. A. With the catheter tip in the RA, the balloon is inflated. B. The catheter is advanced into the RV with the baloon inflated and RV pressure tracings are obtained. C. The catheter is advanced through the pulmonary valve into the pulmonary artery. A rise in diastolic pressure will be noted. D. The catheter is advanced to the PAWP position. A typical PAWP tracing will be noted with A and V waves. E. The balloon is deflated. Phasic PA pressure should reappear on the monitor. (See text for details.) (Center figure adapted from Wiedmann HP: Cardiovascular-pulmonary monitoring in the intensive care unit, I. *Chest* 85:540, 1984. With permission.)

Table 2. RELATIVE CONTRAINDICATIONS FOR PULMONARY ARTERY CATHETER

Severe coagulpathy
Significant thrombocytopenia
Prosthetic right heart valve
Endocardial pacemaker
Infection or tissue problem at proposed site
Severe vascular disease at proposed site
Serious ventricular arthythmias
Pulmonary hypertension - moderate to severe

Table 3. COMPLICATIONS ASSOCIATED WITH PULMONARY ARTERY CATHETERIZATION

	Reported Incidence (%)
I. Associated with central venous cannulation	
Arterial puncture	2–16
Local thrombosis	66
Pneumothorax	2–4
Hydrothorax	2
Hemothorax	<1
Brachial plexus damage	<1
Air embolism	<1
Phrenic and recurrent laryngeal nerve damage	<1
Hemorrhage at puncture site	2
II. Associated with advancement of PA catheter	
Atrial and ventricular premature beats	13–87
Ventricular tachycardia	11–63
Ventricular fibrillation	1.5–2.5
Ventricular fibrillation, requiring countershock	0.4–0.85
Right bundle branch block	2.6–5.9
Complete heart block	<1
Cardiac perforation and tamponade	<1
Catheter knotting	<1
III. Associated with maintenance of catheter	
Mural thrombus	14–91
Infection (positive catheter tip culture)	4.9–45
Infection (risk of sepsis)	0.3–0.5
Catheter-related endocardial lesions	33–91
Pulmonary infarction	1–7
Pulmonary artery rupture/hemorrhage	0.06–2.0
Balloon rupture	

TABLE4/ RECOMMENDATIONS TO MINIMIZE COMPLICATIONS OF HEMODYNAMIC MONITORING

Formal outline of procedures, methods of data collection, significance and interpretation
Supervision of physician - operator by expert (one who knows)
In-service supervised programs for nursing and technical personnel,
Independent quality control of data collection and interpretation

Anticipate potential complications
Read listing of potential complications
Identify high-risk patient
- Age
- Short neck
- Cervical Kyphoscoliosis
- Obesity
- Acuity of illness
- Preexisting arrhythmias
- Conduction abnormalities
- Pulmonary hypertension

Insertion - never force catheter through introducer

Full inflation of balloon in the right atrium, firm advancement approximately 2 cm/sec
Use fluoroscopy if available; if not, obtain chest film after procedure
Daily x-ray examination for position and redundant loops
Withdraw catheters if ventricular ectopy or heart block occurs
Avoid distal positioning of catheter tip; slow inflation if position of tip is unknown
Care in interpretation of damped records
Account for respiratory variation in pressure and flow
Remove catheter as soon as clinical situation warrants

Table[5] HEMODYNAMIC-CLINICAL CORRELATIONS IN ACUTELY ILL PATIENTS

Hemodynamic Variables	Clinical Correlates
Cardiac index	
2.2-2.5 L/min/m^2	Subclinical or mild hypoperfusion
1.5-2.2 L/min/m^2	Organ hypoperfusion, moderate
<1.5 L/min/m^2	Shock
Pulmonary Capillary Wedge pressure	
5-15 mm HG	Normal range
18-25 mm HG	Pulmonary congestion, moderate
>25 mm HG	Pulmonary edema

Discrepancies may occur in 20 to 30 percent of acutely ill patients and more frequently in the presence of longstanding cardiac dysfunction.

DERIVED PARAMETERS. Useful hemodynamic parameter that can be derived using data with PA catheters include:

1. Cardiac index = $\frac{\text{cardiac output (CO) in L/min}}{\text{body surface area (BSA) in m}^2}$

2. Stroke Volume = $\frac{\text{cardiac output (L/min)}}{\text{heart rate (beats/min)}}$

3. Stroke index = $\frac{\text{CO (L/min)}}{\text{heart rate (beats/min)} \times \text{BSA (m}^2\text{)}}$

4. Mean arterial pressure (mm Hg) = $\frac{(2 \times \text{diastolic}) + \text{systolic}}{3}$

5. Systemic vascular resistance (dyne/sec/cm^{-5}) =

$$\frac{\text{mean arterial pressure} - \text{mean right atrial pressure (mm Hg)}}{\text{cardiac output (L/Min)}} \times 80$$

6. Pulmonary arteriolar resistance (dyne/sec/cm^{-5}) =

$$\frac{\text{mean PA pressure} - \text{mean PCW pressure (mm Hg)}}{\text{CO (L/min)}} \times 80$$

7. Total pulmonary resistance (dyne/sec/cm^{-5}) =

$$\frac{\text{mean PA pressure (mm Hg)}}{\text{CO (L/min)}} \times 80$$

8. Left ventricular stroke work index =

$$\frac{1.36\,(\text{MAP} - \text{PAWP}) \times \text{SI}}{100}$$

9. Oxygen delivery (DO_2) (ml/min/M^2) = $CI \times CaO_2$

Cardiac index × arterial O_2 content

Normal values are listed in Table 4-5.

Table 6. Selected Hemodynamic Variables Derived from Right Heart Catheterization

Hemodynamic variable	Normal range
Arterial venous content difference	3.5–5.5 ml/100 ml
Cardiac index	2.5–4.5 L/min/m²
Cardiac output	3.0–7.0 L/min
Left ventricular stroke work index	45–60 gm/beat/m²
Mixed venous oxygen content	18.0 ml/100 ml
Mixed venous saturation	75% (approx.)
Oxygen consumption	200–250 ml/min
Pulmonary vascular resistance	120–250 dyne/sec/cm^{-5}
Stroke volume	70–130 ml/contraction
Stroke volume index	40–50 ml/contraction/m²
Systemic vascular resistance	1100–1500 dyne/sec/cm²

Adapted from Gore JM, Alpert JS: *Handbook of Hemodynamic Monitoring*. Boston, Little, Brown, 1984, with permission.

oxygen saturation of 95 percent, and a mixed venous oxgyen saturation of 70 percent, follows:

$$\text{Cardiac output} = \frac{250 \text{ ml/min}}{(0.95)(14)(1.39)(10) - (0.70)(14)(1.39)(10)}$$

$$= \frac{250 \text{ ml/min}}{181 - 136 \text{ ml/L}}$$

$$= 5.55 \text{ L/min}$$

CaO_2=O_2 content
= (HbX1.34*) x % saturation + (PaO_2X0.0031) x 10
= (19.5+0.5) x 10
= 200 ml

Table 7. Normal Resting Pressures Obtained During Right Heart Catheterization

Cardiac chamber	Pressure (mm Hg)
Right atrium	
Range	0–6
Mean	3
Right ventricle	
Systolic	17–30
Diastolic	0–6
Pulmonary artery	
Systolic	15–30
Diastolic	5–13
Mean	10–18
Pulmonary artery wedge (mean)	2–12

Adapted from Gore JM, Alpert JS: *Handbook of Hemodynamic Monitoring*. Boston, Little, Brown, 1984, with permission.

Table 8. Approximate Normal Oxygen Saturation and Content Values

Chamber sampled	Oxygen content (vol%)	Oxygen saturation (%)
Superior vena cava	14	70
Inferior vena cava	16	80
Right atrium	15	75
Right ventricle	15	75
Pulmonary artery	15	75
Pulmonary vein	20	98
Femoral artery	19	96
A–V oxygen content difference	3.5–5.5	

Adapted from Gore JM, Alpert JS: *Handbook of Hemodynamic Monitoring*. Boston, Little, Brown, 1984, with permission.

The latter problem is more frequently encountered in shorter patients [43].

Table 9. Hemodynamic Parameters in Commonly Encountered Clinical Situations (Idealized)

	RA	RV	PA	PAWP	AO	CI	SVR	PVR
Normal	0–6	25/0–6	25/6–12	6–12	130/80	≥2.5	1500	≤250
Hypovolemic shock	0–2	15–20/0–2	15–20/2–6	2–6	≤90/60	<2.0	>1500	≤250
Cardiogenic shock	8	50/8	50/35	35	≤90/60	<2.0	>1500	≤250
Septic shock								
Early	0–2	20–25/0–2	20–25/0–6	0–6	≤90/60	≥2.5	<1500	<250
Late[a]	0–4	25/4–10	25/4–10	4–10	≤90/60	<2.0	>1500	>250
Acute massive pulmonary embolism	8–12	50/12	50/12–15	≤12	≤90/60	<2.0	>1500	>450
Cardiac tamponade	12–18	25/12–18	25/12–18	12–18	≤90/60	<2.0	>1500	≤250
AMI without LVF	0–6	25/0–6	25/12–18	≤18	140/90	≤2.5	1500	≤250
AMI with LVF	0–6	30–40/0–6	30–40/18–25	>18	140/90	>2.0	>1500	>250
Biventricular failure 2° to LVF	>6	50–60/>6	50–60/25	18–25	120/80	~2.0	>1500	>250
RVF 2° to RVI	12–20	30/12–20	30/12	<12	≤90/60	<2.0	>1500	>250
COR pulmonale	>6	80/>6	80/35	<12	120/80	~2.0	>1500	>400
Idiopathic pulmonary hypertension	0–6	80–100/0–6	80–100/40	<12	100/60	<2.0	>1500	>500
Acute VSR[b]	6	60/6–8	60/35	30	≤90/60	<2.0	>1500	>250

RA = right atrium; RV = right ventricle; PA = pulmonary artery; PAWP = pulmonary artery wedge pressure; AO = aortic; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; AMI = acute myocardial infarction; LVF = left ventricular failure; RVI = right ventricular infarction; RVF = right ventricular failure; VSR = ventricular septal rupture; CI = cardiac index

[a] Hemodynamic profile seen in approximately ⅓ of patients in late septic shock.

[b] Confirmed by appropriate RA–PA oxygen saturation step-up. See text for discussion.

Adapted from Gore JM, Alpert JS: *Handbook of Hemodynamic Monitoring*. Boston, Little, Brown, 1984, with permission.

TABLE 10 HEMODYNAMIC PROFILE OF SELECTED CLINICAL DISORDERS

Clinical Syndrome	Salient hemodynamic Alterations	Additional Comments
Cardiogenic (ventriculopenic) shock	↑PCWP, ↓SV, ↓CO, ↑SVR, ↓AP	Reflex sinus tachycardia may be present
Hypovolemic shock	↓PCWP, ↓SV, ↓CO, ↑SVR, ↓AP	Orthostatic tachycardia
Ischemic RVP dysfunction	↑RAP, ≥PCWP, ↓SV, ↑SVR, ↓AP	Steep "Y" descent on RAP tracing, early diastolic dip and plateau in RVP tracing may be present
Acute mitral regurgitation	↑PCWP, prominent "V" waves in PCWP	Transmitted "V" waves may be also be seen in PAP tracing
Acute ventricular septal rupture	O_2 saturation in PAP and RVP exceeds that in RAP (O_2 step up) forward output	Early recirculation on thermodilution curve, RVP forward output exceeds LVP
Acute cardiac tamponade	↑RAP = ↑PAP, ↓SVR, ↓CO, ↓AP	Systemicarterial pulsus paradoxus; blunted "Y" and prominent "X" descent, Kussmaul sign rare
Systemic sepsis (early phase)	↓PVR, ↑PAP, ↓SVR, ↑SV, ↑CO	
Noncardiac pulmonary edema	nl PCW	Pulmonary edema with a normal heart size
Acute massive pulmonary embolism	↑PVR, ↑PAP, nl PCWP, ↓SV, ↓CO, ↓AP	
Constrictive pericarditis	↑RAP = ↑PCWP, dip and plateau in RVP pressure, steep "Y" descent in	Positive Kussmaul sign, pulsus paradoxus is rare, may simulate
RV		RAP pressure infarction or restrictive cardiomyopathy
Restrictive cardiomyopathy	As above ; but often PCWP>RAP	Distinction from constrictive pericarditis can be difficult and additional studies are often needed

Table 11. Does management with pulmonary artery catheters improve patient outcomes?

Disease/Disorder and Question Number	Answer	Grade	Randomized, Controlled Trial Recommended
Myocardial Infarction With			
Hypotension or cardiogenic shock (*I A*)	Yes[a]	E	Yes
Mechanical complication (*I B*)	Yes	E	Yes
Right ventricular infarction (*I C*)	Yes	E	Yes
Congestive heart failure (*I D*)	Uncertain	D	Yes
Pulmonary hypertension (*I E*)	Uncertain[c]	E	Yes
Shock or hemodynamic instability (*I F*)	Uncertain	E	Yes
Cardiac Surgery (*II A*)	—	—	Yes
Low risk	No	C	—
High risk	Uncertain	C	—
Peripheral Vascular Surgery (*II B*)	—	—	Yes
Reduced complications	Yes	D	—
Reduced morbidity	Uncertain	D	—
Aortic Surgery (*II C*)	—	—	Yes
Low risk	Uncertain	B	—
High risk	Yes	E	—
Geriatric patients undergoing surgery (*II D*)	No	E	Yes
Neurosurgery (*II E*)	Uncertain	E	Yes
Preeclampsia (*II F*)	Not routinely	E	Yes
Trauma (*III A*)	Yes	E	Yes
Sepsis/septic shock (*IV*)	Uncertain	D	Yes
Supranormal Oxygen Delivery	—	—	Yes
SIRS (*V A*)	Uncertain	B	—
High-risk surgery (*V B*)	Uncertain	C	—
Respiratory failure (*VI B*)	Uncertain	E	Yes
Pediatric patients (*VII B*)	Yes[a]	E	Yes

Table 12. Grading of responses to questions and levels of evidence

Grading of Responses to Questions	
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 evidence
Levels of Evidence	
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) 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

Adapted from Sackett (31).

TABLE 7 THERAPEUTIC GUIDELINES BASED ON HEMODYNAMIC PROFILE

Condition	Suggested Immediate Intervention
Pulmonary congestion or edema with elevated PCW	Diuretics Vasodilators : nitrates, nitroprusside Consider IABP if associated with Continuing or recurrent ischemia Shock Acute severe mitral regurgitation or ventricular septal rupture Poor response to vasodilators and diuretics Consider hemofiltration or dialysis if associated with severe renal insufficiency or resistant oliguria
Low-output or shock syndrome with low or normal PCWP and PAP	Rapid volume expansion till PCWP of 15-18 mm Hg; If no response, add an inotropic catecholamine (dopamine or dobutamine)
With high RAP, normal PCWP and PAP with ECG evidence of inferior infarction	Consider RVP infarction; use Inotropes with or without additional volume
With high PCWP and PAP	Vasodilators to reduce preload and afterload Diuretics to reduce preload Inotropic vasopressors if patient is hypotensive Consider IABP as indicated above
With high RAP, RAP=PCWP and pulsus paradoxus and echo evidence of pericardial effusion	Consider tamponade, confirm with echocardigraphy and perform pericardiocentesis
With high RAP, high PAP but normal PCWP	Consider pulmonary embolism, confirm with angiography or lung scan, and treat accordingly with thrombolytic and anticoagulant therapy. May also be caused by pulmonary parenchymal or obliterative vascular or airway disease.
With high CO, low SVR	Consider early sepsis, look for source and type of infection, and treat accordingly.

DIASTOLIC OR PULMONARY ARTERY WEDGE PRESSURE MONITORING

Fluid Challenge: P_{PAW}, P_{PAD} mm Hg (7-3 rule)

Observe P_{PAD}/P_{PAW}	< 12 mm Hg	200 ml x 10 min
for 10 min	< 16 mm Hg	100 ml x 10 min
	≤ 16 mm Hg	50 ml x 10 min
During infusion 0-9 min	> 7 mm Hg	STOP
Immediately following	> 3 < 7 mm Hg	Wait 10 min
10 min infusion	> 3 mm Hg	Wait STOP
	≤ 3 mm Hg	Continue infusion

GUIDELINES FOR FLUID CHALLENGE

UTILIZING CENTRAL VENOUS PRESSURE MONITORING

Fluid Challenge: CVP, cm H_2O (5-2 rule)

Observe CVP for 10 min	<8 cm H_2O	200 ml x 10 min	Peripher IV
	<14 cm H_2O	100 ml x 10 min	
	≤14 cm H_2O	50 ml x 10 min	
During infusion 0-9 min	5 cm	STOP	
Following infusion	>2 cm<5 cm	Wait 10 min	
	>2 cm	Wait STOP	
	≤2 cm	Continue infusion	

Choice of Pulmonary Artery Catheters

- Variety of choices: Range 4-7.5 F, length 60 to 110 cm.
  3 lumen is standard. Has CVP, PA Balloon & thermodilution for CO
- 4 Lumen catheter (VIP)
- 4 lumen Pacing version (ventricular)
- 4 -5 lumenn fiberoptic
- Rt Ventricular Ejection Fraction

Clinical Use of the Pulmonary Artery Catheter

Diagnosis

Differentiation among causes of shock
- Cardiogenic
- Hypovolemic
- Distributive (sepsis)
- Obstructive (massive pulmonary embolism)

Differentiation between mechanisms of pulmonary edema
- Cardiogenic
- Noncardiogenic

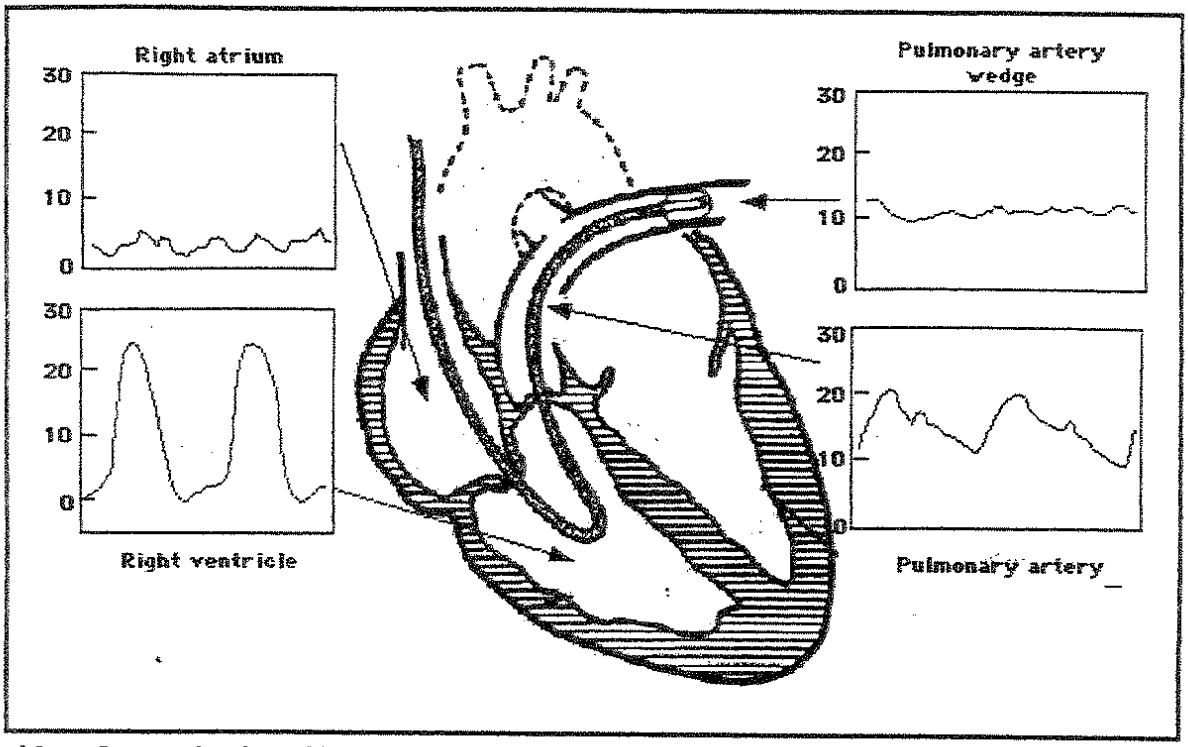
Evaluation of pulmonary hypertension
Diagnosis of pericardial tamponade
Diagnosis of left-to-right intracardiac shunt
Diagnosis of lymphangitic spread of tumor and fat embolism (case reports based on blood aspirated from wedge position)

Therapy

Management of perioperative patient with unstable cardiac status
Management of complicated myocardial infarction
Management of patients following cardiac surgery
Management of severe preeclampsia
Guide to pharmacologic therapy
- Vasopressors
- Inotropes
- Vasodilators (for patients with pulmonary hypertension)

Guide to nonpharmacologic therapy:
- Fluid management
  - Gastrointestinal bleed
  - Traumatic exsanguination
- Burns
- Renal failure
- Sepsis
- Heart failure
- Decompensated cirrhosis

Ventilator management (assessment of best PEEP for O2 delivery)



Waveforms by location of the Swan-Ganz catheter tip Tracings obtained in the right atrium or pulmonary capillary wedge position share similar morphology. The transition from the right ventricle to the pulmonary artery tracing can be identified by the increase in diastolic pressure and the presence of a dicrotic notch. The diastolic "step-up" results from the transducer crossing the pulmonic valve; the dicrotic notch reflects closing of the pulmonic valve. Redrawn from Marino, PI. The ICU Book, Philadelphia, Lea and Feliger, 1991, p. 103.

Generic/Trade Names

Generic names and trade names (in parentheses) of drugs mentioned in this article are clonidine (Catapres), aminoglutethamide (Cytadren), and metyrapone (Metopirone).

References

1. Ferns, Brown, Fraser, Lever, Robertson. Primary hyperaldosteronism. Clin Endocrinol Metab 1981; 10(3):419-445.
2. Lange, Current medical diagnosis and treatment. 1983; 715-716.
3. Scoggins et al. Primary hyperaldosteronism. Pharmacol Ther 1980; 9:367-394.
4. Hiramatsu et al. A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Arch Intern Med 1981; 141:1589-93.
5. Streeten, Tomycz, Gunnar. Reliability of screening methods for the diagnosis of primary hyperaldosteronism. Am J Med 1979; 67:403-413.
6. Vaughn, Slater, Lightman, Payne, Jouett, Wiggins. The diagnosis of primary hyperaldosteronism. Lancet 1981; 1:120-125.
7. Machet, Crane, Smith. Surgical management of aldosterone-producing adrenal adenoma. Am J Surg 1981; 142:89-95.
8. Brennan, Saxe. Adrenal neoplasms. Surg Oncol 1983; 428-431.

Medical Grand Rounds

West Virginia University Medical Center

Edited by Irma H. Ullrich, M.D., Professor of Medicine

Physiologic Profile And The Critically Ill Patient

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Introduction

In some critically ill patients, hypotension, hypoxemia and oliguria cannot be explained despite close monitoring of pulse rate, central and systemic blood pressure. The fact that fluid overload, hypovolemia, pulmonary edema and tissue hypoperfusion can develop in patients with normal systemic blood pressure and arterial oxygen tension, indicates that some additional hemodynamic, respiratory, oxygen transport and oxygen consumption variables should be considered in the diagnosis and treatment of high-risk, critically ill patients.

The introduction in critical care of the pulmonary artery catheter and later development of the "Automated Physiologic Profile" (APP) have provided the critical care specialist with rapid and easy bedside measurement of some very useful cardiovascular, respiratory and metabolic parameters. This information can be obtained as frequently as needed in order to guide the therapy rationally with inotropic and vasoactive drugs as well as fluid administration.

The "Automated Physiologic Profile" can be obtained with a simple pocket calculator, though a significant amount of time can be saved with a "built-in," programmable calculator (Hewlett-Packard; Clinic Data Service, Inc.). In Addition, most of the modern ICU bedside monitors (Marquett Electronic, Inc. Gould Electronics; Hewlett-Packard and cardiac output computers (Waters Instruments, Inc.) already have a program incorporated which allows some hemodynamic variable to be obtained.

Through the APP, the three components of the cardiovascular system (preload, afterload and cardiac pump) can be evaluated separately (Figure 1). Further, some respiratory, oxygen transport and oxygen consumption variables can also be determined.

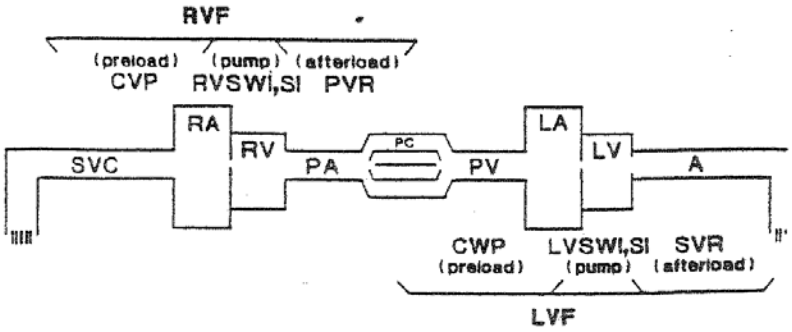

Figure 1. Cardiovascular compartments and hemodynamic variables representing them. (See glossary for abbreviations.)

Indications

Obtaining a physiologic profile is indicated for the assessment of patients with a wide variety of conditions:

1) management of hypotension and circulatory shock
2) assessment of cardiac function in:
   a) congestive heart failure
   b) myocardial infarction
   c) cardiomyopathies
   d) valvular dysfunction
   e) pericardial tamponade
   f) cardiovascular surgery
   g) monitoring of the surgical patient with unstable cardiovascular status
3) fluid status in:
   a) acute renal failure
   b) shock
   c) burn
   d) sepsis
   e) liver failure

TABLE 1

Physiologic Profile (see glossary for abbreviations)

Hemodynamic Values		
__Syst BP (M)	__PA Syst (M)	__CO (M)
__Dias BP (M)	__PA Dias (M)	__CI (C)
__MAP (C)	__MPAP (C)	__HR (M)
__CVP (M)	__PCWP (M)	__SV (C)
__SVR (C)	__PVR (C)	__SI (C)
__SVRI (C)	__PVRI (C)	__LVSWI (C)
		__BSA (C)

Blood Gases		
__P_aO_2 (M)	__A_aDO_2 (C)	__P_{50} (C)
__Art pH (M)	__PvO_2 (M)	__Temp (M)
__Art BE (M)	__MV pH (M)	__Hgb (M)
__$PaCO_2$ (M)	__MV BE (M)	__F_iO_2 (M)
__SaO_2 (M)	__SvO_2 (C)	__$\dot{V}O_2$ (C)
__CaO_2(M)	__CvO_2 (C)	__$\dot{V}O_2I$ (C)
__$\dot{D}O_2$ (C)	__$avDO_2$ (C)	__O_2ER (C)
__$\dot{D}O_2I$ (C)	__$\dot{Q}s/\dot{Q}t$ (C)	

(M) = measured parameters
(C) = calculated parameters

4) respiratory distress:
   a) to differentiate cardiogenic from non-cardiac causes
   b) as an aid in diagnosis of pulmonary hypertension (pulmonary vs. non-pulmonary)
5) monitor therapy:
   a) vasodilators (CHF, dissenting aortic aneurysm)
   b) inotropics (low cardiac output states, shock)
   c) fluid replacement
   d) barbiturate coma

Methodology

In order to calculate the different variables of a physiologic profile, the measured parameters listed in Table 1 are needed. This information is collected at the bedside with the use of pulmonary artery catheter and cardiac output computer. Cardiac outputs are obtained by thermodilution technique.

For blood gas analysis, two blood samples are withdrawn simultaneously, one from the pulmonary artery port (mixed venous), the other from a systemic artery. The mixed venous sample should be withdrawn slowly (1 cc/20 sec) to avoid aspiration of arterialized blood from the pulmonary capillary or pulmonary vein territory.

When the above data is fed into one of the previously mentioned computers, the calculated, derived variables outlined in Table 1 will be obtained. These variables can be separated into two categories: A) Hemodynamics, related to the cardiovascular system; and B) "Blood Gases," concerning gas exchange, oxygen delivery and oxygen consumption.

In addition, plotting the patient's left ventricular stroke work index (LVSWI) and capillary wedge pressure (CWP) over a Sarnoff's ventricular function curve, the level of myocardial performance can be determined (Figure 2).

Derived Hemodynamic Parameters

A) Cardiac Index (CI) = $\frac{\text{Cardiac Output}}{\text{BSA}}$;
Normal 2.5-4.5 L $min^{-1}.m^{-2}$

CI is increased by: anemia, exercise, sepsis, hyperthyroidism, positive inotropic drugs.

CI is decreased in: cardiogenic shock, hypovolemia, congestive heart failure, large pulmonary embolism, cardiomyopathies, pericardial diseases, negative inotropic drugs.

B) Stroke Volume (SV) = $\frac{CO}{HR}$;
Normal 60-85 ml

Stroke Volume Index (SI) = $\frac{CI}{HR}$;
Normal 35-48 $ml.m^{-2}$

SI is increased in: sepsis, bradycardia, positive inotropics, hypervolemia, hypertension, aortic regurgitation, physical fitness and "high output failure."

SI is decreased in: hypovolemia, cardiogenic shock, cardiomyopathies, aortic stenosis, and negative inotropics.

C) Left Ventricular Stroke Work Index (LVSWI) = $\frac{(CI \times MAP) \times 13.6}{HR}$;
Normal 44-70 $gm.m.m^{-2}$

LVSWI increases in hypervolemic states and hypertension.

LVSWI decreases in: left ventricular failure, cardiogenic shock, severe aortic stenosis, and late stages of septic shock.

D) Systemic Vascular Resistance (SVR) = $\frac{(MAP - CVP) \times 79.9}{CO}$;
Normal 800-1200 dyne $sec^{-1}.cm^{-5}$

Systemic Vascular Resistance Index (SVRI) = $\frac{(MAP - CVP) \times 79.9}{CI}$;
Normal 1500-2600 dyne $sec^{-1}.cm^{-5}.m^2$

SVRI increases in: hypertension, hypovolemia, cardiogenic shock, left ventricular failure, hypothermia and vasoconstrictive drugs.

SVRI decreases in: sepsis, arteriovenous fistulas, hyperthermia, hypervolemia, liver failure, and vasodilators.

E) Right Ventricular Stroke Work Index (RVSWI) = $\frac{(CI \times MPAP) \times 13.6}{HR}$;
Normal 7-10 $gm.m.m^{-2}$

RVSWI is increased in: pulmonary hypertension, pulmonary embolism, left ventricular failure, mitral valvulopathies, and hypervolemia.

RVSWI is decreased in: right ventricular failure, hypovolemia, cardiogenic shock, and severe pulmonic valve stenosis.

F) Pulmonary Vascular Resistance Index (PVRI) = $\frac{(MPAP - CWP) \times 79.9}{CI}$;
Normal 80-240 $dyne.sec.^{-1}cm^{-5}.m^2$

PVRI increases in: pulmonary hypertension, pulmonary embolism, left ventricular failure, mitral valve disease, adult respiratory distress syndrome (ARDS), congestive heart failure, mechanical ventilation and positive and expiratory pressure (PEEP).

PVRI is decreased by therapy with nitroprusside, isoproterenol and nitroglycerine.

Interpretation of Hemodynamic Profile

The variables obtained with hemodynamic profiles can be separated into three groups: values representing preload, pump and afterload (Figure 1).

The most frequent conditions affecting the different cardiovascular "compartments" are listed in Table 2. A further evaluation of the right and left myocardial performance can be done independently: "right heart" by CVP, RVSWI and PVR; "left heart" by CWP, LVSWI and SVR.

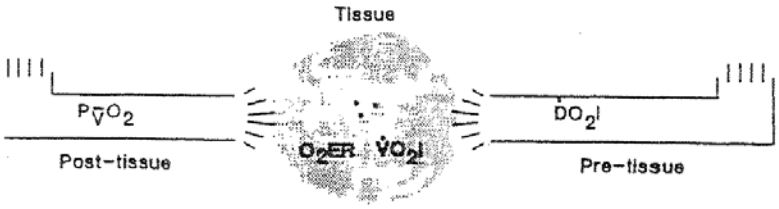

Figure 3. Diagram of oxygen transport-consumption. See glossary for abbreviations.

nixed venous oxygen saturation SvO_2) 70-75 per cent. Abnormal values of O_2ER,A-VO_2 Diff or PvO_2. n the absence of peripheral rteriovenous shunting or abnormal ffinity of oxygen for hemoglobin. vould indicate a mismatch between issue demand for oxygen and its upply.

Additional information about pulmonary gas exchange is obtained n this part of the profile with the ntrapulmonary shunt ($\dot{Q}_s/\dot{Q}_t$) and lveolar-arterial oxygen gradient A-aDO_2).

The P_{50} or the oxygen tension at which 50 per cent of hemoglobin is saturated is also calculated. This value would indicate the position of the oxygen hemoglobin dissociation curve. Under normal conditions, the P_{50} is approximately 27mmHg; in other words, normal adult hemoglobin is 50 per cent saturated at a PaO_2 of 27 mmHg. A higher P_{50} indicates a shift to the right, and a lower value represents a shift to the left.

Derived 'Blood Gases' Variables

Once the information required in Table 1 has been obtained and fed into the computer, the calculated physiologic parameters that we called "Blood Gases" will be available. These variables derived from the following formulas:

A) Total Oxygen Delivery ($\dot{D}O_2$) =
$\dot{D}O_2 = (1.36 \times Hgb \times 10 \times CO \times SaO_2) + PaO_2 \times 0.003$
Normal 800-1200 ml·min^{-1}
Oxygen Delivery Index ($\dot{D}O_2I$) =
$\dot{D}O_2I = \frac{\dot{D}O_2}{BSA}$
Normal 500-700 ml·min^{-1}·m^{-2}

B) Total Oxygen Consumption ($\dot{V}O_2$) =
$\dot{V}O_2 = CO(CaO_2 - C\bar{v}O_2) \times 10$
Normal 220-280 mL·min^{-1}
Oxygen Consumption Index ($\dot{V}O_2I$) =
$\dot{V}O_2I = \frac{\dot{V}O_2}{BSA}$
Normal 110-160 mL·min^{-1}·m^{-2}

C) Arteriovenous Oxygen Difference (A-VO_2 Diff or a$\bar{v}DO_2$) =
A-VO_2 Diff = $CaO_2 - C\bar{v}O_2$
Normal 3-5 ml·dl^{-1}
$CaO_2 = Hgb \times 1.36 \times SaO_2 + PaO_2 \times 0.003$
$C\bar{v}O_2 = Hgb \times 1.36 \times S\bar{v}O_2 + P\bar{v}O_2 \times 0.003$

D) Alveolar—Arterial Oxygen Gradient (A-aDO_2) =
A-aDO_2 = $PAO_2 - PaO_2$
Normal 5-15 mmHg on room air.
This gradient increases with a higher concentration of F_iO_2.

E) Venoarterial Admixture or Intrapulmonary Shunt ($\dot{Q}s/\dot{Q}t$) =
$\frac{\dot{Q}s}{\dot{Q}t} = \frac{C_c - Ca}{C_c - C\bar{v}}$
Normal 3-5%

C_c = alveolar oxygen content
Ca = arterial oxygen content
$C\bar{v}$ = venous oxygen content

Interpretation of 'Blood Gases' Profile

The data obained in this part of the profile can be approached and analyzed in a similar manner to the steps taken above to interpret the hemodynamic variables.

The "oxygen transport-consumption system" could also be divided into three compartments, each of them being represented by certain variables (Figure 3):

A) Pre-tissue oxygen load is represented by the oxygen delivery ($\dot{D}O_2$). A decreased $\dot{D}O_2$ results from low cardiac output, anemia and hypoxemia. Increased $\dot{D}O_2$ is characteristic of hyperdynamic states: sepsis, stress, exercise, agitation, and excess catecholamines.

B) Tissue metabolic status is determined by oxygen consumption ($\dot{V}O_2I$). Decreased $\dot{V}O_2I$ results from hypothermia, hypothyroidism, circulatory shock, bartiburates, sedatives, muscle relaxants, severe reduction in $\dot{D}O_2$, late sepsis, cyanide, carbon monoxide, and improper mixed venous blood sampling. Increased $\dot{V}O_2I$ is caused by hyperthermia, agitation, exercise, early sepsis, hyperthyroidism, and catecholamines.

C) Post-tissue oxygen load is represented by PvO_2 and SvO_2. Decreased values may result from anemia, hypoxemia or low cardiac output. They also can be caused by an increased oxygen consumption, which is not matched by increased $\dot{D}O_2$. Increased PvO_2 is seen when an excess of oxygen delivery in relation to demands exists; also by left-shifted oxygen hemoglobin dissociation curve or by impaired cell metabolism. Occasionally, the high PvO_2 represents a mixed venous sample "contaminated" with arterialized blood due to a fast collection of the sample or arteriovenous fistula.

Once the interpretation of the "Blood Gases" profile has been completed, any significant abnormality of the oxygen transport-consumption system should be corrected.

Clinical Applications

The following case illustrates the diagnostic and therapeutic applications of serial physiologic profiles in a patient admitted to ICU.

Case report: A 51-year-old stuporous female with a negative medical history for cardiac or thyroid disease or intake of any medication. On admission, the patient's temperature was 29.9°C, pulse 55/min. and regular. Her respiratory rate was 8 breaths/min. and systemic blood pressure 90/65 mmHg. Skin was cool. There was no thyroid enlargement. Heart sounds were distant, soft and regular. No murmur, gallop or rub were detected. Breath sounds were diminished but there were no rales or wheezes. A moderate bilateral pleural effusion and significant cardiomegaly were present on chest x-ray. Electrocardiogram showed junctional rhythm.

TABLE 2

Conditions Affecting Preload, Pump and Afterload

	Increase	*Decrease*
Preload (CVP, CWP)	Hypervolemia Congestive Failure Cardiogenic Shock Valvular Heart Disease	Hypovolemia Nitroglycerine Nitroprusside
Pump (SI, LVSWI, RVSWI, CI)	Hyperdynamic States Hypervolemia Inotropics (+) Exercise	Cardiomyopathies Myocardial Necrosis Valvulopathies Pulmonary Embolism High PEEP
Afterload (SVR, SVRI)	Hypertension Hypovolemia Low Cardiac Output Vasopressors Hypothermia	Sepsis Hyperthermia Anemia A-V Fistula Vasodilators

TABLE 3

Therapeutic Measures to Modify Preload, Pump and Afterload

	Increased	*Decreased*
Preload	Fluids (Colloids or Crystalloids) Trendelenberg Position Straight Leg Elevation MAST Garment	Diuretics Nitroglycerine Phlebotomy Tourniquets
Pump	Beta, Sympathicomimetic Agents (Dopamine, Dobutamine) Phosphodiesterase Inhibitors (Amrinone)	Beta, Blockers (Propranolol, Metaprolol) Calcium Channel Blockers (Verapamil)
Afterload	Alpha, Sympathicomimetic Agonist (Norepinephrine, Phenylephrine, High Dose Dopamine) MAST Garment	Nitroprusside, Captopril, Apresoline, Nifedipine, Intra-aortic Balloon Pump

In most instances, the above values will determine if the patient has preload, pump or afterload failure. The following alteration characterizes each of these groups:

	CVP	CWP	CI	LVSWI	SI	SVRI
A) Preload Failure (Hypovolemic)	↓	↓	↓	↓	↓	↑
B) Pump Failure (Cardiogenic)	↑	↑	↓	↓	↓	↑
C) Afterload Failure (Vasogenic)	=	=	↑	↓	↑	↓

Occasionally, the values of the hemodynamic profile, though abnormal, are not typical for any of the above conditions. These atypical profiles can be obtained from patients already under therapy with vasoactive drugs, diuretics or fluids as well as those with a combination of either poor left ventricular function, sepsis and/or hypovolemia.

Management Through Hemodynamic Monitoring

Upon obtaining and interpreting the profile and reaching a diagnosis, treatment should be started. The need to correct any of the abnormal values will be determined by the patient's clinical condition and the goal of therapy.

Therapeutic intervention can be done by pharmacologic and mechanical means following the approach in Table 3. Once therapy is either established or readjusted, its effect should be evaluated by serial determinations of physiologic profiles.

"BLOOD GASES" PROFILE

Survival of critical-care patients is closely related to optimal supply of oxygen and nutrients to the different organ systems. The main function of the cardiopulmonary system is to maintain the amount o oxygen delivery necessary for tissu metabolic needs. When oxygen supply does not match the demanc a deficit of oxygen at the cellular level develops, causing alteration o normal cellular functions leading tc anaerobic metabolism, cellular degeneration and cellular death. Calculating oxygen transport and oxygen consumption variables enables the determination of the balance between oxygen demand and supply.

In this part of the physiologic profile, information is obtained of the oxygen delivery ($\dot{D}O_2$) and cor sumption ($\dot{V}O_2$). Further, the relationship between oxygen demand and oxygen supply can be determined by the oxygen extraction ratio (O_2ER) and arteriovenous oxygen content difference (A-$\dot{V}O_2$ Diff). Under normal metabolic con ditions, the O_2ER is approximately 25 per cent of the $\dot{D}O_2$, and the A-$\dot{V}O_2$ Diff 5 ml O_2/dl. Therefore, if the arterial blood is fully saturated, the mixed venous oxygen tension (PvO_2) should be 36-44 mmHg and

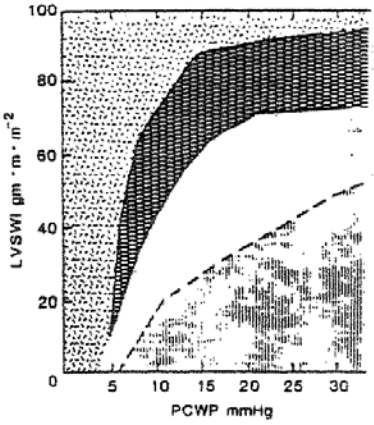

Figure 2. Sarnoff ventricular functi curve.
LVSWI—Left ventricular stroke work index.
PCWP—Pulmonary capillary wedge pressure.

Enhance Ventricular Function
Normal Ventricular Function
Mildly Depressed Ventricular Function
Markedly Depressed Ventricular Functi

A pulmonary artery catheter (Swan-Ganz) was inserted and the following profile was obtained:

90 SYST BP	26 PA SYST	3.80 CO
65 DIAS BP	14 PA DIAS	2.31 CI
73 MAP	18 MPAP	55 HR
2 CVP	8 CWP	69 SV
1500 SVR	210 PVR	42 SVI
2468 SVRI	346 PVRI	37 LVSWI
		1.65 BSA

QUESTION 1: Which one of the following conditions is least likely to be compatible with the above profile?

a) Hyperosmolar coma
b) Ruptured abdominal aortic aneurysm
c) Sepsis
d) Addisonian crisis
e) Hypothyroidism

QUESTION 2: A presumptive diagnosis of myxedema coma was made and Synthroid 500 mcg and Hydrocortisome 100 mg were administered intravenously. The patient's intravascular volume deficit was corrected. Twenty-four hours later the systemic blood pressure was 95/65 mmHg and urine output was less than 20 ml/hour. A new profile was obtained which showed: CWP 18 mmHg, CI 2.3 L.min.$^{-1}$.m^{-2} and SVR 1479 dyne.sec.$^{-1}$cm^{-5}. A rhythm strip demonstrated a regular sinus rhythm of 72 beats/min. Body temperature was 36.5°C. At this point would you consider?

a) Phenylephrine
b) Fluid challenge
c) Dobutamine
d) Isoproterenol
e) Norepinephrine

QUESTION 3: The admission "Blood Gases" profile is shown below.

68 PaO_2	37 PvO2	29.9 TEMP
7.36 ART PH	7.35 MvPH	9.8 HBG
-2.1 ART BE	-0.5 MV BE	0.5 F_iO_2
97 SaO_2	86 SvO_2	59 $\dot{V}O_2$
13 CaO_2	11.5 CvO_2	35 $\dot{V}O_2I$
494 $\dot{D}O_2$	1.6 avDO2	0.12 O_2ER
500 $\dot{D}O_2I$	41 QS/QT	18.8 P_{50}
41 PaCO2	247 AaDO2	

In general, the least likely explanation for a decreased oxygen delivery index ($\dot{D}O_2I$) would be?

a) Anemia
b) Carbon monoxide intoxication
c) Adriamycin toxicity
d) Thyrotoxicosis

QUESTION 4: The oxygen delivery was normalized, but the oxygen consumption index remained below normal. The most likely explanation for this abnormality would be?

a) Hypothermia
b) Myxedema
c) Arteriovenous fistula
d) Administration of muscle relaxants with sedatives
e) All of the above

DISCUSSION: Though this patient had a negative history of thyroid disease, the presence of hypothermia, bradypnea and bradycardia as well as clinical findings of decreased mental status, brittle hair, nonpitting edema and slow relaxation phase of the deep tendon reflexes, were indications of possible myxedema coma. This was later confirmed by a TT_4 2 µg/dl and TSH 50 µIU/ml.

Answer to question 1 is C: Since sepsis is generally characterized by high cardiac output and low systemic vascular resistance. The initial profile was consistent with hypovolemia (low CWP, low CI and high SVR). Hyperosmolar coma, rupture of abdominal aortic aneurysm, and Addisonian crisis usually present with hypovolemia. Hypothyroidism causes prolongation of the pre-ejection period, pericardial effusion and bradyarrythmias which can result in a decreased CI. In addition, a deficient intake of fluid during myxedema may cause a decrease in preload.

Answer to question 2 is C: Hypovolemia can mask a depressed myocardial function. This may only become manifest after fluid correction, as it happened in our patient. The low cardiac output will result in a decreased glomerular filtration rate and urinary output. Dobutamine increases cardiac output and decreases SVR. The vasoconstrictive effect of phenylephrine and norepinephrine is unwanted in this case because it could cause further reduction in urinary and cardiac output. The arrhythmogenic properties of Isoproterenol, and the diversion of blood flow to the mesenteric and skeletal muscle territories caused by this drug, would make its use a bad choice. Since CWP is already optimal, further administration of fluids would be contraindicated.

Answer to question 3 is d: Thyrotoxicosis usually presents a hyperdynamic state with high DC Reduction of any of the three ma components of oxygen delivery (CO, Hgb and arterial oxygen saturation) could affect this varia Therefore, anemia and carbon monoxide intoxication could decrease $\dot{D}O_2I$. Adriamycin, a chemotherapeutic agent, can caus cardiomyopathy with a significan decrement in cardiac output and $\dot{D}O_2I$.

Answer to question 4 is e: The oxygen consumption obtained in the "Blood Gases" profile is calculated: therefore, in the presence of an arterio-venous fistula, the high oxygen saturatio of the mixed venous sample wou underestimate the degree of metabolic rate. Hypothermia and hypothyroidism decrease the tiss metabolic activity and $\dot{V}O_2I$. In IC patients are occasionally iatrogenically sedated and paraly during mechanical ventilation.Th results in a decrease in muscle ac tivity and oxygen consumption.

In conclusion, the care of the critically ill patient can be significantly improved with the s ple determination of physiologic profiles. These variables can markedly expand the diagnostic therapeutic horizons of physician

Glossary

A = Aorta
$AaDo_2$ or $A\text{-}aDO_2$ = Alveolar arte oxygen difference
Art BE = Arterial bases excess
$avDO_2$ or $A\text{-}VO_2$ Diff = Arteriovenous oxygen differen
BSA = Body surface area
CaO_2 = Arterial oxygen content
CI = Cardiac index
CO = Cardiac output
CvO_2 = Mixed venous oxygen content
CVP = Central venous pressure
CWP or PCWP = Pulmonary capillary wedge pressure
$\dot{D}O_2$ = Oxygen delivery
$\dot{D}O_2I$ = Oxygen delivery index
F_iO_2 = Fraction of inspired oxy
HR = Heart Rate
LA = Left atrium

LV = Left ventricle
LVF = Left ventricular function
LVSW = Left ventricular stroke work
LVSWI = Left ventricular stroke work index
MAP = Mean arterial pressure
MPAP = Mean pulmonary artery pressure
MV BF = Mixed venous blood flow
O_2ER = Oxygen extraction ratio
PA = Pulmonary artery
$PaCO_2$ = Arterial carbon dioxide tension
PC = Pulmonary capillary
PV = Pulmonary vein
PvO_2 = Mixed venous oxygen tension
PVR = Pulmonary vascular resistance
PVRI = Pulmonary vascular resistance index
Q_s/Q_t = Pulmonary shunt fraction
RA = Right atrium
RV = Right ventricle
RVF = Right ventricular function
RVSW = Right ventricular stroke work
RVSWI = Right ventricular stroke work index
SaO_2 = Arterial oxygen saturation
SI or SVI = Stroke volume index
SV = Stroke volume
SVC = Superior vein cava
SvO_2 = Mixed venous oxygen saturation
SVR = Systemic vascular resistance
SVRI = Systemic vascular resistance index
$\dot{V}O_2$ = Oxygen consumption
$\dot{V}O_2I$ = Oxygen consumption index

References

1. Del Guercio LRM. Physiologic monitorin of the surgical patient. In: Schwartz SI, ed. Prin ciples of surgery. New York: McGraw-Hill, 1984 485-505.

2. Swan HJC. Invasive hemodynami monitoring in critical care units. In: Parrillo JE Ayres SM, eds. Major issues in critical car medicine. Baltimore: Williams & Wilkin 1984:153-180.

3. Daily EK, Schroeder JS. Techniques in bed side hemodynamic monitoring. 3rd ed. St. Louis CV Mosby, 1985:1-305.

4. Urbach DR, Rippe JM. Pulmonary arter placement and care. In: Rippe JM, Irwin RS Alpert JS, Dalen JE, eds. Intensive care medicin 3rd ed. Boston: Little, Brown & Co, 1985:43-57

5. McGregor LM. Hemodynamic monitoring In: Zschoche DA, ed. Comprehensive review c critical care. St. Louis: CV Mosby, 1986:163-170

6. Bustin D. Hemodynamic monitoring fo critical care. 1st ed. Norwalk: Appleton-Centur Crofts, 1986:1-128.

Sepsis

Surviving Sepsis Campaign: Guidelines for Management of Severe Sepsis and Septic Shock

TABLE 1. Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

TABLE 2. Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

TABLE 5. Recommendations: Initial Resuscitation and Infection Issues

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

B. Screening for Sepsis and Performance Improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital–based performance improvement efforts in severe sepsis (UG).

C. Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).
2. Use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

D. Antimicrobial Therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

(*Continued*)

TABLE 5. (*Continued*) Recommendations: Initial Resuscitation and Infection Issues

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

F. Infection Prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.

TABLE 6. Recommendations: Hemodynamic Support and Adjunctive Therapy

G. Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic Therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

TABLE 8. Recommendations: Other Supportive Therapy of Severe Sepsis

K. Blood Product Administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, we recommend that red blood cell transfusion occur only when hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0–9.0 g/dL in adults (grade 1B).
2. Not using erythropoietin as a specific treatment of anemia associated with severe sepsis (grade 1B).
3. Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).
4. Not using antithrombin for the treatment of severe sepsis and septic shock (grade 1B).
5. In patients with severe sepsis, administer platelets prophylactically when counts are <10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are < 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3 [50×10^9/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

L. Immunoglobulins

1. Not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).

M. Selenium

1. Not using intravenous selenium for the treatment of severe sepsis (grade 2C).

N. History of Recommendations Regarding Use of Recombinant Activated Protein C (rhAPC)

A history of the evolution of SSC recommendations as to rhAPC (no longer available) is provided.

O. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)

1. Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs. 12 mL/kg).
2. Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H_2O (grade 1B).
3. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
4. Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis-induced moderate or severe ARDS (grade 2C).
5. Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia (grade 2C).
6. Prone positioning be used in sepsis-induced ARDS patients with a Pao_2/Fio_2 ratio ≤ 100 mm Hg in facilities that have experience with such practices (grade 2B).
7. That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30–45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
8. That noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).
9. That a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low Fio_2 requirements which can be met safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).
10. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).
11. A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).
12. In the absence of specific indications such as bronchospasm, not using beta 2-agonists for treatment of sepsis-induced ARDS (grade 1B).

P. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. Continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (grade 1B).
2. Neuromuscular blocking agents (NMBAs) be avoided if possible in the septic patient ***without ARDS*** due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).

TABLE 8. (*Continued*) Recommendations: Other Supportive Therapy of Severe Sepsis

3. A short course of NMBA of not greater than 48 hours for patients with early sepsis-induced ARDS and a Pao_2/Fio_2 < 150 mm Hg (grade 2C).

Q. Glucose Control

1. A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose ≤180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (grade 1A).
2. Blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

R. Renal Replacement Therapy

1. Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).
2. Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 2D).

S. Bicarbonate Therapy

1. Not using sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (grade 2B).

T. Deep Vein Thrombosis Prophylaxis

1. Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). This should be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus twice daily UFH, grade 2C versus three times daily UFH). If creatinine clearance is <30 mL/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).
2. Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
3. Septic patients who have a contraindication for heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not receive pharmacoprophylaxis (grade 1B), but receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases start pharmacoprophylaxis (grade 2C).

U. Stress Ulcer Prophylaxis

1. Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).
2. When stress ulcer prophylaxis is used, proton pump inhibitors rather than H2RA (grade 2D)
3. Patients without risk factors do not receive prophylaxis (grade 2B).

V. Nutrition

1. Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock (grade 2C).
2. Avoid mandatory full caloric feeding in the first week but rather suggest low dose feeding (eg, up to 500 calories per day), advancing only as tolerated (grade 2B).
3. Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).
4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

W. Setting Goals of Care

1. Discuss goals of care and prognosis with patients and families (grade 1B).
2. Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B).
3. Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (grade 2C).

ARDSnet Ventilator Management

Assist control mode–volume ventilation

Reduce tidal volume to 6 mL/kg lean body weight

Keep plateau pressure < 30 cm H_2O

–Reduce tidal volume as low as 4 mL/kg predicted body weight to limit plateau pressure

Maintain Sa_{O_2}/Sp_{O_2} between 88% and 95%

Anticipated PEEP settings at various Fi_{O_2} requirements

Fi_{O_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24

Predicted Body Weight Calculation

Male– 50 + 2.3 [height (inches) – 60] or 50 + 0.91 [height (cm) – 152.4]

Female–45.5 + 2.3 [height (inches) – 60] or 45.5 + 0.91 [height (cm) – 152.4]

Sa_{O_2} – arterial oxygen saturation, PEEP – positive end-expiratory pressure, Sp_{O_2} – oxygen saturation on pulse oximetry. Adapted from Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.
N Engl J Med 2000; 342:1301–1308.

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P=0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7 percent vs. 65.3±11.4 percent), a lower lactate concentration (3.0±4.4 vs. 3.9±4.4 mmol per liter), a lower base deficit (2.0±6.6 vs. 5.1±6.7 mmol per liter), and a higher pH (7.40±0.12 vs. 7.36±0.12) than the patients assigned to standard therapy ($P\leq 0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0±6.3 vs. 15.9±6.4, $P<0.001$).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock.[1] Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.[2] An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death.[2] The transition to serious illness occurs during the critical "golden hours," when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department,[3] hospital ward,[4] or the intensive care unit.[5]

Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure,[6] and urinary output[7] fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.[2] End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.[8] Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.[9] In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.[10]

Whereas the incidence of septic shock has steadily increased during the past several decades, the associated mortality rates have remained constant or have decreased only slightly.[11] Studies of interventions such as immunotherapy,[12] hemodynamic optimization,[9,13] or pulmonary-artery catheterization[14] enrolled patients up to 72 hours after admission to the intensive care unit. The negative results of studies of the use of hemodynamic variables as end points ("hemodynamic

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optimization"), in particular, prompted suggestions that future studies involve patients with similar causes of disease[13] or with global tissue hypoxia (as reflected by elevated lactate concentrations)[15] and that they examine interventions begun at an earlier stage of disease.[16,17]

We examined whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock.

METHODS

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research and was conducted under the auspices of an independent safety, efficacy, and data monitoring committee.

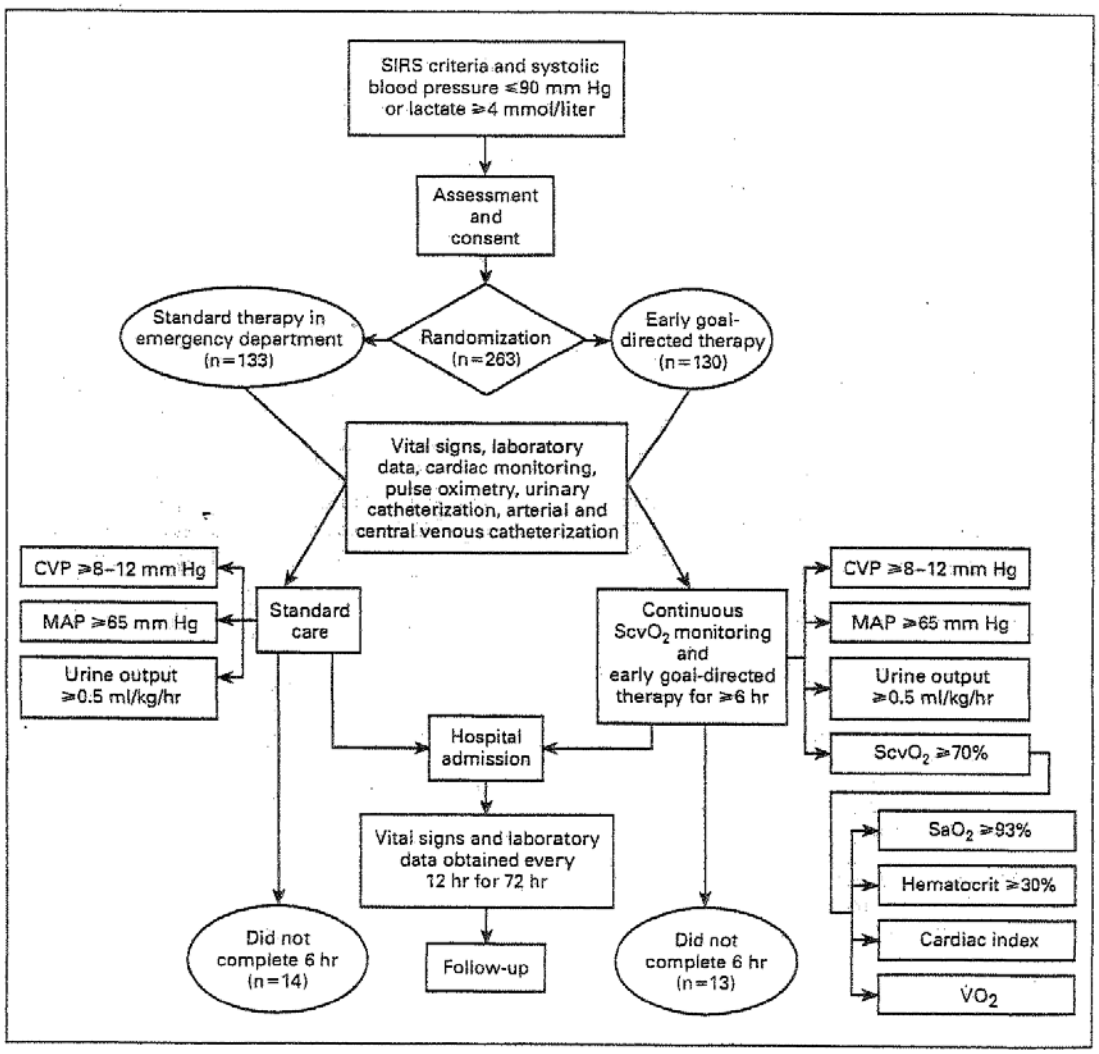

Figure 1. Overview of Patient Enrollment and Hemodynamic Support.

SIRS denotes systemic inflammatory response syndrome, CVP central venous pressure, MAP mean arterial pressure, $ScvO_2$ central venous oxygen saturation, SaO_2 arterial oxygen saturation, and $\dot{V}O_2$ systemic oxygen consumption. The criteria for a diagnosis of SIRS were temperature greater than or equal to 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute or partial pressure of arterial carbon dioxide less than 32 mm Hg, and white-cell count greater than 12,000 per cubic millimeter or less than 4000 per cubic millimeter or the presence of more than 10 percent immature band forms.

Eligibility

Eligible adult patients who presented to the emergency department of an 850-bed academic tertiary care hospital with severe sepsis, septic shock, or the sepsis syndrome from March 1997 through March 2000 were assessed for possible enrollment according to the inclusion[18,19] and exclusion criteria (Fig. 1). The criteria for inclusion were fulfillment of two of four criteria for the systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg (after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-minute period) or a blood lactate concentration of 4 mmol per liter or more. The criteria for exclusion from the study were an age of less than 18 years, pregnancy, or the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate status, or advanced directives restricting implementation of the protocol.

The clinicians who assessed the patients at this stage were unaware of the patients' treatment assignments. After written informed consent was obtained (in compliance with the Helsinki Declaration[20]), the patients were randomly assigned either to early goal-directed therapy or to standard (control) therapy in computer-generated blocks of two to eight. The study-group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators.

Treatment

The patients were treated in a nine-bed unit in the emergency department by an emergency physician, two residents, and three nurses.[3] The study was conducted during the routine treatment of other patients in the emergency department. After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians' discretion according to a protocol for hemodynamic support[21] (Fig. 1), with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture were obtained in the emergency department before the administration of antibiotics. Antibiotics were given at the discretion of the treating clinicians. Antimicrobial therapy was deemed adequate if the in vitro sensitivities of the identified microorganisms matched the particular antibiotic ordered in the emergency department.[22]

The patients assigned to early goal-directed therapy received a central venous catheter capable of measuring central venous oxygen saturation (Edwards Lifesciences, Irvine, Calif.); it was connected to a computerized spectrophotometer for continuous monitoring. Patients were treated in the emergency department according to a protocol for early goal-directed therapy (Fig. 2) for at least six hours and were transferred to the first available inpatient beds. Monitoring of central venous oxygen saturation was then discontinued. Critical-care clinicians (intensivists, fellows, and residents providing 24-hour in-house coverage) assumed the care of all the patients; these physicians were unaware of the patients' study-group assignments. The study investigators did not influence patient care in the intensive care unit.

The protocol was as follows. A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. After the central venous pressure, mean arterial pressure, and hematocrit were thus optimized, if the central venous oxygen saturation was less than 70 percent, dobutamine administration was started at a dose of 2.5 μg per kilogram of body weight per minute, a dose that was increased by 2.5 μg per kilogram per minute every 30 minutes until the central venous oxygen saturation was 70 percent or higher or until a maximal dose of 20 μg per kilogram per minute was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives.

Outcome Measures

The patients' temperature, heart rate, urine output, blood pressure, and central venous pressure were measured continuously for the first 6 hours of treatment and assessed every 12 hours for 72 hours. Arterial and venous blood gas values (including central venous oxygen saturation measured by in vitro co-oximetry; Nova Biomedical, Waltham, Mass.), lactate concentrations, and coagulation-related variables and clinical variables required for determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction),[23] the Simplified Acute Physiology Score II (SAPS II, on a scale from 0 to 174, with higher scores indicating more severe organ dysfunction),[24] and the Multiple Organ Dysfunction Score (MODS, on a scale from 0 to 24, with higher scores indicating more severe organ dysfunction)[25] were obtained at base line (0 hours) and at 3, 6, 12, 24, 36, 48, 60, and 72 hours.[2,26] The results of laboratory tests required only for purposes of the study were made known only to the study investigators. Patients were followed for 60 days or until death. The consumption of health care resources (indicated by the duration of vasopressor therapy and mechanical ventilation and the length of the hospital stay) was also examined.

Statistical Analysis

In-hospital mortality was the primary efficacy end point. Secondary end points were the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources. Assuming a rate of refusal or exclusion of 10 percent, a two-sided type I error rate of 5 percent, and a power of 80 percent, we calculated that a sample size of 260 patients was required to permit the detection of a 15 percent reduction in in-hospital mortality. Kaplan–Meier estimates of mortality, along with risk ratios and 95 percent confidence intervals, were used to describe the relative risk of death. Differences between the two groups at base line were tested with the use of Student's t-test, the chi-square test, or Wilcoxon's rank-sum test. Incremental analyses of the area under the curve were performed to quantify differences during the interval from base line to six hours after the start of treatment. For the data at six hours, analysis of covariance was used with the base-line values as the covariates. Mixed models were used to assess the effect of treatment on prespecified secondary variables during the interval from 7 to 72 hours after the start of treatment.[27] An independent, 12-member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data after one third and two thirds of the patients had been enrolled and at both times recommended that the trial be continued. To adjust for the two interim analyses, the alpha spending function of DeMets and Lan[28] was used to determine that a P value of 0.04 or less would be considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

We evaluated 288 patients; 8.7 percent were excluded or did not consent to participate. The 263 patients enrolled were randomly assigned to undergo either standard therapy or early goal-directed therapy; 236 patients completed the initial six-hour study period.

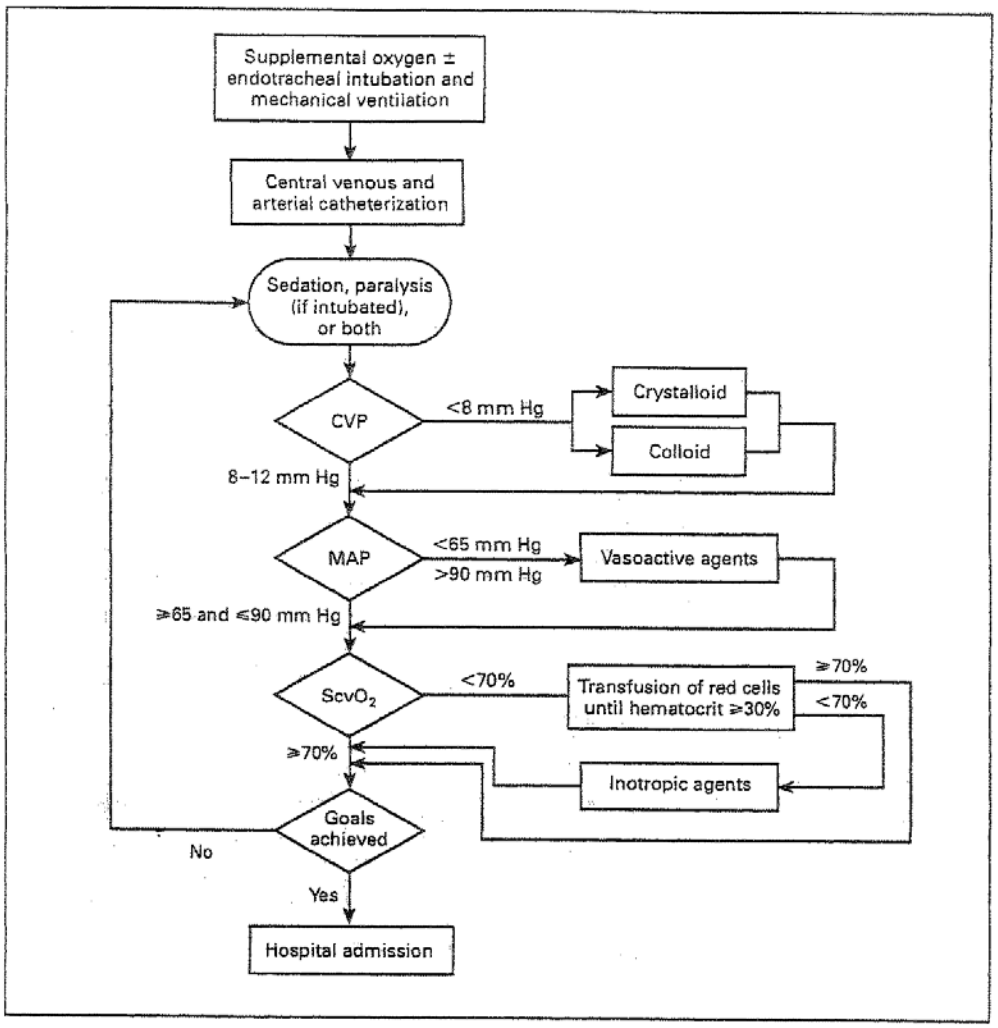

Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and $ScvO_2$ central venous oxygen saturation.

All 263 were included in the intention-to-treat analyses. The patients assigned to standard therapy stayed a significantly shorter time in the emergency department than those assigned to early goal-directed therapy (mean [±SD], 6.3±3.2 vs. 8.0±2.1 hours; $P<0.001$). There was no significant difference between the groups in any of the base-line characteristics, including the adequacy and duration of antibiotic therapy (Table 1). Vital signs, resuscitation end points, organ-dysfunction scores, and coagulation-related variables were also similar in the two study groups at base line (Table 2).

Twenty-seven patients did not complete the initial six-hour study period (14 assigned to standard therapy and 13 assigned to early goal-directed therapy), for the following reasons: discontinuation of aggressive medical treatment (in 5 patients in each group), discontinuation of aggressive surgical treatment (in 2 patients in each group), a need for immediate surgery (in 4 patients assigned to standard therapy and in 3 assigned to early goal-directed therapy), a need for interventional urologic, cardiologic, or angiographic procedures (in 2 patients in each group), and refusal to continue participation (in 1 patient in each group) ($P=0.99$ for all comparisons). There were no significant differences between the patients who completed

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)
Age (yr)	64.4±17.1	67.1±17.4
Sex (%)		
Female	49.6	49.2
Male	50.4	50.8
Time from arrival at emergency department to enrollment		
Mean (hr)	1.5±1.7	1.3±1.5
Median (min)	50.5	59.0
Entry criteria		
Temperature (°C)	36.6±2.3	35.9±3.2
Heart rate (beats/min)	114±27	117±31
Systolic blood pressure (mm Hg)	109±34	106±36
Respiratory rate (breaths/min)	30.2±10.6	31.8±10.8
Partial pressure of carbon dioxide (mm Hg)	30.6±15.1	31.5±15.7
White-cell count (per mm³)	14,200±9,600	13,600±8,300
Lactate (mmol/liter)	6.9±4.5	7.7±4.7
Base-line laboratory values		
Anion gap (mmol/liter)	21.4±8.5	21.7±7.6
Creatinine (mg/dl)	2.6±2.0	2.6±2.0
Blood urea nitrogen (mg/dl)	45.4±33.0	47.1±31.3
Total bilirubin (mg/dl)	1.9±3.0	1.3±1.7
γ-Glutamyltransferase (U/liter)	123±130	117±159
Albumin (g/dl)	2.8±0.7	2.8±0.7
Chronic coexisting conditions (%)†		
Alcohol use	38.7	38.5
Congestive heart failure	30.2	36.7
Coronary artery disease	23.5	26.5
Chronic obstructive pulmonary disease or emphysema	13.4	18.0
Diabetes	31.9	30.8
Human immunodeficiency virus infection	1.7	4.3
Hypertension	66.4	68.4
Liver disease	23.5	23.1
History of cancer	10.1	12.8
Neurologic disease	31.9	34.2
Renal insufficiency	21.9	21.4
Smoking	31.1	29.9
Diagnosis (%)†		
Medical condition	93.3	90.6
Pneumonia	39.5	38.5
Urosepsis	27.7	25.6
Peritonitis	4.2	3.4
Other	21.9	23.1
Surgical condition	6.7	9.4
Intraabdominal process	5.9	7.7
Abscess of the arms or legs	0.8	1.7
Types and features of sepsis (%)		
Severe sepsis	48.7	45.3
Septic shock	51.3	54.7
Sepsis syndrome	71.4	75.2
Culture positive	76.5	76.1
Culture negative	23.5	23.9
Blood culture positive	36.1	34.2
Antibiotic therapy		
Antibiotics given in the first 6 hr (%)	92.4	86.3
Antibiotics adequate (%)	94.3	96.7
Duration (days)	11.3±15.8	11.7±16.2

*Plus–minus values are means ±SD. There were no significant differences between groups in any of the variables. To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; and to convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

†Values sum to more than 100% because patients could have more than one condition.

TABLE 2. VITAL SIGNS, RESUSCITATION END POINTS, ORGAN-DYSFUNCTION SCORES, AND COAGULATION VARIABLES.

VARIABLE AND TREATMENT GROUP	BASE LINE (0 hr)	HOURS AFTER START OF THERAPY		
		6	0–6†	7–72‡
Heart rate (beats/min)				
Standard therapy	114±27	105±25	108±23	99±18
EGDT	117±31	103±19	105±19	96±18
P value	0.45	0.12	0.25	0.04
Central venous pressure (mm Hg)				
Standard therapy	6.1±7.7	11.8±6.8	10.5±6.8	11.6±6.1
EGDT	5.3±9.3	13.8±4.4	11.7±5.1	11.9±5.6
P value	0.57	0.007	0.22	0.68
Mean arterial pressure (mm Hg)				
Standard therapy	76±24	81±18	81±16	80±15
EGDT	74±27	95±19	88±16	87±15
P value	0.60	<0.001	<0.001	<0.001
Central venous oxygen saturation (%)				
Standard therapy	49.2±13.3	66.0±15.5	65.4±14.2	65.3±11.4
EGDT	48.6±11.2	77.3±10.0	71.6±10.2	70.4±10.7
P value	0.49	<0.001	<0.001	<0.001
Lactate (mmol/liter)				
Standard therapy	6.9±4.5	4.9±4.7	5.9±4.2	3.9±4.4
EGDT	7.7±4.7	4.3±4.2	5.5±4.2	3.0±4.4
P value	0.17	0.01	0.62	0.02
Base deficit (mmol/liter)				
Standard therapy	8.9±7.5	8.0±6.4	8.6±6.0	5.1±6.7
EGDT	8.9±8.1	4.7±5.8	6.7±5.6	2.0±6.6
P value	0.81	<0.001	0.006	<0.001
Arterial pH				
Standard therapy	7.32±0.19	7.31±0.15	7.31±0.12	7.36±0.12
EGDT	7.31±0.17	7.35±0.11	7.33±0.13	7.40±0.12
P value	0.40	<0.001	0.26	<0.001
APACHE II score				
Standard therapy	20.4±7.4	17.6±6.2	—	15.9±6.4
EGDT	21.4±6.9	16.0±6.9	—	13.0±6.3
P value	0.27	<0.001		<0.001
SAPS II				
Standard therapy	48.8±11.1	45.5±12.3	—	42.6±11.5
EGDT	51.2±11.1	42.1±13.2	—	36.9±11.3
P value	0.08	<0.001		<0.001
MODS				
Standard therapy	7.3±3.1	6.8±3.7	—	6.4±4.0
EGDT	7.6±3.1	5.9±3.7	—	5.1±3.9
P value	0.44	<0.001		<0.001
Hematocrit (%)				
Standard therapy	34.7±8.5	32.0±6.9	—	30.1±4.1
EGDT	34.6±8.3	33.3±4.8	—	32.1±4.2
P value	0.91	0.03		<0.001
Prothrombin time (sec)				
Standard therapy	16.5±6.3	17.5±8.1	—	17.3±6.1
EGDT	15.8±5.0	16.0±3.6	—	15.4±6.1
P value	0.17	0.02		0.001
Partial-thromboplastin time (sec)				
Standard therapy	32.9±12.0	37.6±21.0	—	37.0±14.2
EGDT	33.3±20.4	32.6±8.7	—	34.6±14.1
P value	0.17	0.01		0.06
Fibrinogen (mg/dl)				
Standard therapy	361±198	319±142	—	358±134
EGDT	370±209	300±157	—	342±134
P value	0.51	0.01		0.21
Fibrin-split products (μg/dl)				
Standard therapy	39.0±61.6	54.9±84.0	—	62.0±71.4
EGDT	44.8±71.3	45.8±66.0	—	39.2±71.2
P value	0.76	0.13		<0.001
D-Dimer (μg/ml)				
Standard therapy	3.66±8.45	5.48±11.95	—	5.65±9.06
EGDT	4.46±10.70	3.98±9.41	—	3.34±9.02
P value	0.71	0.05		0.006
Platelet count (per mm³)				
Standard therapy	205,000± 110,000	164,000± 84,000	—	144,000± 84,000
EGDT	220,000± 135,000	156,000± 90,000	—	139,000± 82,000
P value	0.65	0.001		0.51

*Plus–minus values are means ±SD. EGDT denotes early goal-directed therapy, APACHE II Acute Physiology and Chronic Health Evaluation, SAPS II Simplified Acute Physiology Score II, and MODS Multiple Organ Dysfunction Score.

†For the period from base line (0 hours) to 6 hours, the area under the curve was calculated, except for noncontinuous variables (as indicated by dashes).

‡For the period from 7 to 72 hours, the adjusted mean value was obtained from a mixed model.

the initial six-hour study period and those who did not in any of the base-line characteristics or base-line vital signs, resuscitation end points, organ-dysfunction scores, or coagulation-related variables (data not shown).

Vital Signs and Resuscitation End Points

During the initial six hours after the start of therapy, there was no significant difference between the two study groups in the mean heart rate ($P=0.25$) or central venous pressure ($P=0.22$) (Table 2). During this period, the mean arterial pressure was significantly lower in the group assigned to standard therapy than in the group assigned to early goal-directed therapy ($P<0.001$), but in both groups the goal of 65 mm Hg or higher was met by all the patients. The goal of 70 percent or higher for central venous oxygen saturation was met by 60.2 percent of the patients in the standard-therapy group, as compared with 94.9 percent of those in the early-therapy group ($P<0.001$). The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output (with adjustment for patients with end-stage renal failure) were achieved in 86.1 percent of the standard-therapy group, as compared with 99.2 percent of the early-therapy group ($P<0.001$). During this period, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation ($P<0.001$) and a greater base deficit ($P=0.006$) than those assigned to early goal-directed therapy; the two

groups had similar lactate concentrations (P=0.62) and similar pH values (P=0.26).

During the period from 7 to 72 hours after the start of treatment, the patients assigned to standard therapy had a significantly higher heart rate (P=0.04) and a significantly lower mean arterial pressure (P< 0.001) than the patients assigned to early goal-directed therapy; the two groups had a similar central venous pressure (P=0.68). During this period, those assigned to standard therapy also had a significantly lower central venous oxygen saturation than those assigned to early goal-directed therapy (P<0.001), as well as a higher lactate concentration (P=0.02), a greater base deficit (P<0.001), and a lower pH (P<0.001).

Organ Dysfunction and Coagulation Variables

During the period from 7 to 72 hours, the APACHE II score, SAPS II, and MODS were significantly higher in the patients assigned to standard therapy than in the patients assigned to early goal-directed therapy (P<0.001 for all comparisons) (Table 2). During this period, the prothrombin time was significantly greater in the patients assigned to standard therapy than in those assigned to early goal-directed therapy (P=0.001), as was the concentration of fibrin-split products (P<0.001) and the concentration of D-dimer (P=0.006). The two groups had a similar partial-thromboplastin time (P=0.06), fibrinogen concentration (P=0.21), and platelet count (P=0.51) (Table 2).

Mortality

In-hospital mortality rates were significantly higher in the standard-therapy group than in the early-therapy group (P=0.009), as was the mortality at 28 days (P=0.01) and 60 days (P=0.03) (Table 3). The difference between the groups in mortality at 60 days primarily reflected the difference in in-hospital mortality. Similar results were obtained after data from the 27 patients who did not complete the initial six-hour study period were excluded from the analysis (data not shown). The rate of in-hospital death due to sudden cardiovascular collapse was significantly higher in the standard-therapy group than in the early-therapy group (P=0.02); the rate of death due to multiorgan failure was similar in the two groups (P=0.27).

Administered Treatments

During the initial six hours, the patients assigned to early goal-directed therapy received significantly more fluid than those assigned to standard therapy (P<0.001) and more frequently received red-cell transfusion (P<0.001) and inotropic support (P<0.001), whereas similar proportions of patients in the two groups required vasopressors (P=0.62) and mechanical ventilation (P=0.90) (Table 4). During the period from 7 to 72 hours, however, the patients assigned to standard therapy received significantly more fluid than those assigned to early goal-directed therapy (P=0.01) and more often received red-cell transfusion (P< 0.001) and vasopressors (P=0.03) and underwent mechanical ventilation (P<0.001) and pulmonary-artery catheterization (P=0.04); the rate of use of inotropic agents was similar in the two groups (P=0.14) (Table 4). During the overall period from base line to 72 hours after the start of treatment, there was no significant difference between the two groups in the total volume of fluid administered (P=0.73) or the rate of use of inotropic agents (P=0.15), although a greater proportion of the patients assigned to standard therapy than of those assigned to early goal-direct-

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

TABLE 4. TREATMENTS ADMINISTERED.

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

*Plus–minus values are means ±SD. Because some patients received a specific treatment both during the period from 0 to 6 hours and during the period from 7 to 72 hours, the cumulative totals for those two periods do not necessarily equal the values for the period from 0 to 72 hours. EGDT denotes early goal-directed therapy.

†Administered vasopressors included norepinephrine, epinephrine, dopamine, and phenylephrine hydrochloride.

‡All pulmonary-artery catheters were inserted while patients were in the intensive care unit.

ed therapy received vasopressors (P=0.02) and mechanical ventilation (P=0.02) and underwent pulmonary-artery catheterization (P=0.01), and a smaller proportion required red-cell transfusion (P<0.001). Though similar between the groups at base line (P=0.91), the mean hematocrit during this 72-hour period was significantly lower in the standard-therapy group than in the early-therapy group (P<0.001). Despite the transfusion of red cells, it was significantly lower than the value obtained at base line in each group (P<0.001 for both comparisons) (Table 2).

Consumption of Health Care Resources

There were no significant differences between the two groups in the mean duration of vasopressor therapy (2.4±4.2 vs. 1.9±3.1 days, P=0.49), the mean duration of mechanical ventilation (9.0±13.1 vs. 9.0±11.4 days, P=0.38), or the mean length of stay in the hospital (13.0±13.7 vs. 13.2±13.8 days, P=0.54). However, of the patients who survived to hospital discharge, those assigned to standard therapy had stayed a significantly longer time in the hospital than those assigned to early goal-directed therapy (18.4±15.0 vs. 14.6±14.5 days, P=0.04).

DISCUSSION

Severe sepsis and septic shock are common and are associated with substantial mortality and substantial consumption of health care resources. There are an estimated 751,000 cases (3.0 cases per 1000 population) of sepsis or septic shock in the United States each year, and they are responsible for as many deaths each year as acute myocardial infarction (215,000, or 9.3 percent of all deaths).[29] In elderly persons, the incidence of sepsis or septic shock and the related mortality rates are substantially higher than those in younger persons. The projected growth of the elderly population in the United States will contribute to an increase in incidence of 1.5 percent per year, yielding an estimated 934,000 and 1,110,000 cases by the years 2010 and 2020, respectively.[29] The present annual cost of this disease is estimated to be $16.7 billion.[29]

The transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves a myriad of pathogenic changes, including circulatory abnormalities that result in global tissue hypoxia.[1,2] These pathogenic changes have been the therapeutic target of previous outcome studies.[12] Although this transition occurs over time, both out of the hospital and in the hospital, in outcome studies interventions have usually been initiated after admission to the intensive care unit.[12] In studies of goal-directed hemodynamic optimization, in particular, there was no benefit in terms of outcome with respect to normal and supranormal hemodynamic end points, as well as those guided by mixed venous oxygen saturation.[9,13] In contrast, even though we enrolled patients with lower central venous oxygen saturation and lower central venous pressure than those studied by Gattinoni et al.[9] and with a higher lactate concentration than those studied by Hayes et al.,[13] we found significant benefits with respect to outcome when goal-directed therapy was applied at an earlier stage of disease. In patients with septic shock, for example, Hayes et al. observed a higher in-hospital mortality rate with aggressive hemodynamic optimization in the intensive care unit (71 percent) than with control therapy (52 percent), whereas we observed a lower mortality rate in patients with septic shock assigned to early goal-directed therapy (42.3 percent) than in those assigned to standard therapy (56.8 percent).

The benefits of early goal-directed therapy in terms of outcome are multifactorial. The incidence of death due to sudden cardiovascular collapse in the standard-therapy group was approximately double that in the group assigned to early goal-directed therapy, suggesting that an abrupt transition to severe disease is an important cause of early death. The early identification

of patients with insidious illness (global tissue hypoxia accompanied by stable vital signs) makes possible the early implementation of goal-directed therapy. If sudden cardiovascular collapse can be prevented, the subsequent need for vasopressors, mechanical ventilation, and pulmonary-artery catheterization (and their associated risks) diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone.[30] These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction.[2,30] When early therapy is not comprehensive, the progression to severe disease may be well under way at the time of admission to the intensive care unit.[16] Aggressive hemodynamic optimization and other therapy[12] undertaken thereafter may be incompletely effective or even deleterious.[13]

The value of measurements of venous oxygen saturation at the right atrium or superior vena cava (central venous oxygen saturation) instead of at the pulmonary artery (mixed venous oxygen saturation) has been debated,[31] in particular, when saturation values are above 65 percent. In patients in the intensive care unit who have hyperdynamic septic shock, the mixed venous oxygen saturation is rarely below 65 percent.[32] In contrast, our patients were examined during the phase of resuscitation in which the delivery of supplemental oxygen is required (characterized by a decreased mixed venous oxygen saturation and an increased lactate concentration), when the central venous oxygen saturation generally exceeds the mixed venous oxygen saturation.[33,34] The initial central venous oxygen saturation was less than 50 percent in both study groups. The mixed venous oxygen saturation is estimated to be 5 to 13 percent lower in the pulmonary artery[33] and 15 percent lower in the splanchnic bed.[35] Though not numerically equivalent, these ranges of values are pathologically equivalent and are associated with high mortality.[32,36] Among all the patients in the current study in whom the goals with respect to central venous pressure, mean arterial pressure, and urine output during the first six hours were met, 39.8 percent of those assigned to standard therapy were still in this oxygen-dependent phase of resuscitation at six hours, as compared with 5.1 percent of those assigned to early goal-directed therapy. The combined 56.5 percent in-hospital mortality of this 39.8 percent of patients, who were at high risk for hemodynamic compromise, is consistent with the results of previous studies in the intensive care unit.[32,36]

In an open, randomized, partially blinded trial, there are unavoidable interactions during the initial period of the study. As the study progressed, the patients in the standard-therapy group may have received some form of goal-directed therapy, reducing the treatment effect. This reduction may have been offset by the slight but inherent bias resulting from the direct influence of the investigators on the care of the patients in the treatment group. The potential period of bias was 9.9±19.5 percent of the overall hospital stay in the standard-therapy group and 7.2±12.0 percent of that in the group assigned to early goal-directed therapy ($P=0.20$). This interval was minimal in comparison with those in previous studies[9,13] because the clinicians who assumed responsibility for the remainder of hospitalization were completely blinded to the randomization order.

We conclude that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock, though accounting for only a brief period in comparison with the overall hospital stay, has significant short-term and long-term benefits. These benefits arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. In the future, investigators conducting outcome trials in patients with sepsis should consider the quality and timing of the resuscitation before enrollment as an important outcome variable.

Supported by the Henry Ford Health Systems Fund for Research, a Weatherby Healthcare Resuscitation Fellowship, Edwards Lifesciences (which provided oximetry equipment and catheters), and Nova Biomedical (which provided equipment for laboratory assays).

We are indebted to the nurses, residents, senior staff attending physicians, pharmacists, patient advocates, technicians, and billing and administrative personnel of the Department of Emergency Medicine; to the nurses and technicians of the medical and surgical intensive care units; and to the staff members of the Department of Respiratory Therapy, Department of Pathology, Department of Medical Records, and Department of Admitting and Discharge for their patience and their cooperation in making this study possible.

APPENDIX

The following persons participated in the study: **External Safety, Efficacy, and Data Monitoring Committee:** A. Connors (Charlottesville, Va.), S. Conrad (Shreveport, La.), L. Dunbar (New Orleans), S. Fagan (Atlanta), M. Haupt (Portland, Oreg.), R. Ivatury (Richmond, Va.), G. Martin (Detroit), D. Milzman (Washington, D.C.), E. Panacek (Palo Alto, Calif.), M. Rady (Scottsdale, Ariz.), M. Rudis (Los Angeles), and S. Stern (Ann Arbor, Mich.); **the Early-Goal-Directed-Therapy Collaborative Group:** B. Derechyk, W. Rittinger, G. Hayes, K. Ward, M. Mullen, V. Karriem, J. Urrunaga, M. Gryzbowski, A. Tuttle, W. Chung, P. Uppal, R. Nowak, D. Powell, T. Tyson, T. Wadley, G. Galletta, K. Rader, A. Goldberg, D. Amponsah, D. Morris, K. Kumasi-Rivers, B. Thompson, D. Ander, C. Lewandowski, J. Kahler, K. Kraiovich, H. Horst, S. Harpatoolian, A. Latimer, M. Schubert, M. Fallone, B. Fasbinder, L. Defoe, J. Hanlon, A. Okunsanya, B. Sheridan, Q. Rivers, H. Johnson, B. Sessa-Boji, K. Gunnerson, D. Fritz, K. Rivers, S. Moore, D. Huang, and J. Farrerer (Henry Ford Hospital, Detroit).

REFERENCES

1. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. JAMA 1995;273:117-23.
2. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. JAMA 1994;271:226-33.
3. Nguyen HB, Rivers EP, Havstad S, et al. Critical care in the emergency department: a physiologic assessment and outcome evaluation. Acad Emerg Med 2000;7:1354-61.

4. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: an analysis of outcomes for patients with onset on hospital wards versus intensive care units. Crit Care Med 1998;26:1020-4.
5. Lefrant JY, Muller L, Bruelle P, et al. Insertion time of the pulmonary artery catheter in critically ill patients. Crit Care Med 2000;28:355-9.
6. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 1996;14:218-25.
7. Cortez A, Zito J, Lucas CE, Gerrick SJ. Mechanism of inappropriate polyuria in septic patients. Arch Surg 1977;112:471-6.
8. Elliott DC. An evaluation of the end points of resuscitation. J Am Coll Surg 1998;187:536-47.
9. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-32.
10. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest 1989;95:1216-21.
11. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med 1998;26:2078-86.
12. Opal SM, Cross AS. Clinical trials for severe sepsis: past failures, and future hopes. Infect Dis Clin North Am 1999;13:285-97.
13. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22.
14. Connors AFJ, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276:889-97.
15. Haupt MT. Goal-oriented hemodynamic therapy. N Engl J Med 1996; 334:799.
16. Hinds C, Watson D. Manipulating hemodynamics and oxygen transport in critically ill patients. N Engl J Med 1995;333:1074-5.
17. Shoemaker WC. Goal-oriented hemodynamic therapy. N Engl J Med 1996;334:799-800.
18. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-74.
19. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA 1997;278:234-40.
20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000;284:3043-5.
21. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med 1999;27:639-60.
22. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
24. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63. [Erratum, JAMA 1994;271:1321.]
25. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple Organ Dysfunction Score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
26. Pittet D, Thievent B, Wenzel RP, Li N, Gurman G, Suter PM. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 1993;19:265-72.
27. Rutter CM, Elashoff RM. Analysis of longitudinal data: random coefficient regression modelling. Stat Med 1994;13:1211-31.
28. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341-56.
29. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29: 1303-10.
30. Karimova A, Pinsky DJ. The endothelial response to oxygen deprivation: biology and clinical implications. Intensive Care Med 2001;27:19-31.
31. Edwards JD, Mayall RM. Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. Crit Care Med 1998; 26:1356-60.
32. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients: the role of defined events. Chest 1993;103:900-6.
33. Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock: a study in man. Anesthesiology 1972;36:472-8.
34. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation 1969;40:165-72.
35. Dahn MS, Lange MP, Jacobs LA. Central mixed and splanchnic venous oxygen saturation monitoring. Intensive Care Med 1988;14:373-8.
36. Heiselman D, Jones J, Cannon L. Continuous monitoring of mixed venous oxygen saturation in septic shock. J Clin Monit 1986;2:237-45.

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62. Stehling L: Evaluation of the airway, in *1989 Annual Refresher Course Lectures*. Chicago, American Society of Anesthesiologists, 1989, p 262/1.
63. Demers RR, Saklad M: Mechanical aspiration: A re-appraisal of its hazards. *Respir Care* 20:661, 1975.
64. Ovassapian A, Dykes MHM: The role of fiber-optic endoscopy in airway management. *Semin Anesth* 6:93, 1987.
65. Gaynor EB, Greenberg SB: Untoward sequelae of prolonged intubation. *Laryngoscope* 12:1461, 1985.
66. Kastanos N, Miro RE, Perez AM, et al: Laryngotracheal injury due to endotracheal intubation: Incidence, evolution, and predisposing factors—A prospective long-term study. *Crit Care Med* 11:362, 1983.
67. Quick C, Merwin G: Arytenoid dislocation. *Arch Otolaryngol* 104:267, 1978.
68. Levine PA: Hypopharyngeal perforation: An untoward complication of endotracheal intubation. *Arch Otolaryngol* 6:578, 1980.
69. Myers EM: Hypopharyngeal perforation: A complication of endotracheal intubation. *Laryngoscope* 92:583, 1982.
70. Willms D, Shure D: Pulmonary edema due to upper airway obstruction in adults. *Chest* 94:1090, 1988.
71. Gibbs JM: The effects of endotracheal intubation on cardiac rate and rhythm. *N Z Med J* 66:465, 1967.
72. Takeshima K, Noda K, Higaki M: Cardiovascular response to rapid anesthesia induction and endotracheal intubation. *Anesth Analg* 43:201, 1964.
73. Dubick MM, Wright BD: Problems of prolonged endotracheal intubations. *Chest* 74:479, 1978.
74. Vogelhut MM, Downs JB: Prolonged endotracheal intubation. *Chest* 76:110, 1979.
75. Baron SH, Kohlmoos HW: Laryngeal sequela of endotracheal anesthesia. *Ann Otol Rhinol Otolaryngol* 60:767, 1961.
76. Winkel E, Knudson J: Effect on the incidence of postoperative sore throat of one percent cinchocaine gel for endotracheal intubation. *Anesth Analg* 50:92, 1971.
77. Stout DM, Bishop MJ, Dwersteg JF, et al: Correlation of endotracheal tube size with sore throat and hoarseness following general anesthesia. *Anesthesiology* 67:419, 1987.
78. Teichner RL: Lingual nerve injury: A complication of lower tracheal anesthesia. *Br J Anaesth* 43:413, 1971.
79. Jones BC: Lingual nerve injury: A complication of intubation. *Br J Anaesth* 43:730, 1971.
80. Hahn SW, Martin JT, Lillie JC: Vocal cord paralysis of endotracheal intubation. *Arch Otolaryngol* 92:226, 1970.
81. Holley HS, Gildea JE: Vocal cord paralysis of endotracheal intubation. *JAMA* 215:281, 1971.
82. Cook WR: A comparison of idiopathic laryngeal paralysis in man and horse. *J Laryngol* 84:819, 1970.
83. Brandwein M, Abramson AL, Shikowitz MJ: Bilateral vocal cord paralysis following endotracheal intubation. *Arch Otolaryngol Head Neck Surg* 112:877, 1986.
84. Holinger P, Johnson K: Factors responsible for laryngeal obstruction in infants. *JAMA* 143:1229, 1950.
85. Jackson C: Contact ulcers, granuloma and other laryngeal complications of endotracheal anesthesia. *Anesthesiology* 14:425, 1953.
86. Eckerbom B, Lindholm CE, Alexopous C: Airway lesions caused by prolonged intubation with standard and with anatomically shaped tracheal tubes: A post-mortem study. *Acta Anaesthesiol Scand* 30:366, 1986.
87. Snow JC, Harano M, Balogy K: Post intubation granuloma of the larynx. *Anesth Analg* 45:425, 1966.
88. Bishop MJ, Weymuller EA, Fink BR: Laryngeal effects of prolonged intubation. *Anesth Analg* 63:335, 1984.
89. Berlauk JF: Prolonged endotracheal intubation vs. tracheostomy. *Crit Care Med* 14:742, 1986.
90. Stauffer JL, Olson DE, Petty TL: Complications and consequences of endotracheal intubation and tracheotomy. *Am J Med* 70:65, 1981.
91. Heffner JE, Miller S, Sahn SA: Tracheostomy in the intensive care unit, 1: Indications, technique, management. *Chest* 90:269, 1986.

2. Central Venous Catheters

Michael Seneff

Central venous catheterization remains an integral skill for the practice of critical care medicine. Continued technological advancements in catheter design and increased insight from animal and human research into the causes of catheter-related complications have made central venous catheterization easier and safer for physicians and patients. This chapter reviews the art and science of central venous catheterization, with special attention to the techniques and complications of the various routes of cannulation.

Historical Perspective

Although isolated experiments with central venous cannulation were performed in the early twentieth century [1], Aubaniac is credited with the first description of infraclavicular subclavian venipuncture in humans in 1952 [2]. A major advance in intravenous catheter technique came the following year, when Seldinger described the replacement of a catheter needle using a guidewire, a technique that now bears his name [3]. During the mid-1950s percutaneous catheterization of the inferior vena cava via a femoral vein approach became popular until reports of a high incidence of complications were published [4,5].

An important development occurred in 1959, when Hughes and Magovern described the clinical use of central venous pressure (CVP) measurements in humans undergoing thoracotomy [6]. In 1962, Wilson and associates extended the practicality of CVP monitoring by using percutaneous infraclavicular subclavian vein (SV) catheterization [7]. This technique achieved wide clinical acceptance, but enthusiasm was tempered when various, sometimes fatal, complications were reported. Subsequently, Yoffa reported his experience with supraclavicular subclavian venipuncture, claiming a lower incidence of complications, but his results were not uniformly reproduced [8].

Motivated by the search for a "golden route" [9], Nordlund and Thoren [10] and then Rams and associates [11] performed external jugular vein (EJV) catheterization and advocated a more extensive use of this approach. Although EJV catheterization met the goal of causing fewer complications during venipuncture, positioning of the catheter tip in a central venous location was sometimes impossible.

The first large series on internal jugular vein (IJV) catheterization appeared in 1969, when English et al. [12,13] reported their series of 500 percutaneous IJV catheterizations. Reports confirming this route's efficiency and low complication rate followed, and it has remained a popular site for central venous access.

The best route to establish central venous access remains controversial, and the search for the golden route continues. New techniques and concepts of central venous catheterization (CVC) are regularly introduced, but the four traditional routes are adequate to manage virtually all critically ill patients. Physicians must be aware of each route's advantages and disadvantages to be able to choose an appropriate site for the clinical situation.

Indications and Site Selection

Technical advances and a better understanding of anatomy have made insertion of central venous catheters easier and safer, but there still is an underappreciation of the inherent risks. Like any medical procedure, CVC has specific indications and should be reserved for the patient who has the potential truly to benefit from it (Table 2-1). After determining that CVC is necessary, inexperienced physicians often proceed with subclavian vein catheterization without a thoughtful consideration of the risk-benefit ratio for that route in that particular patient. The consequences of this cavalier approach can be disastrous [14]. It is the responsibility of all critical care physicians to conduct a scientific consideration of the risks and benefits of CVC for every patient who requires it. This will minimize the number of preventable complications and clinically justify those that do occur as a necessary risk of caring for the critically ill.

Volume resuscitation alone is not an indication for CVC. A 2.5-inch, 16-gauge catheter used to cannulate a peripheral vein can infuse two times the amount of fluid as an 8-inch, 16-gauge central venous catheter [15]. However, peripheral vein cannulation can be impossible in the hypovolemic, shocked individual. In this instance, the SV is the most reliable central site because it remains patent due to its fibrous attachments to the clavicle [16]. Depending on the clinical situation, the femoral vein (FV) is a reasonable alternative.

Central venous access is often required for the infusion of irritant medications (concentrated potassium chloride) or vasoactive agents, certain diagnostic or therapeutic radiologic procedures, and, obviously, in any patient in whom peripheral access is not possible. For these indications, the IJV is an ideal route because of its reliability and low rate of major complications with insertion. For experienced operators, the SV is an excellent alternative, as the risk of pneumothorax is low. The FV has many advantages as a primary alternative site but remains underutilized because of concern about the risk of complications from long-term (>72 hr) cannulation.

Long-term total parenteral nutrition with hyperosmolar solutions is best administered through SV catheters, which should be surgically implanted if appropriate. Acute hemodialysis is best accomplished with a subclavian catheter. Flow is more predictable, the catheter less prone to kinking, overall maintenance easier, and complications are rare [17,18]. There are increasing reports, however, of SV thrombosis and stenosis following temporary hemodialysis, causing some centers to switch to the IJV for temporary dialysis access in ambulatory patients [19,20]. The FV is also suitable for acute short-term hemodialysis or plasmapheresis in nonambulatory patients [21].

Table 2-1. Indication for CVC

	Site Selection		
	1st	2nd	3rd
Pulmonary artery catheterization	RIJV	LIJV	LSV
With coagulopathy	REJV	LEJV	RIJV
With pulmonary compromise or high-level PEEP	RIJV	LIJV	EJV
Total parenteral nutrition	SV	IJV	
Long-term	SV (surgically implanted)		
Acute hemodialysis/plasmapheresis	SV	FV	
		IJV (ambulatory)	
Cardiopulmonary arrest	FV	SV	IJV
Emergency transvenous pacemaker	RIJV	SV or LIJV	FV
Hypovolemia, inability to perform peripheral catheterization	SV or FV	IJV	
Preoperative preparation	IJV	EJV	SV
Neurosurgical procedure	AV	FV	SV
General-purpose venous access, vasoactive agents, caustic medications, radiological procedures	IJV	SV or FV	EJV
With coagulopathy	FV or EJV	IJV	AV
Emergency airway management	FV	SV	IJV
Inability to lie supine	FV	EJV	AV

SV, subclavian vein; IJV, internal jugular vein; EJV, external jugular vein; FV, femoral vein; R, right; L, left.

Emergency transvenous pacemakers are best inserted through the right IJV because of the direct path to the right ventricle. This route is associated with the fewest catheter tip malpositions. For the same reason, the right IJV is the primary route for insertion of flow-directed pulmonary artery catheters. In patients with coagulopathy, the EJV, if part of the surface anatomy, is a good alternative. When the SV is used for pulmonary artery catheterization, the left SV is the appropriate choice, for two reasons. First, in many patients, the tip of a standard introducer inserted into the right SV extends into the superior vena cava (SVC), requiring the pulmonary artery catheter to make a sharp bend when it exits the introducer. Malpositioning or kinking of the catheter may result [22]. This does not occur with left SV insertion because of the greater distance from the venipuncture site to the SVC. Second, catheters inserted from the left SV follow a natural curve, traversing the right ventricle into the right pulmonary artery. The reader is referred to Chapter 4 for additional information on the insertion and care of pulmonary artery catheters.

Preoperative CVC is desirable in a wide variety of clinical situations. If fluid status requires close monitoring, a pulmonary artery catheter should be inserted, since CVP is an unreliable predictor of left heart filling pressures [23–26]. In most preoperative patients, the IJV or EJV is the best route, since pneumothorax is very rare with these approaches and even a small pneumothorax is at risk of expanding under general anesthesia [27]. One specific indication for preoperative right ventricular catheterization is the patient undergoing a posterior craniotomy or cervical laminectomy in the sitting position. These patients are at risk for air embolism, and the catheter can be used to aspirate air from the right ventricle [28]. Neurosurgery is the only common indication for an antecubital approach, as IJV catheters can obstruct blood return from the cranial vault and increase intracranial pressure.

Venous access during cardiopulmonary resuscitation deserves special comment. Peripheral vein cannulation in circulatory arrest may prove impossible, and circulation times of

drugs administered peripherally are prolonged when compared to central injection. Drugs injected through femoral catheters also have a prolonged circulation time unless the catheter tip is advanced beyond the diaphragm, although the clinical significance of this is controversial. Effective drug administration is an extremely important element of successful cardiopulmonary resuscitation, and all physicians should understand the appropriate techniques for establishing venous access. It is logical to establish venous access as quickly as possible, either peripherally or centrally if qualified personnel are present. Prolonged attempts at arm vein cannulation are not warranted, and under these circumstances the FV is a good alternative. If circulation is not restored after administration of appropriate drugs and defibrillation, then central access should be obtained by the most experienced operator available with a minimum interruption of cardiopulmonary resuscitation (CPR) [29,30,31]. Generally, SV cannulation can be achieved most rapidly during CPR, but IJV catheterization requires less interruption of external chest compressions and may be preferable if airway management is secured [30].

General Considerations and Complications

General considerations for CVC independent of the site of insertion are catheter tip location, vascular erosions, catheter-associated thrombosis, air and catheter embolism, and coagulopathy, which are discussed below. Catheter-associated infection is a complicated topic that is discussed separately.

CATHETER TIP LOCATION. Catheter tip location is a very important but often ignored consideration in CVC. The ideal location for the catheter tip is the distal innominate or proximal SVC, 3 to 5 cm proximal to the caval-atrial junction. Positioning of the catheter tip within the right atrium or right ventricle must be avoided. Cardiac tamponade secondary to catheter tip perforation of the cardiac wall is not rare, and two-thirds of patients suffering this complication die [32–35]. Perforation results from catheter tip migration that occurs from the motion of the beating heart as well as patient arm and neck movements. Migration of catheter tips can be impressive: 5 to 10 cm with antecubital catheters and 1 to 5 cm with IJV or SV catheters [36–39]. Other complications from intracardiac catheter tip position include provocation of arrhythmias from mechanical irritation or infusion of caustic medications or unwarmed blood [40].

Correct placement of the catheter tip is relatively simple, beginning with an appreciation of anatomy. The caval-atrial junction is approximately 13 to 16 cm from right-sided SV or IJV skin punctures and 15 to 20 cm from left-sided insertions. Insertion of a standard triple-lumen catheter to its full 20 cm almost always places the tip within the heart, especially with right-sided insertions. Catheters should therefore be secured at the 13- to 18-cm mark prior to obtaining a chest radiograph [41,42].

An accurate way to ensure proper catheter tip location is intravascular electrocardiography. Using an adapter, the catheter is inserted while monitoring lead II on a standard ECG. Advancement of the catheter tip into the right atrium is heralded by large P waves on the lead II tracing. Subsequent withdrawal of the catheter tip 3 to 5 cm usually ensures correct positioning [43]. Regardless of the technique used, a chest radiograph should be obtained following every initial central venous catheter insertion to ascertain catheter tip location and to detect complications. Although a cost-benefit analysis of this approach, especially with non-SV insertions, may not be favorable, the importance of correct placement of the catheter tip cannot be overstated.

VASCULAR EROSIONS. Large-vessel perforations secondary to central venous catheters are uncommon and often not immediately recognized. Vessel erosion typically occurs 1 to 7 days after catheter insertion. Patients usually present with sudden onset of dyspnea and often with new pleural effusions on chest radiograph [44]. Catheter stiffness, position of the tip within the vessel, and the site of insertion are probably important factors in causing vessel perforation. The relative importance of these variables is unknown. Repeated irritation of the vessel wall by a stiff catheter tip or infusion of hyperosmolar solutions may be the initiating event. Vascular erosions are more common with left IJV and EJV catheters, because for anatomic reasons the catheter tip is more likely to be positioned laterally under tension against the SVC wall [42,44–47]. Positioning of the catheter tip within the vein parallel to the vessel wall must be confirmed on chest radiograph. Free aspiration of blood from the catheter is not always sufficient to rule out a vascular perforation [44].

AIR AND CATHETER EMBOLISM. Significant air and catheter embolism are rare and preventable complications of CVC. Catheter embolism can occur at the time of insertion when a catheter-through- or over-needle technique is used and the operator withdraws the catheter without simultaneously retracting the needle. It more commonly occurs with antecubital or femoral catheters after insertion, because they cross joint lines and are prone to breakage when the agitated patient vigorously bends an arm or leg. Prevention, recognition, and management of catheter embolism are covered in detail elsewhere [48].

Air embolism is of greater clinical importance, often goes undiagnosed, and may prove fatal [49,50,51]. Theoretically, it is totally preventable with compulsive attention to proper catheter insertion and maintenance. Factors resulting in air embolism during insertion are well known, and methods to increase venous pressure, such as use of the Trendelenburg position, should not be forgotten. Catheter disconnect, typically occurring after insertion, is a more common cause. Air embolism should be suspected in any patient with an intrathoracic catheter tip who develops sudden unexplained hypoxemia or cardiovascular collapse, often after being moved between stretchers. A characteristic mill wheel sound may be auscultated over the precordium. Treatment involves placing the patient in the left lateral decubitus position and using the catheter to aspirate air from the right ventricle. Hyperbaric oxygen therapy to reduce bubble size has a controversial role in treatment [51]. The best treatment is prevention, including use of Luer-Lok equipment at all catheter connections [52].

COAGULOPATHY. Central venous access in the patient with a bleeding diathesis is problematic. The SV and IJV routes have increased risks in the presence of coagulopathy, but it is not known at what degree of abnormality the risk becomes unacceptable. A coagulopathy is generally defined as a prothrombin time greater than 15 seconds, platelet count less than 50,000, or bleeding time greater than 10 minutes. Although it is clear that safe venipuncture is possible with greater degrees of coagulopathy, the literature is fraught with case reports of serious

hemorrhagic complications [53–56]. In patients with coagulopathy, the EJV is an excellent alternative for central venous access, especially pulmonary artery catheterization [57], while the FV offers a safe alternative for general-purpose venous access. If these sites cannot be used, the IJV is the best alternative, since it is a compressible site and there is positive experience with this route in patients with coagulopathy [58]. The SV is not a directly compressible site and is contraindicated except under unusual circumstances.

Although the antecubital veins can be safely cannulated in the presence of coagulopathy, this route is often not as practical as the alternatives. Triple-lumen catheters do not reach a central location when placed through antecubital veins, and the advantages of multilumen catheters in the patient at high risk for venipuncture are apparent; long single-lumen catheters are simply not as versatile. Consequently, antecubital vein CVC is a good option only in the patient with severe coagulopathy (i.e., disseminated intravascular coagulation with multiple sites of clinical bleeding).

THROMBOSIS. Catheter-related thrombosis is very common but usually of little clinical significance. The spectrum of thrombotic complications ranges from a sleeve of fibrin that surrounds the catheter from its point of entry into the vein distal to the tip, to mural thrombus, a clot that forms on the wall of the vein secondary to mechanical or chemical irritation, or occlusive thrombus, which occludes flow and may result in collateral formation [59]. All of these lesions are usually clinically silent, therefore studies that do not use venography to confirm the diagnosis are irrelevant. Using venography, fibrin sleeve formation can be documented in a majority of catheters, mural thrombi in 10 to 30 percent, and occlusive thrombi in 0 to 10 percent [59–65]. In contrast, clinical symptoms of thrombosis occur in only 0 to 3 percent of patients [59,63,66]. The incidence of thrombosis probably increases with duration of catheterization [62] but does not appear related to the site of insertion [59–65]. Recent studies have not confirmed the long-held impression that thrombosis is more common and/or more clinically relevant following FV catheterization than at other sites [67,68].

Catheter design and composition impact on the frequency of thrombotic complications. The ideal catheter material is nonthrombogenic and relatively stiff at room temperature to facilitate percutaneous insertion, yet soft and pliable at body temperature to minimize intravascular mechanical trauma. The catheter materials currently in use include polyethylene, polyvinylchloride, polyurethane, Teflon, and silicone elastomer (Silastic). All catheter materials are thrombogenic, but catheters with smooth surfaces are less prone to platelet aggregation [69]. Although not all studies are consistent, polyurethane, especially when coated with hydromer, appears to be the best material available for bedside catheter insertions. Silastic catheters have low thrombogenicity but must be surgically implanted, and pressure monitoring is usually not possible [38,70–73]. Heparin bonding of catheters decreases thrombogenecity, but the clinical importance of this remains uncertain [52,74,75,76]. Very-low-dose warfarin therapy also decreases the incidence of venogram-proved and clinically apparent thrombosis [77]. This approach holds promise, but since clinical sequelae from catheter-associated thrombosis are rare and warfarin has several relevant drug interactions in the critically ill patient, further study is needed.

Many physicians underappreciate the potential for catheter-associated thrombosis and are unaware of current catheter technology and research, but it is not a trivial issue. Physicians should be aware of the type of catheter in use in their hospital and be able to justify its use on a benefit-risk-cost basis.

Routes of Central Venous Cannulation

ANTECUBITAL APPROACH

Anatomic Considerations. Since the introduction of multilumen catheters and greater experience with the EJV and FV approaches, the antecubital veins are not commonly used for CVC. Advantages to this approach are a low incidence of major complications with insertion and the ability to use it in the presence of clotting abnormalities. Disadvantages include the fact that it is more time-consuming, the relative success rate is lower, the anatomy is less predictable, and catheters must be removed within 72 hours because of a high incidence of phlebitis and infection. These considerations have generally limited use of the antecubital veins to preoperative preparation of the neurosurgical patient at risk for intraoperative air embolism and as an alternative site in patients with severe coagulopathy.

The antecubital venous channels used for CVC are the basilic, cephalic, and brachial veins (Fig. 2-1). The basilic and cephalic veins are usually part of the surface anatomy and are cannulated percutaneously. A cutdown approach to the antecubital veins is not recommended because of a prohibitively high incidence of complications, especially infection. Although the brachial vein is occasionally cannulated percutaneously, it is rarely used for CVC.

Anatomy. The basilic vein is formed in the ulnar part of the dorsal venous network of the hand (Fig. 2-1). It may be found in the medial part of the antecubital fossa, where it is usually joined by the median basilic vein. It then ascends in the groove between the biceps brachii and pronator teres on the medial aspect of the arm to perforate the deep fascia distal to the midportion of the arm, where it joins the brachial vein to become the axillary vein. The basilic vein is almost always of substantial size and the anatomy is predictable; since the axillary vein is a direct continuation of it, the basilic vein provides an unimpeded path to the central venous circulation [78–81].

The cephalic vein begins in the radial part of the dorsal venous network of the hand and ascends around the radial border of the forearm (Fig. 2-1). In the lateral aspect of the antecubital fossa, it forms an anastomosis with the median basilic vein and then ascends the lateral part of the arm in the groove along the lateral border of the biceps brachii. It pierces the clavipectoral fascia in the deltopectoral triangle and empties into the proximal part of the axillary vein caudal to the clavicle. The variability of the cephalic vein anatomy renders it less suitable than the basilic vein for CVC. It joins the axillary vein at nearly a right angle, which can be difficult for a catheter to traverse. Instead of passing beneath the clavicle, the cephalic vein may pass through the clavicle, compressing the vein and making catheter passage impossible. Furthermore, in a significant percentage of cases, the cephalic does not empty into the axillary vein but divides into smaller branches or a venous plexus, which empties into the ipsilateral external jugular vein. The cephalic vein may also simply terminate or become attenuated just proximal to the antecubital fossa [78–81].

Technique of Cannulation. Several kits are available for antecubital CVC; the technique using a 24-inch, 16-gauge catheter-through-needle device is described here, but other devices have comparable efficacy [82].

The right basilic vein should be selected for the initial attempt at CVC because of anatomical considerations and clinical studies that confirm a higher success rate with the basilic than the cephalic vein [83,84,85]. The success rates from either arm are

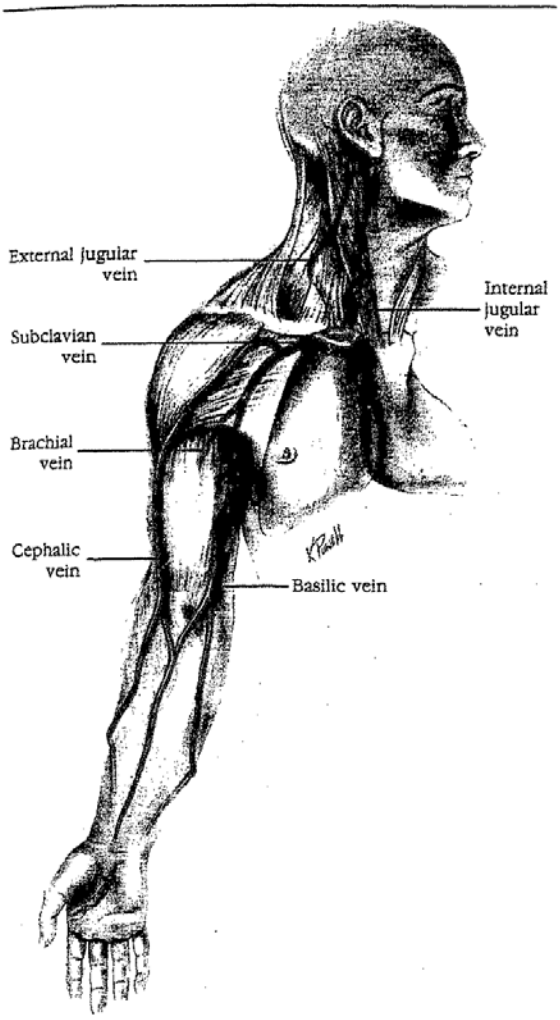


Fig. 2-1. Venous anatomy of the upper extremity. The internal jugular, external jugular, and subclavian veins are also shown.

comparable, although the catheter must traverse a greater distance when inserted via the left arm, which may result in a slightly higher rate of malposition [86].

With the patient's arm at his or her side, the antecubital fossa is prepared and draped, adhering to strict aseptic technique. A tourniquet is placed proximally to distend the vein, which is then entered at a 45-degree angle with the needle bevel pointing up and cephalad. When free backflow of blood is confirmed, the tourniquet is released and the catheter carefully threaded into the vein. The catheter should advance easily without undue resistance until the operator estimates the tip to be in the distal innominate or SVC. The length of insertion is estimated by measuring the distance from the venipuncture site to the manubriosternal junction; a more accurate method is intravascular electrocardiography (as discussed above) [87].

If resistance to advancing the catheter is met, options are limited. Techniques such as abducting the arm are of limited value. With a catheter-through- or over-needle device, the catheter must never be withdrawn without simultaneously retracting the needle to avoid catheter embolism. If the catheter cannot be advanced easily, another site should be chosen.

Once the catheter has advanced the estimated distance, the stiff inner wire is removed and the catheter connected to an intravenous solution. Air embolism can occur with antecubital catheters; prophylactic measures are necessary. After the IV is infusing freely, the tubing should be placed in a dependent position to check for backflow of blood. The catheter is then sutured securely, the arm placed on an arm board to prevent bending at the elbow, and the insertion site bandaged in standard fashion. A chest radiograph is indicated to ascertain catheter tip position.

Success Rate and Complications. Using the above technique, a central venous catheter is placed successfully on the first attempt in approximately 70 percent of cases with the basilic vein and 40 to 50 percent with the cephalic vein [80–85,88,89,90]. In 5 percent or less, the failure is a result of an inability to perform venipuncture, but the major cause of failure is an inability to advance the catheter tip into the proper position. Several measures—abducting the arm to 90 degrees, turning the head to the ipsilateral side, and infusing intravenous solutions during cannulation—are advocated to improve the success rate; the efficacy of these measures is unproved.

Important complications resulting from antecubital CVC include sterile phlebitis, thrombosis (especially of the SV and IJV), infection, limb edema, and pericardial tamponade. Phlebitis is more common with antecubital central venous catheters, probably due to less blood flow in these veins as well as the proximity of the venipuncture site to the skin [91]. The risk of pericardial tamponade may also be increased because of greater catheter tip migration occurring with arm movements [38,92]. Complications are minimized by strict adherence to recommended techniques for catheter placement and care.

INTERNAL-EXTERNAL JUGULAR APPROACH.

The IJV provides one of the most favorable sites for access to the great thoracic veins. Internal jugular vein cannulation offers a high success rate with few complications. Pediatricians used the IJV for venous access [93] long before Hermosura and colleagues described the technique and advocated its use in adults in 1966 [94]. In 1969, English et al. reported the first large series of IJV cannulations [12]; subsequently the procedure became commonplace, and in many centers the preferred method of CVC. In 1974, Blitt et al. described a technique of CVC via the EJV employing a J wire [95]. Although the success rate of this route is lower than with the IJV, a "central" venipuncture is avoided, and in selected cases catheterization via the EJV is an excellent alternative.

Anatomy. The IJV emerges from the base of the skull through the jugular foramen and enters the carotid sheath dorsally with the internal carotid artery (ICA) (Fig. 2-1). It then courses posterolaterally to the artery and runs beneath the sternocleidomastoid (SCM) muscle. The vein lies medial to the anterior portion of the SCM muscle in its upper part, then runs beneath the triangle formed by the two heads of the muscle in its medial portion before entering the SV near the medial border of the anterior scalene muscle beneath the sternal border of the clavicle. The junction of the right IJV (which averages 2–3 cm in diameter) with the right SV and then the innominate vein forms a straight path to the SVC. As a result, malpositions and looping

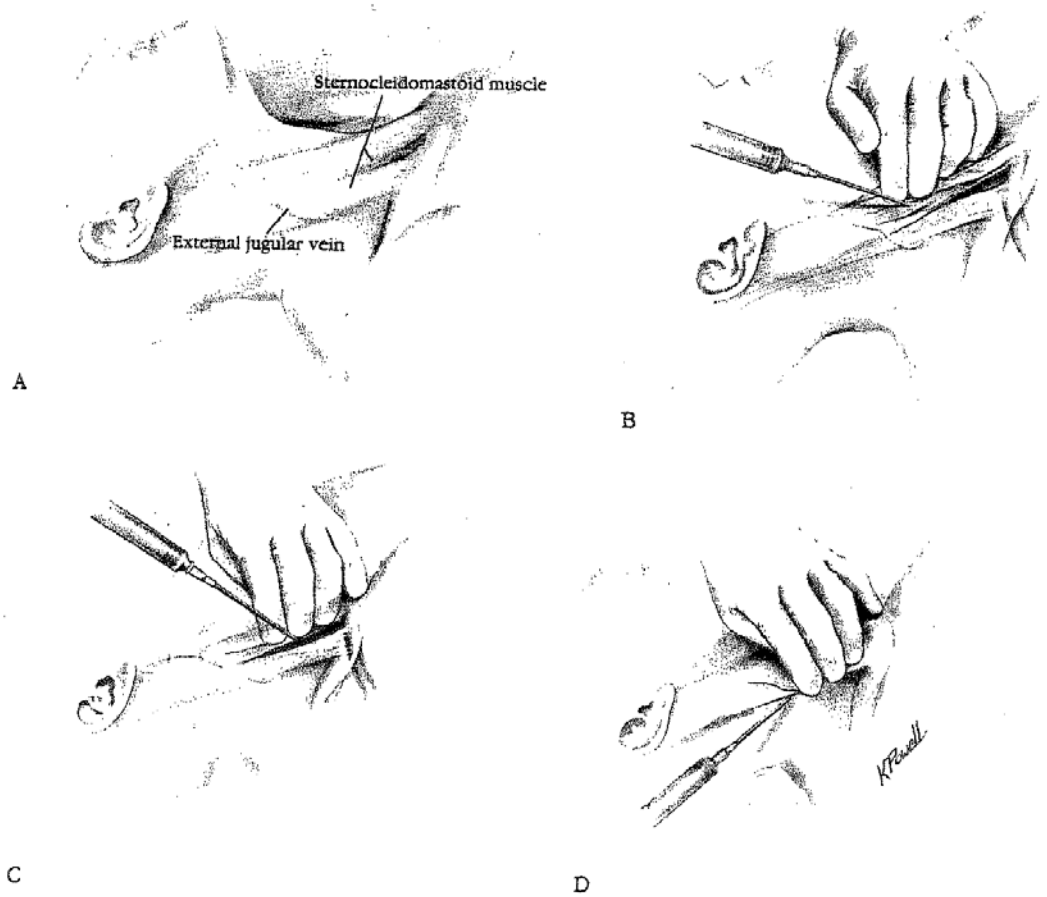
of a catheter inserted through the right IJV are unusual. In contrast, a catheter passed through the left IJV must negotiate a sharp turn at the left jugulosubclavian junction, which results in a greater percentage of catheter malpositions [96,97]. This sharp turn may also produce tension and torque at the catheter tip, resulting in a higher incidence of vessel erosion [44–47,98].

Knowledge of the structures neighboring the IJV is essential, because they may be invaded by a misdirected needle. The ICA runs medial to the IJV but, rarely, may lie directly posteriorly. Behind the ICA, just outside the sheath, lie the stellate ganglion and the cervical sympathetic trunk. The dome of the pleura, which is higher on the left, lies caudal to the junction of the IJV and SV. Posteriorly, at the root of the neck, course the phrenic and vagus nerves [78-81]. The thoracic duct lies behind the left IJV and enters the superior margin of the SV near the jugulosubclavian junction. The right lymphatic duct has the same anatomical relationship but is much smaller, and chylous effusion occurs only with left-sided IJV cannulations [96,97].

Techniques of Cannulation. Internal jugular venipuncture may be accomplished by a variety of methods; as many as 14 variations have been described [99]. All methods use the same landmarks but differ in the site of venipuncture or orientation of the needle. Defalque grouped the methods into three general approaches: anterior, central, and posterior [100] (Fig. 2-2). I prefer the central approach for the initial attempt, but the method chosen varies with the institution and operator's experience. All approaches require identical equipment, and the operator may choose from many different catheters and prepackaged kits. Multilumen catheters are now in common use, and the insertion of a triple-lumen catheter is described below. Insertion of an introducer for pulmonary artery catheterization follows the same basic technique and is described in detail in Chapter 4.

Standard triple-lumen catheter kits include a 7 Fr. triple-lumen catheter with 20 or 30 cm of usable length, a 0.035-inch diameter guidewire with straight and J tip, 18-gauge thin-wall needle, a 16-gauge catheter-over-needle, a 7 Fr. vein dilator, a 22-gauge "finder" needle, and appropriate syringes and suture material. Preparation of the guidewire and catheter prior to insertion is important; all lumens should be flushed with saline

Fig. 2-2. Surface anatomy and various approaches to cannulation of the internal jugular vein. A. Surface anatomy. B. Anterior approach. C. Central approach. D. Posterior approach.



and the cap to the distal lumen removed. The patient is placed in a 15-degree Trendelenburg position to distend the vein and minimize the risk of air embolism, with the head turned gently to the contralateral side. The surface anatomy is identified, especially the angle of the mandible, the two heads of the SCM, the clavicle, the EJV, and the trachea (Fig. 2-2). The neck is then prepared with an iodine-containing solution, which is allowed to dry, and draped, with care to avoid covering the patient's eyes to minimize anxiety. For the central approach [13,100–103], skin puncture is at the apex of the triangle formed by the two muscle bellies of the SCM and the clavicle. The ICA pulsation is usually felt 1 to 2 cm medial to this point, beneath or just medial to the sternal head of the SCM. The skin at the apex of the triangle is infiltrated with 1% lidocaine using the 22-gauge needle, which is then used to locate the IJV. Use of a small-bore finder needle to locate the IJV should prevent inadvertent ICA puncture and unnecessary probing with a larger-bore needle. The operator should maintain slight or no pressure on the ICA with the left hand and insert the finder needle with the right hand at the apex of the triangle (or slightly more caudal) at a 30- to 45-degree angle with the frontal plane, directed at the ipsilateral nipple. After expulsion of any skin plug, the needle is advanced steadily with constant back pressure and venipuncture occurs within 3 to 5 cm. Deeper penetration is not recommended. If venipuncture does not occur on the initial thrust, back pressure should be maintained and the needle slowly withdrawn, as venipuncture frequently occurs on withdrawal. If the first attempt is unsuccessful, the operator should reassess patient position, landmarks, and techniques to ensure that he or she is not doing anything to decrease IJV lumen size (see below). Subsequent attempts may be directed slightly laterally or medially to the initial thrust, as long as the plane of the ICA is not violated. If venipuncture does not occur after three to five attempts, further attempts are likely to be unsuccessful and only increase complications [58,104,105]. When venipuncture has occurred with the finder needle, the operator can either withdraw the finder needle and introduce the large-bore needle in the identical plane or leave the finder needle in place and introduce the larger needle directly above it. If using the latter technique, the operator or assistant must be careful not to exert tension on the finder needle, as this may decrease the lumen size of the IJV and make catheterization more difficult. Many kits provide both an 18-gauge thin-wall needle through which a guidewire can be directly introduced and a 16-gauge catheter-over-needle device. With the latter apparatus, the catheter is threaded over the needle into the vein, the needle withdrawn, and the guidewire inserted through the catheter. Both techniques are effective; the choice is strictly a matter of operator preference. With the 18-gauge thin-wall needle, the operator must be sure to secure the needle in place with one hand while removing the syringe with the other, so that the needle does not migrate out of the vein prior to guidewire insertion. Many operators prefer the catheter-over-needle device for IJV catheterization because standard intravenous technique is used and the catheter is less likely to migrate from the vein before guidewire insertion. However, this technique requires that the catheter and needle be inserted and withdrawn simultaneously to avoid catheter embolism, and often the catheter does not pierce the tissue planes easily. Regardless of which large-bore needle is used, once venipuncture has occurred the syringe is removed during expiration or Valsalva maneuver and the hub occluded with a finger after ensuring that the backflow of blood is not pulsatile. The J tip of the guidewire is then inserted and should pass freely up to 20 cm, at which point the thin-wall needle or catheter is withdrawn. The tendency to insert the guidewire deeper than 15 to 20 cm should be avoided, as it is the most common cause of ventricular arrhythmias during insertion and also poses a risk for cardiac perforation. Occasionally, the guidewire does not pass easily beyond the tip of the thin-wall needle (especially) or catheter. The guidewire should then be withdrawn, the syringe attached, and free backflow of blood reestablished and maintained while the syringe and needle are brought to a more parallel plane with the vein. The guidewire should then pass easily. If resistance is still encountered, rotation of the guidewire during insertion often allows passage, but extensive manipulation and force only lead to complications.

With the guidewire in place, a scalpel is used to make two generous 90-degree stab incisions at the skin entry site to facilitate passage of the 7 Fr. vein dilator. The dilator is inserted down the wire to the hub, ensuring that control and sterility of the guidewire is not compromised. The dilator is then withdrawn and gauze used at the puncture site to control oozing and prevent air embolism down the needle tract. The triple-lumen catheter is then inserted over the guidewire, ensuring that the guidewire protrudes from the distal lumen hub before the catheter tip penetrates the skin. The catheter is then advanced 15 to 17 cm (17–19 cm for left IJV) into the vein, the guidewire withdrawn, and the distal lumen capped. The catheter is sutured securely to limit tip migration and bandaged in a standard manner. A chest radiograph should be obtained to detect complications and tip location.

Alternative Approaches. The anterior and posterior approaches are identical in technique, differing only in venipuncture site and plane of insertion. For the anterior approach (Fig. 2-2) [99, 100,106,107,108], the important landmark is the midpoint of the sternal head of the SCM, approximately 5 cm from both the angle of the mandible and the sternum. At this point, the carotid artery can be palpated 1 cm inside the lateral border of the sternal head. The index and middle fingers of the left hand gently palpate the artery, and the needle is introduced 0.5 to 1 cm lateral to the pulsation. The needle should form a 30- to 45-degree angle with the frontal plane and be directed caudally parallel to the carotid artery toward the ipsilateral nipple. Venipuncture occurs within 2 to 4 cm, sometimes only while the needle is slowly withdrawn. If the initial thrust is unsuccessful, the next attempt should be at a 5-degree lateral angle, followed by a cautious attempt more medially, never crossing the plane of the carotid artery.

The posterior approach (Fig. 2-2) [99,100,109,110,111] uses the EJV as a surface landmark. The needle is introduced 1 cm dorsally to the point where the EJV crosses the posterior border of the SCM or 5 cm cephalad from the clavicle along the clavicular head of the SCM. The needle is directed caudally and ventrally toward the suprasternal notch at an angle of 45 degrees to the sagittal plane, with a 15-degree upward angulation. Venipuncture occurs within 5 to 7 cm. If this attempt is unsuccessful, the needle should be aimed slightly more cephalad on the next attempt.

Success Rates and Complications. Internal jugular vein catheterization is associated with a high rate of successful catheter placement regardless of the approach used. Elective procedures are successful more than 90 percent of the time, generally within the first three attempts, and catheter malposition is rare [96,97,100,101,102,104,106,107]. Operator experience does not appear to be as important a factor in altering the success rate of venipuncture as it is in increasing the number of complications [104,112]. Emergent IJV catheterization is less successful and is not the preferred technique during airway emergencies or other situations that may make it difficult to identify landmarks in the neck [104,112]. Some authors advocate the use of ultrasound localization to aid in IJV catheteriza-

tion [113], but routine use of ultrasound is unnecessary for a procedure with such a high success rate. In special circumstances, ultrasound or Doppler localization is helpful in performing difficult or previously unsuccessful IJV catheterization [114,115].

Ultrasound studies have been useful in delineating factors that improve the efficiency of IJV cannulation. The ability to perform IJV venipuncture is directly proportional to its cross-sectional lumen area (CSLA), thus maneuvers that increase or decrease the veins' caliber impact on the success rate [41,113,115,116,117]. Maneuvers that decrease the CSLA include hypovolemia, carotid artery palpation, and excessive tension on a finder needle. Predictably, Valsalva maneuver and Trendelenburg position increase CSLA, as does high-level positive end-expiratory pressure (PEEP). There is also a progressive increase in CSLA as the IJV nears the SV. Overrotation of the neck may place the vein beneath the SCM muscle belly [115].

Often, a difficult IJV cannulation is successful on the first attempt by optimizing CLSA through attention to the above measures. If the IJV is still not punctured after one or two attempts, it is usually because of anatomical variation, not because of the absence of jugular flow [116,117]. In this situation, I use a Doppler device (Smart-Needle) to locate the IJV, because of its portability, overall convenience, and need for less operator expertise [118]. Others use ultrasound in an analogous fashion [119]. Whatever technique is employed, prolonged attempts at catheterization after optimization of IJV CSLA are only likely to increase complications.

Complications. The incidence and types of complications are similar regardless of the approach. Operator inexperience appears to increase the number of complications, but to an undefined extent, and probably does not have as great an impact as it does on the incidence of pneumothorax in subclavian venipuncture [100,120,121].

The overall incidence of complications in IJV catheterization is 0.1 to 4.2 percent [12,100,109,120,122], with a few studies reporting higher rates [58,104,123]. Important complications include ICA puncture, pneumothorax, vessel erosion, thrombosis, and infection. Vessel erosion, thrombosis, and infectious complications are common to all routes of CVC and are reviewed separately in this chapter.

By far the most common complication is ICA puncture, which constitutes 80 to 90 percent of all complications. In the absence of a bleeding diathesis, arterial punctures are benign and are managed conservatively without sequelae by applying local pressure for 10 minutes. Even in the absence of clotting abnormalities, a sizable hematoma may form, frequently preventing further catheterization attempts or, rarely, exerting pressure on vital neck structures [124–128]. Unrecognized arterial puncture can lead to catheterization of the ICA with a large-bore catheter or introducer and can have disastrous consequences, especially when heparin is administered [122]. Management of carotid cannulation with a large-bore catheter, such as a 7 Fr. introducer, is controversial. Some experts advise administration of anticoagulants to prevent thromboembolic complications, while others advise the opposite. My approach is to remove the catheter and avoid heparinization if possible, as hemorrhage appears to be a greater risk than thromboembolism [122].

Chronic complications that rarely complicate ICA puncture include hematomas requiring surgical excision [129], arteriovenous fistula [130], and pseudoaneurysm [131].

Coagulopathy is a relative contraindication to IJV catheterization, and the EJV or FV should be considered as primary alternatives. If these routes cannot be used, I proceed with the IJV approach. Under these circumstances, a finder needle technique is mandatory, because carotid puncture by a 22-gauge needle is still unlikely to cause complications. Goldfarb and Lebrec [58] performed IJV cannulation in 1000 patients with liver disease and coagulopathy, defined as prothrombin activity less than 50 percent and/or bleeding time longer than 10 minutes and/or platelet count under 50,000. Despite a 7 percent incidence of arterial puncture, a clinically detectable hematoma formed in only 10 patients, one of whom required surgical drainage. The coagulopathy associated with liver disease cannot be equated to all coagulation abnormalities, but this experience suggests that the IJV can be used safely as an alternative to the EJV or FV in the presence of coagulopathy.

Pneumothorax is an unusual adverse consequence of IJV cannulation, with an average incidence of 0 to 0.2 percent [12,99,104,110,120]. It usually results from a skin puncture too close to the clavicle or, rarely, a guidewire inserted through a needle that has inadvertently migrated from the IJV lumen [58]. Pneumothorax may be complicated by heme, infusion of intravenous fluid, or tension [58,104,132,133].

An extraordinary number of case reports indicate that any complication from IJV catheterization is possible, even the intrathecal insertion of a Swan-Ganz catheter [134]. In reality, this route is reliable, with a low incidence of major complications. Operator experience is not as important a factor as in SV catheterization, the incidence of catheter tip malposition is low, and patient acceptance is high. It is best suited for elective catheterizations in volume-repleted patients, especially pulmonary artery catheterizations and insertion of temporary transvenous pacemakers. It is not the preferred site during airway emergencies, for administration of parenteral nutrition, or long-term catheterization. Anticoagulation is not an absolute contraindication, but EJV or FV catheterization may be more appropriate for initial attempts.

EXTERNAL JUGULAR VEIN APPROACH.

The main advantages to the EJV route for CVC are that the EJV is part of the surface anatomy, it may be cannulated in the presence of clotting abnormalities, and the risk of pneumothorax is avoided. The main disadvantage is the unpredictability of passage of the catheter to the central compartment.

Anatomy. The EJV is formed anterior and caudal to the ear at the angle of the mandible by the union of the posterior auricular and retromandibular veins (Fig. 2-3). It courses obliquely across the anterior surface of the SCM, then pierces the deep fascia just posterior to the SCM and joins the SV behind the medial third of the clavicle. In 5 to 15 percent of patients, the EJV is not a distinct structure but a venous plexus, in which case it may receive the ipsilateral cephalic vein. The EJV varies in size and contains valves throughout its course. Its junction with the SV may be at a severe, narrow angle that can be difficult for a catheter to traverse.

Technique. The EJV should be cannulated using the 16-gauge catheter-over-needle, since guidewire manipulations are often necessary and secure venous access is preferable with a catheter. On occasion, especially after unsuccessful attempts and hematoma formation, an 18-gauge thin-wall needle must be used. The patient is placed in a slight Trendelenburg position, with arms to the side and head turned gently to the contralateral side. The right EJV should be chosen for the initial attempt and can be identified where it courses over the anterior portion of the clavicular belly of the SCM. The Valsalva maneuver may help identify the vein in the dehydrated patient, but because of venous valves, thoracic pressure is not consistently transmitted to the EJV. After sterile preparation, venipuncture is performed with the 16-gauge catheter-over-needle using the left index

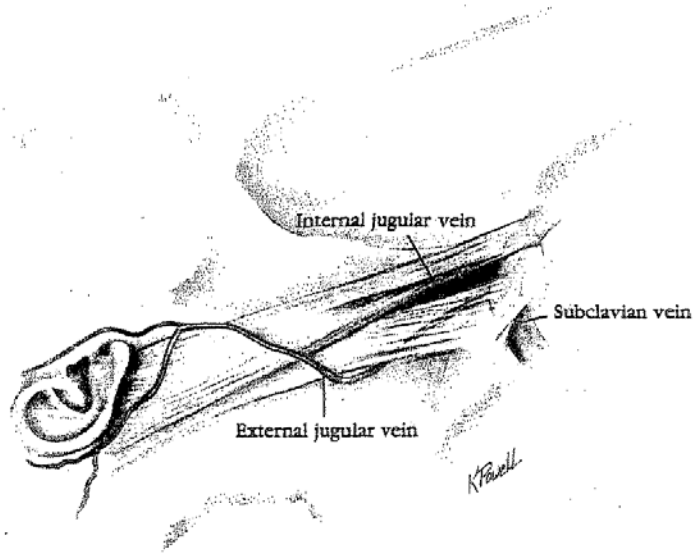


Fig. 2-3. External jugular vein.

finger and thumb to distend and anchor the vein. Skin puncture should be well above the clavicle and the needle advanced in the axis of the vein at 20 degrees to the frontal plane. The EJV may be more difficult to cannulate than expected because of its propensity to roll and displace rather than puncture in response to the advancing needle. A firm, quick thrust is often required to effect venipuncture. When free backflow of blood is established, the needle tip is advanced a few millimeters further into the vein and the catheter is threaded over the needle. The catheter may not thread its entire length because of valves, tortuosity, or the SV junction but should be advanced at least 3 to 5 cm to secure venous access. The syringe and needle can then be removed and the guidewire, J tip first, threaded up to 20 cm and the catheter removed. Manipulation and rotation of the guidewire, especially when it reaches the SV junction, may be necessary but should not be excessive. Various arm and head movements are advocated to facilitate guidewire passage. I have found abduction of the ipsilateral arm and anterior-posterior pressure exerted on the clavicle to be helpful. Once the guidewire has advanced 20 cm, two 90-degree skin stabs are made with a scalpel, and the vein dilator is inserted to its hub. Control of the guidewire should never be lost while the vein dilator is removed. The triple-lumen catheter is then inserted an appropriate length (16–17 cm on the right, 18 cm on the left). The guidewire is withdrawn, the catheter bandaged, and a chest radiograph obtained to screen for complications.

Success Rates and Complications. Central venous catheterization via the EJV is successful in 80 percent of patients (range 75–95%) [95,135,136,137]. Inability to perform venipuncture accounts for up to 10 percent of failures [96,135,138,139] and the remainder are a result of catheter tip malpositioning. Failure to position the catheter tip is a result of an inability to negotiate the EJV-SV junction, loop formation [96,139], or retrograde passage down the ipsilateral arm [112,135].

Serious complications arising from the EJV approach are rare and almost always associated with catheter maintenance rather than venipuncture. A local hematoma forms in 1 to 5 percent of patients at the time of venipuncture [96,135,139,140] but has little consequence unless it distorts the anatomy leading to catheterization failure. External jugular venipuncture is safe in the presence of coagulopathy. Infectious and thrombotic complications are no more frequent than with other central routes. Phlebitis is potentially more common because of lower blood flows, but this is unproved. Vascular erosions may occur more commonly with left-sided EJV catheters for the reasons discussed above [141]. A chest radiograph should be obtained to confirm catheter tip location within the SVC, parallel to the vessel wall.

There is considerable disagreement regarding the true usefulness of EJV catheterization in critical care practice. The reasons for the wide disparity in success rates reported in the literature are not apparent, but experience and enthusiasm for the route may play a role. My own experience with EJV catheterization is similar to the 80 percent success rate reported above, and I find it a valuable alternative to the IJV in anticoagulated patients or those with severe lung disease or on high-level PEEP. All critical care physicians should gain expertise with this route, as its success rate is at least comparable to that of the antecubital approach and major complications are rare.

FEMORAL VEIN APPROACH. The FV is an appealing site for CVC because it is directly compressible, it is remote from the airway and pleura, the technique is relatively simple, and the Trendelenburg position is not required during insertion. Femoral vein catheterization was a common site for CVC in the 1950s but was largely abandoned after 1959 when Moncrief [4]

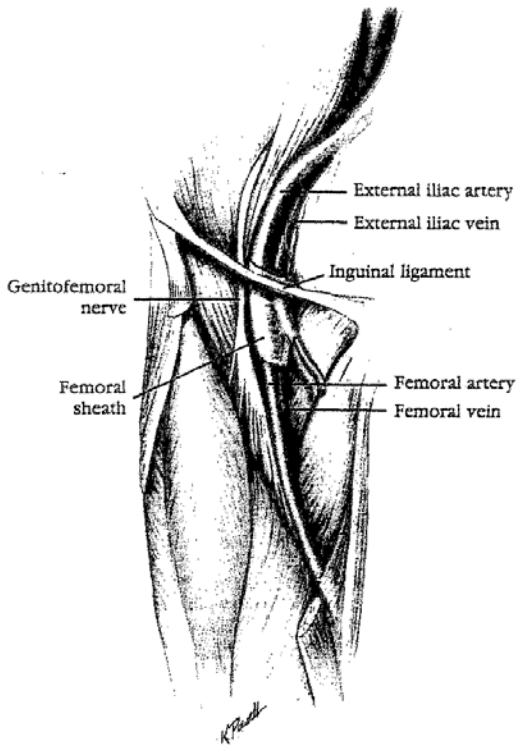


Fig. 2-4. Anatomy of the femoral vein.

and Bansmer et al. [5] reported a high incidence of complications, especially infection and thrombosis. In the subsequent two decades, FV cannulation was restricted to specialized clinical situations. Interest in short-term (<48 hr) FV catheterization was revived by positive experiences during the Vietnam conflict [142] and with patients in the emergency department [143,144]. More recent reports on long-term FV catheterization in children [145] and adults [67,68,146,147] suggest a complication rate no higher than that with other routes.

Anatomy. The FV (Fig. 2-4) is a direct continuation of the popliteal vein and becomes the external iliac vein at the inguinal ligament. At the inguinal ligament the FV lies within the femoral sheath a few centimeters from the skin surface. Within the intermediate compartment of the sheath, the FV lies medial to the femoral artery, which in turn lies medial to the femoral branch of the genitofemoral nerve. The medial compartment contains lymphatic channels and Cloquet's node. The external iliac vein courses cephalad from the inguinal ligament along the anterior surface of the iliopsoas muscle to join its counterpart from the other leg and form the interior vena cava (IVC) anterior to and to the right of the fifth lumbar vertebra [78–81].

Technique. Femoral vein cannulation is the easiest of all central venous procedures to learn and perform [143,148,149]. Either side is suitable, and the side chosen is based on operator convenience. The patient is placed in the supine position (if tolerated) with the leg extended and slightly abducted at the hip. Excessive hair should be clipped with scissors and the skin prepped with an iodine-containing solution and wiped with alcohol or allowed to dry. The FV lies 1 to 1.5 cm medial to the arterial pulsation, and the skin should be infiltrated with 1% lidocaine at this point. In a patient without femoral artery pulsations, the FV can be located in the following manner [142]. The distance between the anterior superior iliac spine and the pubic tubercle is divided into three equal segments. The femoral artery is usually found where the medial segment meets the two lateral ones, and the FV lies 1 to 1.5 cm medial. An 18-gauge thin-wall needle is inserted at this point, 2 to 3 cm inferior to the inguinal ligament, so that venipuncture occurs caudal to the inguinal ligament and minimizes the risk of retroperitoneal hematoma in the event of arterial puncture. While maintaining constant back-pressure on the syringe, the needle, tip pointed cephalad, is advanced at a 45- to 60-degree angle to the frontal plane. Insertion of the needle almost to its hub is sometimes required in obese patients. Venipuncture may not occur until slow withdrawal. If the initial attempt is unsuccessful, landmarks should be reevaluated and subsequent thrusts oriented slightly more medial or lateral. A common error is to direct the needle tip medially, toward the umbilicus. The femoral vessels lie in the sagittal plane at the inguinal ligament (Fig. 2-4), and the needle should be directed accordingly. If inadvertent arterial puncture occurs, pressure is applied for 5 to 10 minutes.

When venous blood return is established, the syringe is depressed to skin level and free aspiration of blood reconfirmed. The syringe is removed, ensuring that blood return is not pulsatile. The guidewire should pass easily and never be forced, although rotation and minor manipulation are sometimes required. The needle is then withdrawn, two scalpel blade stab incisions made at 90 degrees above the guidewire insertion site, and the vein dilator inserted over the wire to the hub. The dilator is next withdrawn and a catheter appropriate to clinical requirements inserted, taking care never to lose control of the guidewire. The catheter is secured with a suture and antiseptic ointment and bandage applied.

Success Rate and Complications. Femoral vein catheterization is successful in 90 to 95 percent of patients, including those in shock or cardiopulmonary arrest [142,143,145,146,149,150]. Unsuccessful catheterizations are usually a result of venipuncture failure, hematoma formation, or inability to advance the guidewire into the vein. Operator inexperience may increase the number of attempts and complication rate but does not significantly decrease the overall success rate [146].

Only three complications occur regularly with FV catheterization: arterial puncture with or without local bleeding, infection, and thromboembolic events. Other reported complications are rare and include scrotal hemorrhage [151], right lower quadrant bowel perforation [152], retroperitoneal hemorrhage [153], puncture of the kidney [154], and perforation of IVC tributaries. These complications occur when skin puncture sites are cephalad to the inguinal ligament or when long catheters are threaded into the FV.

Femoral artery puncture occurs in 5 to 10 percent of adults [142,143,146,148,150], with a slightly higher incidence in children [145]. Most arterial punctures are uncomplicated, but major hematomas may form in 1 percent of patients [142,146]. Even in the presence of coagulopathy, arterial puncture with the 18-gauge thin-wall needle is usually of no consequence, with only rare reports of life-threatening thigh or retroperitoneal hemorrhage [149,155]. The long history of femoral vessel cannulation in the setting of renal failure attests to its safety in patients with bleeding tendencies [156]. Arteriovenous fistula and pseudoaneurysm are rare chronic complications of arterial puncture; the former is more likely to occur when both femoral vessels are cannulated concurrently [157].

Infectious complications from FV catheters are no more frequent than with other routes. The perception that FV catheters are more prone to infection derives from studies in the 1950s already cited, as well as the proximity of the site to the pubic area. All recent series involving both short- and long-term FV catheterization in adults and children have reported catheter-related infection rates of 5 percent or less [142,143,145,146,158]. Further evidence that the inguinal area is not an inherent "dirty" site is provided by experience with femoral artery catheters, which have an infection rate comparable to that with radial artery catheters [159,160].

The most feared complication of FV catheterization is deep venous thrombosis (DVT) of the lower extremity. Moncrief, in 1958, reported an incidence of autopsy-proven thrombosis of 13 percent with catheters left in place an average of 7 to 10 days in burn patients [4]. Bansmer and co-workers, also in 1958, reported a 29 percent incidence of IVC or ileofemoral thrombosis in patients with femoral catheters in place an average of 13 days [5]. These findings were largely responsible for the abandonment of FV catheters, but for several reasons these studies are probably not indicative of the true risk of thromboembolic complications from FV catheters. Both studies reported mainly autopsy findings from a small series of chronically ill patients, which is not a representative patient sample. Due to technological improvements in catheter design and material, catheters are not as thrombogenic as they were in the 1950s. Most important, these reports involved no comparative studies with catheters inserted at other central routes. Catheter-associated thrombosis is a risk of all central venous catheters, regardless of the site of insertion, and comparative studies using contrast venography are needed to better assess the relative risk of FV catheters. The available data suggest that FV catheters are no more prone to thrombosis than SV or IJV catheters [60,61,63,64,65,67,68]. However, thrombosis of the ileofemoral system is potentially more serious than upper extremity thrombosis, and the potential thromboembolic complications of FV catheters cannot be discounted [161,162]. Studies using serial impedance plethysmography or Doppler ultrasound to assess the incidence of DVT from FV catheters are in progress.

In summary, available evidence supports the view that the FV may be cannulated safely in critically ill adults. It is particularly useful for inexperienced operators because of the high rate of success and lower incidence of major complications. Femoral vein catheterizations may be performed during airway emergencies and cardiopulmonary arrest, in patients with coagulopathy, and in patients who are unable to lie flat. The only major complication during venipuncture is arterial puncture, which is usually easily managed. Infection is no more common than with other routes, and expanding clinical experience suggests that thromboembolism is not as clinically significant as once believed.

SUBCLAVIAN VEIN APPROACH. Since Aubaniac [2] described the use of subclavian venipuncture in humans, controversy has surrounded this route of access to the central circulation. Wilson et al.'s 1962 report [7] generated much enthusiasm for SV catheterization, but soon the large number of serious complications, some fatal, resulted in some investigators urging a moratorium on the procedure [163]. The controversy involving SV catheterization probably derives from the significant impact of operator experience on the incidence of complications. Experienced operators (see below) experience a pneumothorax rate of 1 percent or less and can justify use of the SV as primary central venous access in almost all patients. Inexperienced operators have a far greater rate of pneumothorax; therefore, in settings where relatively inexperienced physicians perform the majority of CVC, the SV should be used more selectively [164,165]. The advantages of this route include consistent identifiable landmarks, easier long-term catheter maintenance, and relatively high patient comfort. The SV is the preferred site for CVC in patients with hypovolemia, for long-term total parenteral nutrition (TPN), for acute hemodialysis, and in patients with elevated intracranial pressure who require hemodynamic monitoring.

Anatomy. The SV is a direct continuation of the axillary vein, beginning at the lateral border of the first rib, extending 3 to 4 cm along the undersurface of the clavicle and becoming the brachiocephalic vein where it joins the ipsilateral IJV at Pirogoff's confluence behind the sternoclavicular articulation (Fig. 2-5) [78–81,166]. The vein is 1 to 2 cm in diameter, contains a single set of valves just distal to the EJV junction, and is fixed in position directly beneath the clavicle by its fibrous attachments. These attachments prevent collapse of the vein, even with severe volume depletion. Anterior to the vein throughout its course lies the subclavius muscle, clavicle, costoclavicular ligament, pectoralis muscles, and epidermis. Posteriorly, the SV is separated from the subclavian artery and brachial plexus by the anterior scalenus muscle, which is 10 to 15 mm thick in the adult. Posterior to the medial portion of the SV are the phrenic nerve and internal mammary artery as they pass into the thorax. Superiorly, the relationships are the skin, platysma, and superficial aponeurosis. Inferiorly, the vein rests on the first rib, Sibson's fascia, cupola of pleura (0.5 cm behind the vein), and pulmonary apex [19,42,167,168]. The thoracic duct on the left and right lymphatic duct cross the anterior scalene muscle to join the superior aspect of the SV near its union with the IJV.

Technique. Although there are countless variations, the SV may be cannulated by two basic techniques, the infraclavicular [2,7,9,16,99,166–172] or supraclavicular [16,99,166,167,173–177] approach (Fig. 2-6). The differences in success rate, catheter tip malposition, and complications between the two approaches are negligible, although catheter tip malposition and pneumothorax may be less likely with supraclavicular cannulation [178,179,180]. In general, when discussing the success rate and incidence of complications of SV catheterization, there is no need to specify the approach used. The 18-gauge thin-wall needle is preferable for SV cannulation. The catheter-over-needle device tends to be less effective for two reasons. First, the catheter often hangs up on the clavicle and does not advance easily over the needle. This may result in kinking or breakage of the catheter. Second, the catheter has a tendency to rebound out of the SV lumen after the needle is withdrawn because of tension exerted on it by the clavicle and tissue planes. Vascular access is then lost before insertion of the guidewire.

The patient is placed in a 15- to 30-degree Trendelenburg position, with a small bedroll between the shoulder blades. The head is turned gently to the contralateral side and the arms are kept to the side. The pertinent landmarks are the clavicle, the two muscle bellies of the SCM, the suprasternal notch, and the manubriosternal junction. For the infraclavicular approach (Fig. 2-6), the operator is positioned next to the patient's shoulder on the side to be cannulated. For reasons cited earlier, the left SV should be chosen for pulmonary artery catheterization; otherwise, the success rate appears to be equivalent regardless of the side chosen. Skin puncture is 2 to 3 cm caudal to the midpoint of the clavicle, corresponding to the area where the clavicle turns from the shoulder to the manubrium, and should be distant enough from the clavicle to avoid a downward angle of the needle in clearing the inferior surface of the clavicle, which also obviates the need to bend the needle. The path of

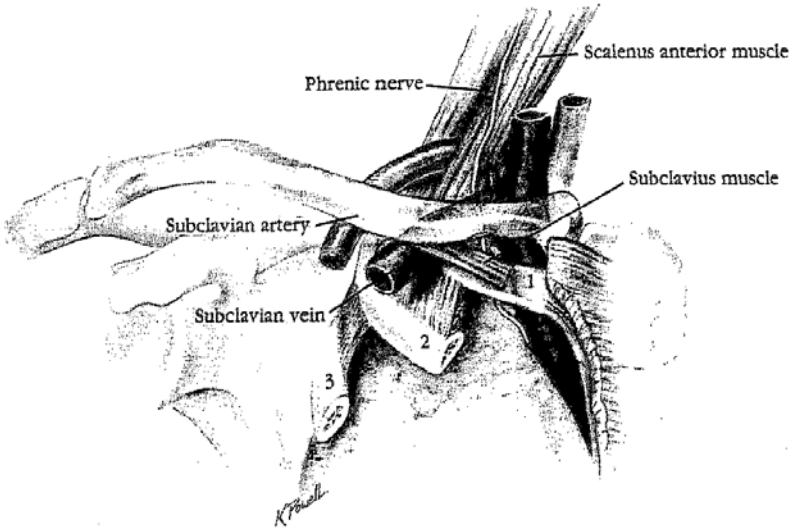


Fig. 2-5. Anatomy of the subclavian vein and adjacent structures.

A B

Fig. 2-6. A. Patient positioning for subclavian cannulation. B. Cannulation technique for supraclavicular approach.

the needle is toward the suprasternal notch or the medial end of the contralateral clavicle. After skin infiltration and liberal injection of the clavicular periosteum with 1% lidocaine, the 18-gauge thin-wall needle is mounted on a 10-ml syringe filled with saline. Skin puncture is accomplished with the needle bevel up, and a small amount of saline is expressed to eliminate any possible skin plug. The needle is advanced in the plane described above until the tip abuts the clavicle. The needle is then "walked" down the clavicle until the inferior edge is cleared. As the needle is advanced, the inferior surface of the clavicle should be felt hugging the needle. This ensures that the needle tip is as superior as possible to the dome of the pleura. The needle is advanced toward the suprasternal notch during breath holding or expiration, and venipuncture occurs when the needle tip lies beneath the medial end of the clavicle. This may require insertion of the needle to its hub. Venipuncture may not occur until slow withdrawal of the needle. If venipuncture is not accomplished on the initial thrust, the next attempt should be directed slightly more cephalad. If venipuncture does not occur by the third or fourth attempt, another site should be chosen, as additional attempts are unlikely to be successful and may result in complications [112,165]. When blood return is established, the bevel of the needle is rotated 90 degrees toward the heart. The needle is anchored firmly with the left hand while the syringe is detached with the right. Blood return should not be pulsatile, and air embolism prophylaxis is necessary at all times. The guidewire is then advanced through the needle to 15 cm and the needle withdrawn. The remainder of the procedure is as previously described. Triple-lumen catheters should be sutured at 13 to 15 cm on the right and 15 cm on the left to avoid intracardiac tip placement.

For the supraclavicular approach (Fig. 2-6), the important landmarks are the clavicular insertion of the SCM muscle and the sternoclavicular joint. The operator is positioned at the head of the patient on the side to be cannulated. The site of skin puncture is the claviculosternocleidomastoid angle, just above the clavicle and lateral to the insertion of the clavicular head of the SCM. The needle is advanced toward or just caudal to the contralateral nipple just under the clavicle. This corresponds to a 45-degree angle to the sagittal plane, bisecting a line between the sternoclavicular joint and clavicular insertion of the SCM [42,178]. The depth of insertion is from just beneath the SCM clavicular head at a 10- to 15-degree angle below the coronal plane. The needle should enter the jugulosubclavian venous bulb after 1 to 4 cm, and the operator may then proceed with catheterization.

Success and Complication Rates. Subclavian vein catheterization is successful in 90 to 95 percent of cases, generally on the first attempt [96,142,171,172,175,176,178,181]. The presence of shock does not alter the success rate as significantly as it does during IJV catheterization [142,181]. Unsuccessful catheterizations are a result of venipuncture failure or inability to advance the guidewire or catheter [96,171]. Catheter tip malposition occurs in 5 to 20 percent of cases [96,171,179,181] and tends to be more frequent with the infraclavicular approach [96,130,171,182]. Malposition occurs most commonly to the ipsilateral IJV and contralateral SV and is usually correctable without repeat venipuncture.

The overall incidence of complications varies depending on the operator's experience and the circumstances under which the catheter is inserted. Large series involving several thousand SV catheters have reported an incidence of major complications of 1 to 3 percent, with an overall rate of 5 percent [167–171]. In smaller, probably more clinically relevant studies, the major complication rate has ranged from 1 to 10 percent [96,142,178,181,183,184,185]. Factors resulting in a higher complication rate are operator inexperience, multiple attempts at venipuncture, emergency conditions, and variance from standardized technique. Major complications include pneumothorax, arterial puncture, thromboembolism, and catheter-related infection. There are many case reports of isolated major complications involving neck structures or the brachial plexus; the reader is referred elsewhere for a complete listing of reported complications [99,167,186]. Infectious complications are reviewed later in this chapter; pneumothorax, arterial puncture, and thromboembolism are discussed in more detail below.

Pneumothorax accounts for one-fourth to one-half of reported complications, with an incidence of 1 to 5 percent [142,171,172,175,176,178,181,183,187–191]. The incidence varies inversely with the operator's experience and the number of "breaks" in technique [112,179,180,181,184,185]. There is no magic figure whereby an operator matures from inexperienced to experienced. Fifty catheterizations is cited frequently as a cutoff number, but it is reasonable to expect an operator to be satisfactorily experienced after having performed fewer [164]. For the experienced operator, a pneumothorax incidence < 0.5 percent is expected [7,142,167,171,176,178]. Most pneumothoraces are a result of lung puncture at the time of the procedure, but late-appearing pneumothoraces have been reported, and it is good practice to obtain a chest radiograph the day after the procedure.

One-fourth to one-half of pneumothoraces may be managed conservatively, without thoracostomy tube drainage [171, 181,183]. Rarely, a pneumothorax is complicated by tension [181,188], heme [175,192], infusion of intravenous fluid (immediately or days or weeks after catheter placement) [193–195], chyle, and massive subcutaneous emphysema [187]. Bilateral pneumothoraces can occur from unilateral attempts at venipuncture [196]. Pneumothorax can result in death, especially when it goes unrecognized [187,197,198].

Subclavian artery puncture occurs in 0.5 to 1.0 percent of cases, constituting one-fourth to one-third of all complications [96,142,171,175,176,185]. Arterial puncture is usually managed easily by applying pressure above and below the clavicle. Bleeding can be catastrophic in patients with coagulopathy. As with other routes, arterial puncture may result in arteriovenous fistula or pseudoaneurysm [199].

Clinical evidence of central venous thrombosis, including SVC syndrome, development of collaterals around the shoulder girdle, and pulmonary embolism, occurs in 0 to 3 percent of SV catheterizations [59,60,63,64,200], but routine phlebography performed at catheter removal reveals a much higher incidence of thrombotic phenomena. The importance of the discrepancy between clinical symptoms and radiologic findings is unknown, but it exists for all routes of CVC. Duration of catheterization, catheter material, and patient condition may have an impact on the frequency of thrombosis, but to an uncertain degree. Detection and treatment of catheter-associated thrombosis remains a controversial issue, discussed in detail elsewhere [38].

Infectious Complications

Infectious sequelae of central venous catheters include local phenomena, such as cellulitis, abscess formation, and suppurative thrombophlebitis, and systemic manifestations of bacteremia, septic shock, and metastatic infection. Catheter-related infection is a broad and complicated topic, and a review of the literature can be confusing. Many large series include peripheral intravenous catheters, peripheral arterial catheters, and central venous catheters of all types. Even in studies limited to central venous catheters, the duration of catheterization, site of veni-

puncture, condition of the patient, indication for placement, and medical decision-making about removal are uncontrolled or poorly recorded. Many frequently cited series are neither randomized nor prospective and include too small a patient sample to generate statistically significant results. The previous edition of this text identified several controversies surrounding infectious complications of central venous catheters. In the few years since publication of that text, human and animal research has provided considerable insight into many of these areas.This discussion will focus on much of these new data and how they impact on areas of particular interest to the critical care physician. Controversial topics that need clarification include the following: What type of site bandage is best? Do triple-lumen catheters have a higher rate of infection than conventional catheters? What is the role of new catheter technology? Are catheter changes over a guidewire an effective method of infection control? How long should catheters remain in place? Are there differences in infection rates among the different insertion sites? There are reasonably good answers to most of these questions, but controversy continues over others. Future prospective, randomized studies—utilizing standardized definitions of catheter-related infection—are needed to develop true consensus. The interested reader is referred to a recent excellent discussion of many of these topics [201].

Consensus regarding the definition and diagnosis of catheter-related infection is a necessary initial step in discussing catheter-related infectious complications [202,203]. The semiquantitative culture method described by Maki et al. [204] for culturing catheter segments is the most accepted technique for diagnosing catheter-related infection [205,206] and is one way to standardize results between institutions. Which catheter segment to culture routinely is controversial, and I do not believe available evidence strongly favors use of the intradermal segment over the catheter tip [201,202,205,206]; most centers routinely culture the catheter tip. Regardless of which segment is cultured, semiquantitative results are used to define catheter contamination as less than 15 colony-forming units (CFU) per culture plate. Catheter-related infection is defined as greater than 15 CFU and is identified as colonization (all other cultures negative); local or site infection (skin site with erythema, cellulitis, or purulence); catheter-related bacteremia (systemic blood cultures positive for identical organism on catheter segment and no other source); and catheter-related sepsis or septic shock.

PATHOPHYSIOLOGY OF CATHETER INFECTION. Catheters can become infected from four potential sources: the skin insertion site; the catheter hub(s); hematogenous seeding; and infusate contamination, which generally results in epidemic nosocomial bacteremia, a distinct entity reviewed elsewhere [207]. Animal and human studies have shown that catheters are most commonly infected from bacteria colonizing the skin site, followed by invasion of the intradermal catheter tract. Once the external surface of the catheter in the tract is infected, bacteria can quickly traverse the entire length and infect the catheter tip, usually encasing the catheter in a slime layer known as a biofilm. From the catheter tip, bacteria may shed into the bloodstream, potentially creating metastatic foci of infection [201,208,209,210]. The pathophysiology of most catheter infections explains why guidewire changes are not effective in preventing or treating catheter-related infection: the colonized tract and, in many cases, biofilm remain intact and quickly reinfect the new catheter [211,212,213].

The catheter hub(s) also becomes colonized but contributes to catheter-related infectious complications less frequently than the insertion site [201,214–217]. Likewise, hematogenous seeding of catheters from bacteremia is an infrequent cause of catheter-related infection.

SITE PREPARATION AND CATHETER MAINTENANCE. That the majority of catheter-related infections are caused by skin flora highlights the importance of site sterility during insertion and catheter maintenance. Organisms that colonize the insertion site originate from the patient's own skin flora or the hands of operators [210]. Iodine-containing disinfectants, such as 10% povidone-iodine, are the most commonly used skin disinfectants and provide a wide range of antibacterial activity. Proper application includes liberally scrubbing the site and allowing it to dry for 30 to 60 seconds before wiping with alcohol; defatting the skin with acetone is not necessary [210,218,219,220]. Excessive hair should be clipped with scissors prior to application of the antiseptic, as shaving can cause minor skin lacerations and disruption of the epidermal barrier to infection.

Iodine-containing solutions may not be the best antiseptic for site preparation. One recent study showed that when a 2% aqueous solution of chlorhexadine was used for site preparation and maintenance, the incidence of catheter-associated infection was reduced fourfold compared to povidone-iodine [221]. Chlorhexadine is a potent germicide, with a broad spectrum and longer duration of action. It is available in the United States primarily as a handwashing preparation. Further studies are needed before this agent can be recommended for site preparation and maintenance.

The hands of medical personnel are also a potential source of organisms for infecting intravascular devices [222,223]. Thorough handwashing and wearing sterile gloves are mandatory for persons involved in catheter insertion or care. Cap, masks, gowns, and a large drape (maximal sterile barriers) were shown to reduce the infection rate in one recent study [224]. If a break in sterile technique occurs during insertion, termination of the procedure and replacement of contaminated equipment is mandatory.

Care of the catheter after insertion is perhaps the single most important step in minimizing infection, and all medical personnel should follow standardized protocols [225,226]. The number of piggyback infusions and medical personnel handling tubing changes and manipulation of the catheter site should be minimized. Tubing changes every 48 to 72 hours are adequate; more frequent changes are unnecessary [227]. The use of transparent, semi-occlusive dressings is prevalent, but these may actually increase the risk of site colonization because of moisture trapping, and no dressing has been proved to be superior to gauze and tape [228,229,230]. Application of iodophor or polymicrobial ointment to the insertion site during dressing changes does not convincingly reduce the overall incidence of catheter infection, and certain polymicrobial ointments may increase the proportion of *Candida* infections [215,231].

FREQUENCY OF CATHETER-ASSOCIATED INFECTION. Observing the above recommendations for catheter insertion and maintenance will minimize but not eliminate catheter-associated infection. Colonization of the insertion site can begin within 24 hours and increases with duration of catheterization; 20 to 40 percent of catheters eventually become colonized [214, 232–236]. Catheter-associated bacteremia and sepsis occurs in 2 to 8 percent of catheters [145,146,158,225,232,234–245], although some recent studies incorporating newer catheter technologies have demonstrated rates of catheter-associated bacteremia of 2 percent or less (see below) [214,246]. Bacteremia

is a significant complication, extending hospitalization and resulting in metastatic infection and death in a significant percentage of patients [207,210,228,244]. Gram-positive organisms, especially *Staphylococcus* species, are the most common infecting agents, but gram-negative enteric organisms are not rare. *Candida* species are less important today than in the past but still cause considerable morbidity, particularly in diabetic patients with prolonged catheterization and on broad-spectrum antibiotics.

TYPE OF CATHETER. The data presented above are derived from large studies and are not necessarily applicable to any given catheter because of variations in definitions, types of catheters, site of insertion, duration of catheterization, types of fluid infused, and policies regarding routine guidewire changes, all of which have been implicated at some point as important factors in the incidence of catheter-associated infection. The duration of catheterization in combination with the type of catheter are major factors; the site of insertion and type of fluid infused have a minor, if any, role. Guidewire changes have an important role in evaluation of the febrile catheterized patient, but routine guidewire changes do not prevent infection or extend the acceptable duration of catheterization at any given site (see below). Under ideal conditions, all of these factors are less important. Long-term TPN catheters can be maintained for months with low rates of infection, and there is no cutoff time at which colonization and clinical infection accelerate. Today, when the need for long-term catheterization is anticipated, surgically implanted silicone elastomer (Silastic) catheters are used. These catheters have low infection rates and are never changed routinely [247]. Catheters inserted percutaneously in the critical care unit, however, are not subject to ideal conditions and have a finite life span. For practical purposes, triple-lumen catheters have replaced single-lumen catheters for many indications for central venous access. Since catheter hubs are a potential source of infection and triple-lumen catheters can require three times the number of tubing changes, it was widely believed that they would have a higher infection rate. Studies have presented conflicting results, but overall the data support the view that triple-lumen catheters have a slightly higher rate of infection [234,238,242–245,248,249]. If used efficiently, however, they provide greater intravascular access per device and can decrease the total number of catheter days and exposure to central venipuncture. A slight increase in infection rate per catheter is therefore justifiable from an overall risk-benefit analysis, if triple-lumen catheters are used only when multiple infusion ports are truly indicated [244].

DURATION OF CATHETERIZATION. How long to leave a triple-lumen catheter in place is controversial and recommendations are changing. Based on older data, many institutions routinely move them to a new site or change over a guidewire every 72 to 96 hours. I have never recommended guidewire exchanges as an effective infection control measure, and two recently completed prospective controlled trials support this view [211,212]. Changing triple-lumen catheters to a new site every 72 to 96 hours minimizes infection but also increases mechanical complications associated with insertion. The intensivist is thus faced with balancing the risk of infection with the risks associated with insertion at a new site. Not surprisingly, the literature is interpreted differently and practices vary between and even within institutions; flexibility in management protocols is necessary. My approach is to leave triple-lumen catheters in place an average of 6 to 7 days before changing to a new site, based on recent series and other data for daily risk of catheter colonization [211,236]. For selected patients, especially those at increased risk of complications from central venipuncture, I do not hesitate to leave triple-lumen catheters in place longer than a week.

The above recommendations do not necessarily apply to other special-use catheters, which can be exposed to different clinical situations and risk. Pulmonary artery catheters (PACs) should ideally be removed after 72 to 120 hours because of the increased risk of infection after this time. [234,239,250–255]. These catheters are at more risk for infection because patients are sicker, the introducer used for insertion is shorter, and catheter manipulations are frequent [256]. When PACs are removed to evaluate for infection, the introducer sheath must also be removed, as this, not the PAC, is in contact with the intradermal tract. Likewise, inserting a triple-lumen catheter through the introducer does not alter the risk of infection. Pulmonary artery catheter sheaths do not reduce the infection rate [257] but are clinically important because they allow frequent repositioning of the catheter if necessary. Catheters inserted for acute temporary hemodialysis historically have a risk of infection of approximately 3 percent per week [258,259]. Logically, patient factors influence the incidence of infection more than the type of catheter or site of insertion [21]. For acutely ill, hospitalized patients, these catheters should be managed similarly to other multiple-lumen catheters. For ambulatory outpatients, they can be left in place longer, akin to single-lumen catheters used for long-term parenteral nutrition.

New catheter technology (see below) is promising and may lead to changes in all of the above recommendations. For the present, every physician caring for the critically ill needs to be cognizant of existing data and infection rates in their own institution so that rational policies can be implemented.

SITE OF INSERTION. The condition of the site is more important than the location. Whenever possible, sites involved by infection, burns, or other dermatologic processes, or in close proximity to a heavily colonized area (e.g., tracheostomy) should not be used as primary access. The site of insertion is a relatively minor factor in infection rates, with the exception of antecubital fossa catheters. Catheters inserted through antecubital veins should be treated as peripheral catheters and removed at 72 hours, or a high incidence of phlebitis and infection results. [91,202,210,239]. Otherwise, there are relatively few and conflicting data demonstrating any difference between the EJV, IJV, FV, and SV. A few studies have reported a trend toward higher colonization rates with FV and IJV catheters and lower rates with SV catheters, but this has not convincingly translated into a higher incidence of clinical infection [236,240,241,254]. Once again, prospective, randomized studies are needed to clarify the issue.

GUIDEWIRE EXCHANGES. Guidewire exchanges have always been theoretically flawed as a form of infection control, because although a new catheter is placed, the site, specifically the intradermal tract, remains the same. Recent animal and human studies have shown that when the tract and old catheter are colonized, the new catheter invariably also becomes infected [213,260,261,262]. Alternatively, if the initial catheter is not colonized, there is no reason the new catheter will be more resistant to subsequent infection than the original one. In neither situation will a guidewire change prevent infection [211,212]. However, guidewire changes continue to have a valuable role for replacing defective catheters, exchanging one