The PiCCO Monitor

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Introduction

Hemodynamic optimization is a complex task requiring, among other things, monitoring of arterial and venous pressures, urine output, acid-base balance, and oxygen content/delivery. These parameters, however, reflect the overall circulatory state and not the basic physiologic determinants of cardiac output (CO), which include preload, afterload, and contractility. To help determining these basic physiologic determinants, the pulmonary artery catheter (PAC) has been used by clinicians for almost 4 decades where it became the mainstay of patient monitoring in the operating room and in the intensive care unit (ICU) setting. It provides direct information on pressure variables such as pulmonary artery pressure, pulmonary artery occlusion pressure, and central venous pressure. It can also provide flow-related data such as CO and mixed venous oxygen saturation. Despite its extensive use, the clinical value of data obtained from pulmonary artery catheters remains unproven.[1]

Therefore, an alternative approach to the PAC monitoring has been proposed—the functional hemodynamic monitoring. This approach focuses on the effects of positive pressure ventilation on left ventricular (LV) output; positive pressure ventilation induces phasic changes in LV stroke volume through similar cyclic changes in venous return. This is a "normal" phenomenon for all patients ventilated with positive pressure ventilation, and can be advantageous in situations of hypovolemia.

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These cyclic changes can be used to predict fluid responsiveness as it has been shown that hypovolemic patients—those who are on the ascending limb of the Frank-Starling curve—are very sensitive to these changes. To date, several functional parameters have been described and used clinically to assess fluid responsiveness. These parameters include the systolic pressure variation, the pulse pressure variation (PPV), and the stroke volume variation (SVV) and are utilized clinically by currently available invasive monitors. They are considered the standard of care in the assessment of fluid responsiveness.

The PiCCO monitor (Fig. 1) uses the dynamic parameters to predict fluid responsiveness. In addition, it has other hemodynamic indices that are very useful in understanding the individual patient physiological state:

1. Fluid responsiveness: PPV and SVV
2. CO measurement
   a. Transpulmonary thermodilution
   b. Pulse contour analysis
3. Extravascular lung water index (EVLWI): a good surrogate assessment of pulmonary edema
4. Global end-diastolic volume index (GEDI): a volumetric preload assessment
5. Cardiac function index: a calculated index of cardiac function

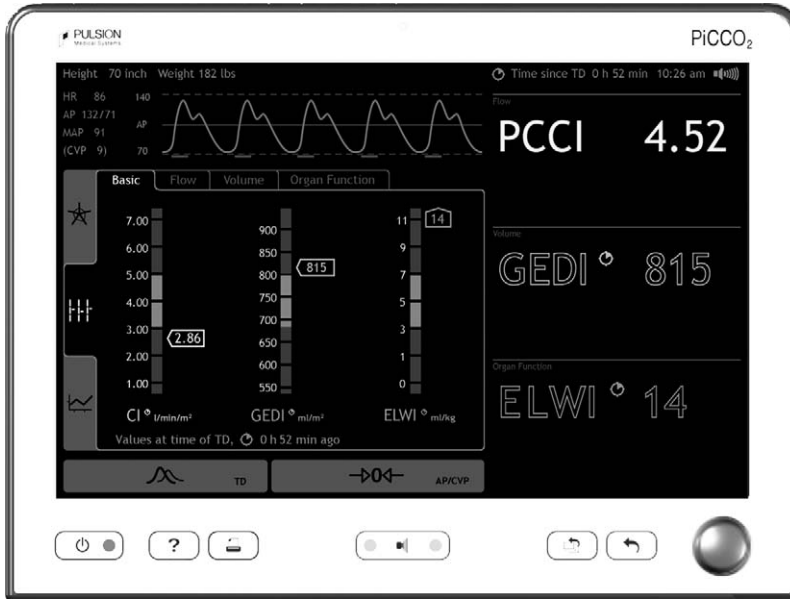


Figure 1. *The newly designed PiCCO$_2$ monitor is a user-friendly touch screen monitor.*

Thus, the PiCCO monitor is an "all inclusive" alternative to current hemodynamic monitors and is very important in the management of hemodynamically unstable patients in the operating room or ICU.

■ Fluid Responsiveness

In the assessment and management of critically ill patients, the actual hemodynamic monitoring questions are physiological in their language but need to be practical and concrete in their application. Perhaps the most frequent hemodynamic question when managing patients in the operating room or ICU is: Will CO increase with volume loading?

Data from numerous studies have documented repeatedly that neither right atrial pressure or pulmonary artery occlusion pressure predict well the subsequent response of the subject to an intravascular fluid challenge.[2–10] Furthermore, measures of absolute LV volumes are only slightly better at predicting preload responsiveness.[7,10–13] In contrast, the dynamic parameters have been shown to be very useful in discriminating between patients who respond to fluid therapy from those who do not.[5,14–16]

Physiological Rationale of the Dynamic Parameters

Positive pressure ventilation is associated with simultaneous but different effects on the left and right sides of the heart. A positive pressure breath results in increased intrathoracic pressure, which in turn leads to increased LV filling of blood due to compression of the pulmonary venous system. The end result is an acute increase in LV stroke volume. Simultaneously, however, the increased intrathoracic pressure causes a decrease in venous return to the right side of the heart due to compression of the inferior vena cava. During exhalation there is a decrease in stroke volume; the heart is relatively "empty"—the pulmonary veins have been "squeezed" during the positive pressure breath and the right ventricle is relatively "empty" due to decreased venous return as above. This is a "normal" physiology during positive pressure ventilation (Figs. 2, 3).

As the left ventricle is more sensitive to preload changes when it is on the ascending limb, or steep portion of the Frank-Starling curve, these variations have been used clinically to assess preload status and predict fluid responsiveness in deeply sedated patients under positive pressure ventilation. Among the dynamic parameters described above, the PiCCO monitor calculates and displays only the PPV and SVV.

PPV

The PPV extends the concept of cyclic variations in LV stroke volume during positive pressure ventilation (Fig. 4). The arterial pulse pressure—the difference between the systolic and the diastolic

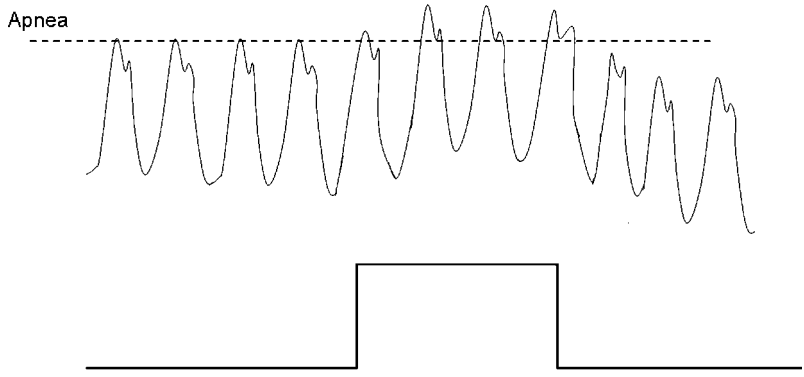


Figure 2. *Schematic diagram showing the increase in stroke volume and pulse pressure during a positive pressure breath.*

pressure—is directly proportional to stroke volume and inversely related to arterial compliance.[17] It is calculated as:

$$\mathrm{PPV} = (\mathrm{PP}_{\max} - \mathit{rmPP}_{\min})/\mathrm{mean} \times 100$$

An index of 13% discriminates between fluid responders (increase in CO >15% from baseline) from nonresponders (increase in CO <15% from baseline). In addition to patients following coronary artery bypass surgery,[18] PPV was found to predict the effect of volume

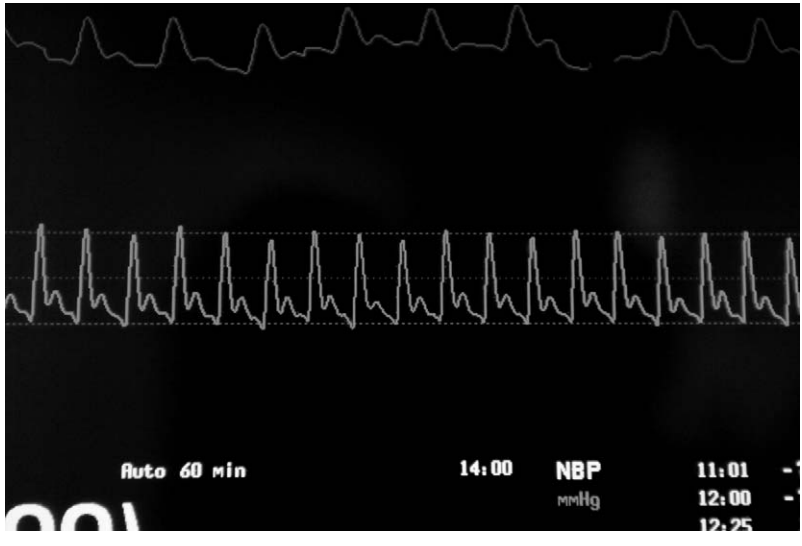


Figure 3. *A photo of an arterial waveform tracing depicting normal variation in stroke volume and blood pressure during positive pressure ventilation.*

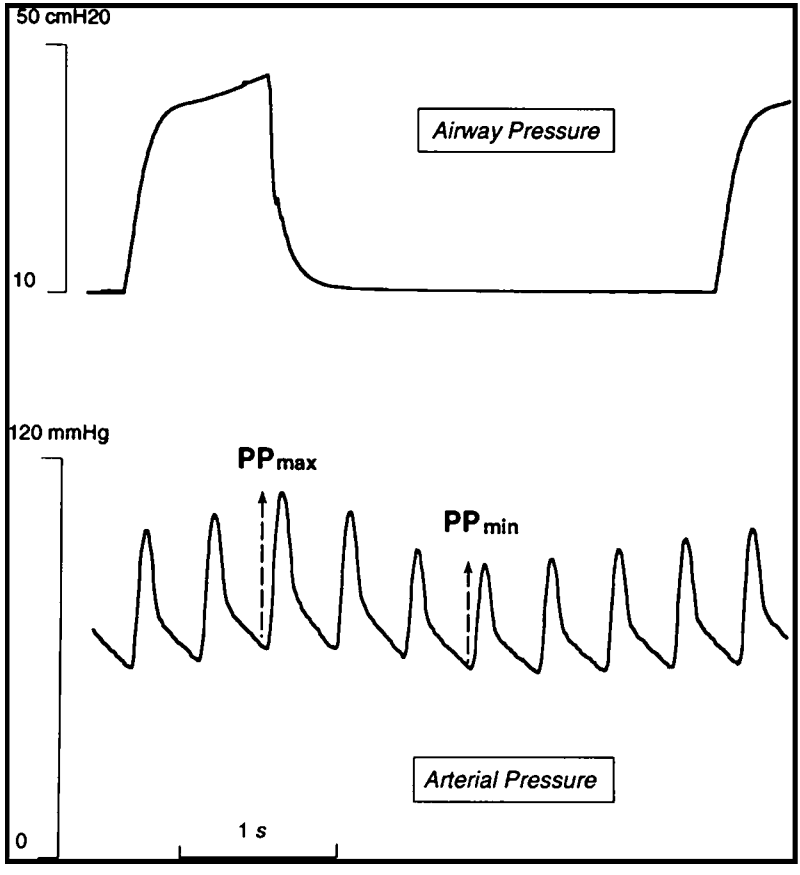


Figure 4. *Schematic diagram showing the variation in pulse pressure during one mechanical breath.*

expansion on CO also in septic shock hypotensive patient[5] and acute lung injury.[19]

SVV

SVV is determined by analysis of the continuous arterial pulse contour. This method uses the area under the systolic portion of the arterial pressure curve for beat-to-beat determination of stroke volume (in relative values) and their variation over the respiratory cycle. Its feasibility and appropriateness in estimating cardiac preload and volume responsiveness has been reported in several clinical trials (Fig. 5).[14,20–22]

Similarly to the PPV, it is calculated as:

$$\mathrm{SSV} = (\mathrm{SV}_{\max} - \mathrm{SV}_{\min})/\mathrm{mean\ times100}$$

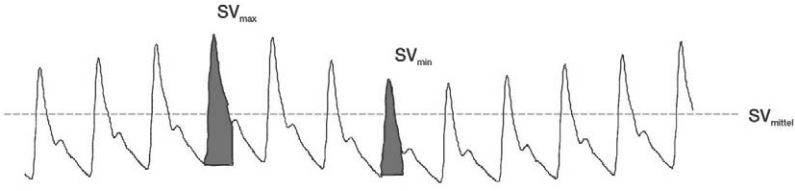


Figure 5. *Schematic diagram showing the variation in stroke volume during one mechanical breath.*

An SVV of 10% is considered as a cutoff discriminating between fluid responders and nonresponders; if SVV is less than 10% CO will not increase in response to volume loading and thus may be avoided as a therapeutic challenge. SVV is now accepted as an index of fluid responsiveness and was validated in ventilated postcardiac patients,[21,23,24] in the operating room during neurosurgery[20] and in septic shock patients.[14]

Limitations of the Dynamic Parameters

1. Need for positive pressure ventilation: The respiratory variation in stroke volume and arterial pressure has been validated as a predictor of fluid responsiveness only in mechanically ventilated patients. This limits the use of these parameters only to ventilated patients in the operating room and ICU.
2. Need for paralysis or heavy sedation: The dynamic parameters have been validated only in patients who are paralyzed or heavily sedated, provided there is no patient initiation of the ventilator. As such, they can be used to analyze fluid responsiveness only in these circumstances. In case where the patient is either initiating the ventilator or breathing spontaneously thorough an endotracheal tube, one cannot use the dynamic parameters to assess fluid responsiveness. This may limit the clinical usefulness of arterial pressure variation in the ICU where current practice guidelines recommend to lower the level of sedation.[25,26] As a result of these guidelines, many patients today are ventilated with minimal respiratory support and breathe spontaneously.
3. Cardiac rhythm: The beat-to-beat variation in stroke volume may no longer reflect the effects of mechanically ventilation in patients with arrhythmias. This is mostly true in patients with atrial fibrillation. Although significant cardiac ectopy will interfere with the continuous and automatic monitoring of dynamic parameters, it is still appropriate to analyze the arterial pressure curve in patients with few extrasystoles, provided that the rhythm is regular during at least one respiratory cycle.

4. Atherosclerosis: Systolic and pulse pressures depend not only on stroke volume, but also on arterial compliance.[17] Thus, PPV could vary from one patient to another according to the arterial compliance. Therefore, if arterial compliance is low (eg, patients with significant peripheral vascular disease), this can be translated to large changes in arterial pressure despite small changes in stroke volume. Conversely, if arterial compliance is high (eg, young patients without vascular disease), small changes in arterial pressure could be seen despite large changes in stroke volume.
5. Variation in pleural pressure: Changes in pleural pressure can affect the dynamic parameters by either falsely decreasing or increasing the variations.
   A. Small variations: During positive pressure ventilation, small variations in pleural pressure can be seen when small tidal volumes are used[27] (eg, 6 mL/kg) or when chest compliance is increased. Theoretically, if the pleural pressure generated during positive pressure ventilation is not high enough to affect venous return, this may affect the dynamic parameters and ability to discriminate between fluid responders and nonresponders. Indeed, SVV has been found to be a reliable predictor of fluid responsiveness only in patients with a tidal volume ranging between 8 and 15 mL/kg.[5,23,28,29] In this regard, caution should be exercised before concluding that a patient will not respond to a fluid challenge because no variation in blood pressure is observed if the tidal volume is low or increased chest compliance.
   B. Large variations: Conversely, large variations in pleural pressure can be seen when large tidal volumes are used or when chest compliance is low. It has been shown that increasing tidal volume[29,30] or reducing chest compliance[31,32] leads to increases in stroke volume and blood pressure variations. Similarly, decreasing chest compliance also affect stroke volume and blood pressure variation as recently shown that opening the chest by sternotomy decreased stroke volume and increased cardiac preload.[33] Thus, by inducing a rightward shift on the Frank-Starling curve, the decrease in chest compliance decreased the sensitivity of the heart to fluid challenge.
6. Technical
   A. Similar to any invasive pressure monitoring, the arterial pressure curve obtained from the fluid-filled catheter is subjected to technical problems (eg, kinks, air bubbles, clots, excessive tubing length, tube compliance), which could affect the dynamic response of the monitoring system.[34]
   B. The site of arterial pressure monitoring can also affect the observed pressures. The recognized fact of pulse amplification from aortic root to the peripheral circulation characterized by

increase in systolic pressure and slight decrease in diastolic pressure in healthy individual[35] is untrue in patients with sepsis[36] or postcardiopulmonary bypass.[37] In these patients, lower systolic pressures have been documented in peripheral arteries. To overcome this problem, the PiCCO catheter is placed in central artery; brachial, axillary, or femoral arteries.

In theory, any state which increase venocapacitance and decrease return of blood to the heart (eg, anesthetics and venodilators) may affect the dynamic parameters; decrease return of blood to the heart will lead to increase in the dynamic parameters which will lead to a state of fluid responsiveness. This is not an artifact, but rather a "true" state whereby a fluid bolus will result in increased CO. However, this does not mean that fluid bolus is needed. In general, after answering the question "will cardiac output increase with volume loading?" one has to decide if fluid therapy is needed. The fact that a patient is fluid responsive should not translate automatically to administration of fluids. Fluid therapy should be given only if the patient is fluid responsive and there is evidence of hypoperfusion (eg, low urine output, tachycardia, hypotension, increased lactate, etc.). As an example, all healthy individuals operate on the ascending limb of the Frank-Starling curve and are fluid responsive, yet do not require fluid bolus or therapy to maintain adequate perfusion.

■ CO

The PiCCO monitor measures CO by 2 ways: the transpulmonary themodilution method and the pulse contour analysis.

Transpulmonary Thermodilution

The indicator-dilution techniques for measurement of CO was introduced at the end of the 19th century by Stewart[38] who first used these techniques to measure the volume of blood in the heart and lungs. Stewart's model was developed and extended by Hamilton and his colleagues[39] who emphasized the use of mean circulation time to determine the volume of a vascular bed. The consequence of Stewart and Hamilton work was the establishment of the fundamental relationship of volume, flow, and circulation time.[40]

$$\text{Volume} = \text{flow} \times \text{mean circulation time}$$

The validity of this method of measurement of flow depends on the assumption that the dye is distributed throughout a "central" pool of blood as it passes from the vein into the right heart chambers, the lungs, and the left heart and out into the arterial system of vessels. The validity and accuracy of the method for determining rates of flow

in mechanical systems and the CO in animals and human participants have been later determined.[39,41]

A simple explanation of this elaborate work goes as follows: when an exogenous substance (an "indicator") is injected into the vascular space it is quickly diluted by flowing blood. Just how quickly or slowly this dilution takes place is a function of the magnitude of flow. If flow between these 2 points is high, then the concentration of the injected substance (eg, "cold") will be diluted quickly. At the downstream detection point, then, the concentration-time curve will change relatively little. Conversely, if flow is low, the concentration of the substance at the detection site will not be diluted as much and temperature change will build and fall less quickly.

With the PiCCO technology the indicator (15 to 20 mL of cold saline) is injected into the circulation at a central vein. The concentration of the thermodilution indicator is measured at some other point downstream from the injection site using a 4 or 5 Fr thermistor-tipped catheter. The catheter should be placed in a central artery—either the femoral, brachial, or axillary arteries (the PiCCO monitor cannot use a radial arterial line due to the inaccuracy of a peripheral arterial waveform as described later under *complications*). Any in situ central venous catheter can be used, including a femoral one. If the arterial catheter is in a femoral position and a femoral central catheter is planned—it should be placed in the contralateral side to prevent the "cross talk" phenomenon.[42] Thus, when measuring CO using the PiCCO monitor, a thermodilution bolus passes through the right side of the heart (right atrium and ventricle), the lungs, the left side of the heart (left atrium and ventricle), and the aorta and smaller artery, depend where the catheter is placed (eg, axillary, brachial, or femoral).

Comparison with the PAC thermodilution technique:

1. The temperature-time curves obtained during transpulmonary thermodilution measurements are broader and lower in magnitude than when obtained via a PAC (Fig. 6), which makes them more vulnerable to errors caused by baseline drift and miscorrections for indicator recirculation. In contrast, and for the same reason, the transpulmonary method is less vulnerable to errors caused by respiratory variation in blood temperature. The greater sensitivity to baseline drift can be minimized in part by using a larger injectate volume of ice-cold saline (the recommended volume is 15 to 20 mL rather than the 10 mL of room temperature saline often used for thermodilution measurements via a PAC.[43]
2. As with any thermodilution technique, intracardiac shunts and valvular insufficiencies may affect absolute CO values. In left to right shunts, recirculation of the indicator splays out the

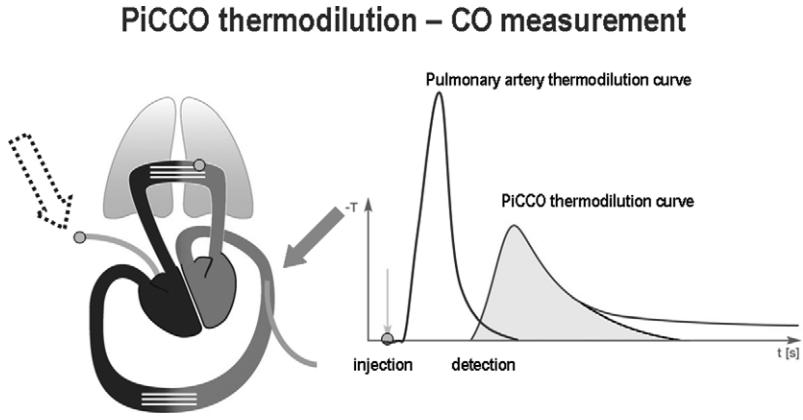


Figure 6. *Comparison between the transpulmonary thermodilution curve and the pulmonary artery catheter (PAC) thermodilution curve. The transpulmonary thermodilution curve is broader and lower in magnitude than when obtained via a PAC, but the area under the curve is similar. Dashed arrow indicates central venous injection point of cold injectate. Full arrow indicates detection point downstream in a large artery.*

thermodilution curve and CO is underestimated. Conversely, right to left shunts result in overestimation due to premature delivery of the indicator. The direction and magnitude of the error introduced by valvular regurgitation is more difficult to predict, and will depend on several factors including the site and severity of the regurgitation and the actual CO. These conditions may less likely to affect the temperature time curve as detected by the transpulmonary measurements of CO.[43] However, caution should be taken in interpreting the transpulmonary CO measurement of patients with significant tricuspid regurgitation (moderate to severe), as it may still lead to inaccurate measurement. In such circumstances, a reasonable alternative approach would be to measure the actual CO "going forward" by the pulse contour analysis (see below), or by echocardiography.

3. The assumption (in the Stewart-Hamilton model) that there is no unaccounted loss of thermal indicator is more likely to be an error during transpulmonary measurements of CO in the presence of extrapulmonary "sinks" for the thermal indicator (such as pericardial or pleural effusions).[44]

These differences between PAC and transpulmonary thermodilution CO measurements do not seem to have clinical significance; a high degree of correlation between the 2 thermodilution CO technique has been established in multiple experimental and clinical settings including cardiac surgery patients, intensive care patients, septic patients, and burn victims.[45–48]

Pulse Contour Analysis

The theory behind using the arterial pulse waveform to measure CO dates back to 1899 where Otto Frank developed a model describing the loads faced by the heart when pumping against the pulmonary or systemic circulation and the relationship between the arterial blood pressure and flow in the systemic and pulmonary arteries (Windkessel model). It was Frank's goal to be able to calculate CO from arterial pulse pressure.[49]

In 1904, Erlanger and Hooker hypothesized that CO was proportional to arterial pulse pressure. It was only in the last several years, however, that the technology to accurately measure CO with the arterial waveform has become available. The limiting factor in this process was the realization that some other method was needed to calibrate the system to accurately measure CO using the pulse waveform. In addition, the compliance of the arterial tree was a major obstacle to the accurate measurement of CO because it was determined that the compliance of the arterial tree is nonlinear; when a volume of blood is introduced into the vasculature at higher pressures, the compliance decreases more rapidly than when the same volume of blood is introduced at a lower pressure.[49]

The principle of pulse contour analysis is based on the physiological relationship between stroke volume and the area under the systolic portion of the aortic pressure waveform on a beat-to-beat basis.[50]

Pulse Contour Algorithm

The basic algorithm for the determination of CO from pulse-contour was developed by Wesseling and co-workers in 1974.[51–53] According to this algorithm, LV stroke volume is computed by dividing the measured area under the systolic portion of the arterial pressure waveform by the aortic impedance. A subsequent multiplication by the heart rate yields pulse-contour CO. To adjust for aortic impedance, which differs from patient to patient, the PiCCO monitor uses the thermodilution measurement of CO for the calibration of the system.[54] The calculation is as follows: $CO = \text{heartrate} \times Asys/Zao$

where $Zao = SVpc/SVtd$

Asys, area under systolic pressure waveform; Zao, aortic impedance; SVpc, uncalibrated stroke volume based on pulse-contour; and SVtd, stroke volume by thermodilution.

PiCCO's new pulse-contour algorithm is a more sophisticated formula that analyzes the actual shape of the pressure waveform in addition to the area under the systolic portion of the pressure wave.[54] In addition, the software takes into account the individual aortic compliance and systemic vascular resistance. An explanation to these considerations is that during the systole phase of a heartbeat, blood is ejected

into the aorta. Simultaneously, blood flows out of the aorta into the peripheral vascular system. However, during the ejection phase the sum of all blood flowing into the aorta is larger than the blood volume entering the peripheral vascular system. Thus, the volume of the aorta increases. In the subsequent diastole, most of the remaining blood will empty into the peripheral vasculature and coronaries. This behavior is dependent on the ability of the aorta to expand and contract in response to ejected volumes (Fig. 7). The volume change and subsequent pressure change is described as the compliance function of the aorta. The relationship between blood flow out of the aorta and pressure measured at the end of the aorta (femoral artery or other large artery) is determined by the compliance function. The compliance function can therefore be characterized by measuring blood pressure and blood flow (CO) simultaneously. Transpulmonary thermodilution CO determined simultaneously with continuous arterial pressure measurement is utilized to calibrate the pulse contour analysis to each individual patient's aortic compliance function (Fig. 8). For the continuous calculation of pulse contour CO the a calibration factor (cal) determined by thermodilution CO measurement and the heart rate, as well as the integrated values for the area under the systolic part of the pressure curve [$P(t)$/SVR], the aortic compliance [$C(p)$] and the shape of the pressure curve represented by change of pressure over change of time (dP/dt) (Fig. 8).

This method of CO measurement has been studied extensively and validated in a variety of patient populations.[45,46,54–57] Although there is a bias between the measurements of the pulmonary thermodilution technique and pulse contour analysis of -0.71 L/min[58] to 0.22 L/m/m^2,[59] bias and precision are clinically acceptable. Concerns that the use of pulse-contour analysis for continuous CO monitoring during profound changes in hemodynamic status might become unreliable were raised by some investigators.[60,61] Interestingly, several other authors have been unable to confirm this problem.[45,59,62,63] In addition, it has been shown recently that the PiCCO pulse-contour new algorithm is reliable and accurate during hemodynamic instability[54] and is currently accepted as a continuous CO measurement.[64,65]

■ EVLW

Pulmonary edema is a common finding in many critically ill patients. The pathophysiological mechanism leading to pulmonary edema is accumulation of fluid in the interstitial and alveolar space in the lungs, a phenomenon termed extravascular lung water. EVLW is a marker for the severity of lung injury, the knowledge of which may improve the outcome in some critically ill patients by guiding volume of fluid therapy.[66,67] The ability to measure EVLW at the bedside to allow for direction in fluid management is of immense significance. The

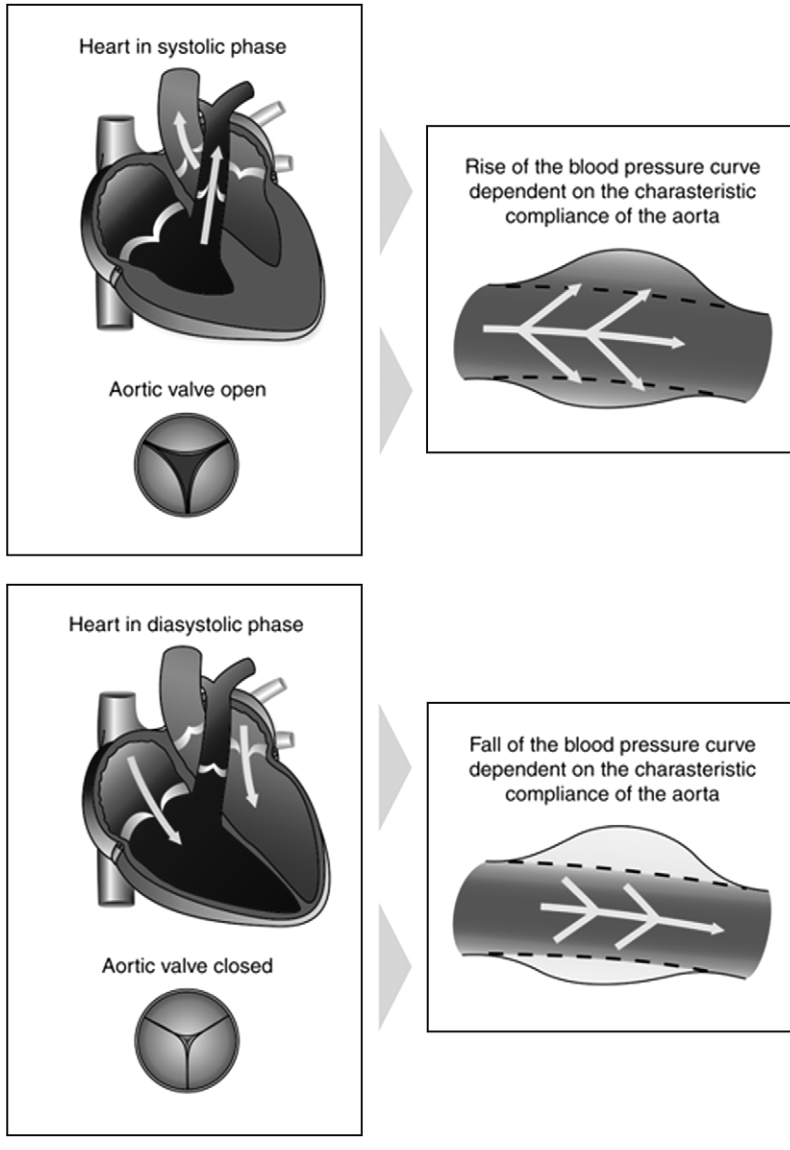
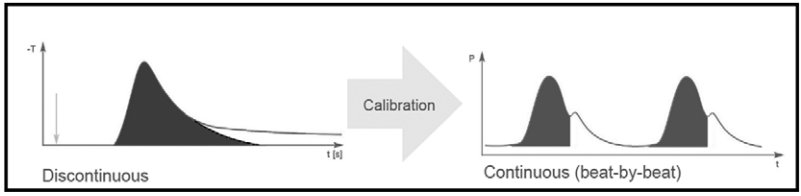


Figure 7. *Characteristic compliance during heart phases. Upper part—heart in systolic phase. Lower part—heart in diastolic phase.*

measurement of EVLW using intravascular indicator-dilution techniques was proposed by Chinard in 1954.[68] Radioactively labeled indicators were used—iodinated albumin for the intravascular space, and tritiated water for the total intravascular and extravascular water space. Several descriptions of EVLW measurement using these indicators were reported during the subsequent 15 years, but results were disappointing.[69]



$$PCCO = cal \times HR \times \int_{Systole} \left(\frac{P(t)}{SVR} + C(p) \times \frac{dP}{dt} \right) dt$$

Patient-specific calibration factor (determined with thermodilution)

Heat rate

Area of pressure curve

Aortic compliance

Shape of pressure curve

Figure 8. *Top, A diagram showing the themodilution cardiac output measurement as a reference for the continuous pulse contour cardiac output measurement. Bottom, The PiCCO monitor pulse contour cardiac output analysis algorithm, which incorporates the aortic compliance, the area under the systolic portion of the arterial waveform, a patient-specific calibration factor based on the thermodilution measurement of cardiac output, and the shape of the pressure curve.*

The Double Dye Technique

Gee and Stage[70] were the first to report use of a thermal indicator with indocyanine green dye as an intravascular volume indicator. In anesthetized dogs, they injected the indicators into the pulmonary artery, sampled in the aorta, and utilized transform functions to correct mean transit times for the response times of the measuring systems. In an unspecified number of dogs, they found that mean EVLW was 6.2 mL/kg body weight, which represented 87% of the gravimetrically measured EVLW.[69] These initial studies were followed by numerous others, validated against the reference gravimetric method, even in humans[71–73] and yields EVLW measurements with a good reproducibility.[74] EVLW estimated by transpulmonary thermodilution has been shown to correlate quite closely with EVLW assessed by the double-indicator dilution technique.[75,76] In animals, this method works also quite well compared with the reference gravimetric method but with a systematic bias due to different and species-dependent relationships between GEDV and intrathoracic blood volume (ITBV).[77–81]

Transpulmonary Thermal Technique

The first use of a thermal indicator to detect water content of the lungs, and the first indication that it would fully detect the actual water content was reported by Pearce and Beazell.[82] They injected a thermal

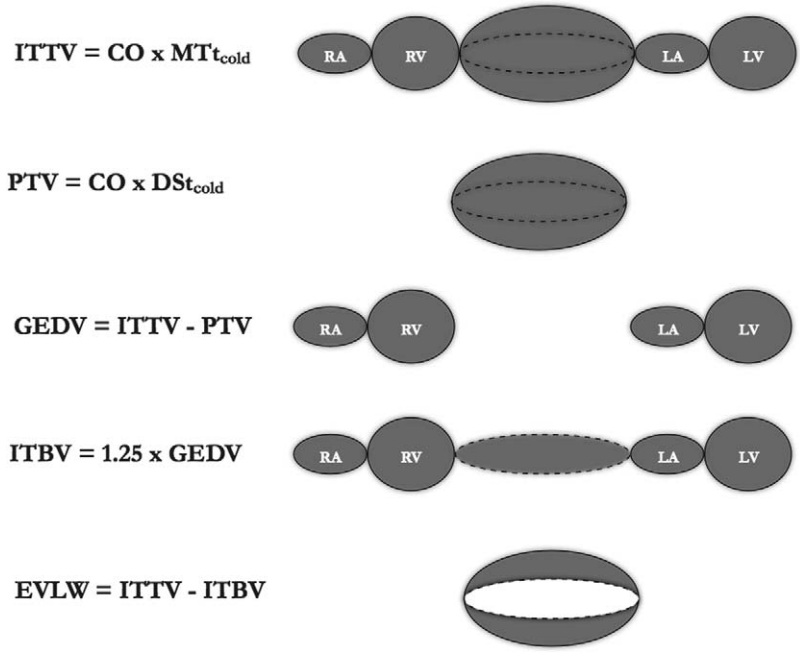


Figure 9. *A diagram showing the volume in the chest and the derivation of the extravascular lung water. CO indicates cardiac output; DSt_{cold}, down-slope time of cold injectate; EVLW, extravascular lung water; GEDV, global end-diastolic volume; ITBV, intrathoracic blood volume; ITTV, intrathoracic thermal volume; MTt_{cold}, mean transit time of cold injectate; PTV, pulmonary thermal volume.*

bolus into the right atrium in 7 dogs, and detected it with a thermistor advanced into the distal airways. Extravascular thermal volume measured by this thermal technique averaged 8.3 mL/kg body weight. The dilution methods are based on mathematical concepts and models described in the 1950s,[83,84] allowing the calculation of the volume of distribution of an indicator injected into the circulation. On the basis of these mathematical and experimental models, if an indicator is injected into a system composed of several mixing chambers organized in series and detected at the exit of the system (dilution curve), the product of the flow passing through the system by the mean transit time of the indicator gives the total volume of distribution between the site of injection and the site of detection.[38,84,85] This can also be seen mathematically from the Stewart-Hamilton principle described above, whereas the relationship between volume, flow and mean transit time is described as:

$$\text{Volume} = \text{Flow} \times \text{mean circulation time}$$

As water is a very good thermal conductor, with the thermal indicator technique the volume of distribution will include not only the intravascular but also the EVLW space (without any distinction between interstitial and alveolar water). From the measurement of volume of distribution of the thermal indicator, the EVLW—a surrogate marker for pulmonary edema can be calculated using the formula as follows (Fig. 9):

Intrathoracic Thermal Volume

The intrathoracic thermal volume (ITTV) is the volume of distribution of the thermal indicator, which includes the volume of the heart (4 chambers) and lungs (intravascular volume, as well as interstitial and alveolar volumes). It is calculated as:

$$\text{ITTV} = \text{CO} \times \text{MT}t_{\text{cold}}$$

whereas CO, cardiac output and $\text{MT}t_{\text{cold}}$, mean transit time of cold indicator.

Pulmonary Thermal Volume

Pulmonary thermal volume (PTV) is based on the work done by Newman et al in the 1950s.[84] In a mathematical experimental model using bottles with different volumes arranged in series, Newman showed that the down-slope shape of the dilutional thermal curve is very important; the exponential down-slope time relates to the largest chamber in a system. If using the thermodilution curve—the down-slope time relates to the lungs, as the lungs represent the largest chamber in the heart-lung volume system. The PTV includes the intravascular, as well as the interstitium and alveoli volumes of the lungs. It is calculated as:

$$\text{PTV} = \text{CO} \times \text{DSt}_{\text{cold}}$$

whereas CO, cardiac output and $\text{DS}t_{\text{cold}}$, down-slope time of cold indicator.

GEDV

This is a volumetric preload index which includes the volume in the 4 chambers of the heart. It is calculated by subtracting the PTV from the ITTV. Although not as good as the dynamic indices for predicting fluid responsiveness, it may help in specific situations such as when a patient with normal sinus rhythm converts to atrial fibrillation and with this loosing the ability to follow the dynamic parameters.

ITBV

The ITBV is the volume within the thoracic vasculature. It includes blood in the 4 chambers of the heart and within the pulmonary vasculature. This volume is closely related to GEDV as showed by Sakka et al,[75] and is calculated as:

$$\text{ITBV} = 1.25 \times \text{GEDV}$$

EVLW

The EVLW is the volume within the interstitium and the alveoli and is a very good clinical surrogate marker of pulmonary edema. It is calculated by subtracting the ITBV from the ITTV:

$$\text{EVLW} = \text{ITTV} - \text{ITBV}.$$

Limitation of the Dilution Method

Like any other modality, this technique has limitations and familiarization with these limitations is important if one is to minimize misinterpretation and maximize patient benefit from data measured.

Vascular Obstruction The thermal indicator cannot equilibrate within the extravascular water space if it is not delivered sufficiently close to reach that space by conduction. Therefore, vascular obstruction may cause errors in EVLW measurement.[86,87] This explains the observation during experimental obstruction of large pulmonary arteries of a significant underestimation of EVLW.[88] Despite this concern of major pulmonary vessel obstruction (mostly due to pulmonary emboli), in clinical practice clinicians are more concerned about pulmonary vasculature micro-obstruction that may occur in patients with acute respiratory distress syndrome (ARDS) [either due to microthrombi or application of high levels of positive end expiratory pressure (PEEP)]. Underestimation of EVLW has been observed in experimental models when vessels $\geq 500\,\mu m$ in size are obstructed.[87] This is not necessarily the case when smaller vessels are embolized,[89] which may be explained by the high conduction speed of water for temperature, which is much greater than the diffusion speed of small molecules,[71] allowing thermal equilibration within embolized or underperfused regions from adjacent well-perfused vessels.[90]

Effect of PEEP The effect of PEEP on EVLW measurement is still controversial since the use of high levels of PEEP could potentially lead to pulmonary vascular defect. This may explain the observation by some experimental studies a decrease in EVLW measured by dilution techniques during PEEP application.[91] In contrast, PEEP may induce a redistribution

of pulmonary blood flow toward previously excluded areas and hence artificially "increase" EVLW by recruiting the lungs.[87,92] It is important to appreciate that in addition to potentially affecting measurement of EVLW by dilution method, PEEP may also have an effect on the real amount of EVLW; in case of elevated pulmonary capillary pressure due to LV dysfunction, the application of PEEP may decrease EVLW by decreasing pulmonary capillary pressure.[93,94] In contrast, PEEP may increase EVLW by increasing central venous pressure leading to reduced lymph flow from the lungs (and thus lymphatic congestion), and by increasing lung volume leading to vascular congestion and edema.[95] In summary, one must keep in mind that PEEP may affect both the amount and the measurement of EVLW by dilution methods. Finally, a recent study showed that despite these concerns, compared with quantitative computed tomography scan (a technique not affected by perfusion defects), dilution methods are very accurate in assessment of EVLW in patients with ARDS ventilated with high levels of PEEP (10 to 20 cm H_2O).[96]

Focal Lung Injury In case of focal or regional pulmonary injury, there is a theoretical concern that the redistribution of blood flow away from injured areas may lead to an underestimation of EVLW, as been described in models of unilateral smoke inhalation[97] or during HCl instillation.[98–100] These experimental models are known to induce heterogeneous lung injuries. In human beings, new data may suggest that the redistribution of regional blood flow may not be as of a problem as in animal models. The redistribution of pulmonary blood flow during cardiogenic pulmonary edema or acute lung injury has been recently studied. Using positron emission tomography scan to assess both pulmonary perfusion and EVLW, it was well demonstrated[101] that hypoxic pulmonary vasoconstriction is severely blunted in this clinical context, such that there is no appreciable perfusion redistribution away from regions with edema. Therefore, in human beings with pulmonary edema, it is unlikely that the accuracy of dilution techniques may be affected by a redistribution phenomenon of pulmonary blood flow, as corroborated by these recent findings.[96]

Lung Resection Lung resection affects the accuracy of transpulmonary thermodilution. The estimation of EVLW by thermodilution is based on the equation ITBV = 1.25 × GEDV. This indicates a ratio between GEDV and ITBV is consistently equals to 4:5. The difference between ITBV and GEDV is the pulmonary blood volume and thus, any decrease in pulmonary blood volume (eg, due to lung resection) may affect the GEDV/ITBV ratio and hence the estimation of EVLW. As an example, after pneumonectomy, the 50% reduction in pulmonary blood volume is not taken into account by the equation above. This leads to overestimation of the ITBV by approximately 10%. As EVLW is

calculated as the difference between ITTV and ITBV (which is overestimated), transpulmonary thermodilution underestimates EVLW after lung resection.

Clinical Utilization of EVLW Measurements

Prognostic Value Eisenberg et al[67] were the first to establish a link between the level of EVLW and mortality. More recently Sakka et al[102] retrospectively analyzed 373 critically ill patients in whom EVLW was assessed by the double-indicator dilution technique. In their study, nonsurvivors had significantly higher EVLW values than survivors, the mortality rate being approximately 65% in patients with EVLW >15 mL/kg and 33% in patients with EVLW<10 mL/kg. On ICU admission, EVLW as a single variable was found to be as accurate as the multivariable Acute Physiology and Chronic Health Evaluation II score for outcome prediction. EVLW may be useful to predict short-term outcomes in a given patient such as the clinical behavior during mechanical ventilation. In addition, EVLV may guide invasive ventilation management as shown by Zeravik et al.[103,104] In their studies they showed that high-frequency ventilation is much more efficient in patients with an elevated EVLW (>15 mL/kg), whereas in contrast, pressure support ventilation is better tolerated in patients with subnormal or normal EVLW (<11 mL/kg). In theory, estimating EVLW may also be useful to predict weaning failure from mechanical ventilation or to diagnose LV dysfunction after transfer from mechanical ventilation to spontaneous breathing, although this is only a theoretical advantage, which has not been studied yet.

Diagnostic Value

1. Pulmonary edema: The diagnostic accuracy of auscultation and radiography is poor, particularly in mechanically ventilated patients. Auscultation—the first bedside step in clinical evaluation—can be significantly altered by intrathoracic transmission of sounds originated from the mechanical ventilator. The accuracy of auscultation in the diagnosis of alveolar-interstitial processes is only 55%.[105] Bedside chest radiograph quality is significantly reduced due to various technical limitations (chest wall movement, supine position, anterior-posterior approach, etc.), and its accuracy in diagnosing alveolar-interstitial processes is slightly higher than auscultation—only 72%.[105] In this regard, several studies have underlined the little value of chest radiograph in detecting a small increase in EVLW and the overall poor correlation between chest radiograph scores of pulmonary edema and the real amount of EVLW.[67,106] In contrast, dilution methods can identify small increases in EVLW[107] and

therefore are useful in discriminating between pulmonary edema and atelectasis.[108,109]

2. ARDS: It has been shown that a significant number (one-fourth to one-third) of patients with acute lung injury or ARDS criteria have no significant pulmonary edema.[110–112] This is because the chest radiograph can be misleading, and the criterion used in the current American-European criterion definition of ARDS showed high inter-observer variability.[113] In addition, arterial hypoxemia can be due to other disease processes than pulmonary edema. Therefore, EVLW measurement could be helpful to better characterize patients with ARDS and identify those who may benefit from fluid restriction.[114,115]
3. Differentiating between high and low pressure pulmonary edema: The ratio between EVLW and ITBV (EVLW/ITBV) may be helpful to identify the mechanism responsible for pulmonary edema. In an experimental model of pulmonary edema, the ratio of EVLW to ITBV was found to be significantly greater in case of permeability (oleic acid infusion) than in case of hydrostatic (atrial balloon inflation) pulmonary edema.[78] A recent study suggests that this ratio may be useful to discriminate between patients with cardiogenic and patients with permeability pulmonary edema, the diagnostic being established on clinical and biological criteria.[116]

Therapeutic Value

Fluid Therapy Guidance Fluid management of patients with acute lung injury or ARDS is a topic of ongoing controversy.[117,118] Fluid restriction—or "drying" of the lungs—may improve arterial oxygenation and lung mechanics and accelerate weaning from mechanical ventilation. However, the concern is that such a fluid-restrictive approach may worsen or induce hemodynamic instability and may even lead to organ failure.[117] The literature, however, does not support this concern; Mitchell et al[66] showed that a fluid restriction/depletion therapy based on the measurement of EVLW is able to decrease the duration of mechanical ventilation and the length of stay in the ICU compared with a strategy based on occlusion pressure measurement. A second study by Eisenberg et al[67] even found a benefit in terms of mortality in using such an EVLW-based fluid-restrictive approach in a small subgroup ($n = 15$) of patients with acute lung injury (defined by the association of EVLW >7 mL/kg and occlusion pressure <18 mm Hg). Despite the positive findings of these studies, one need to recognize that they were done more than 17 years ago. Improvement in other aspects of critical care medicine, they may not apply to current practices. A current ongoing prospective, randomized multicenter fluid restriction trial based on EVLW is expected to finish in 2010 (personal

communication—Dr Charlie Phillips, Oregon Health Sciences University) and it would be interesting to observe if the positive findings of the quoted 2 studies could be replicated in current critical care practices. Finally, a subset of the ARDS-net trail—a large multicenter randomized trial—showed that the so-called "conservative" strategy (fluid restriction/depletion strategy) in patients with acute lung injury improves lung function and shortens the duration of mechanical ventilation.[119] This finding emphasizes the potential usefulness of EVLW measurement to titrate the "conservative" treatment on an individual basis.

Complications

The PiCCO monitor requires a central venous catheter and an arterial catheter placed in a "large" artery (brachial, axillary, or femoral arteries). A radial arterial line cannot be used due to site variability waveform distortion.

Site-variable Waveform Distortion Distinction should be made between central and peripheral arterial pressure; whereas central pressure represents blood pressure in proximity of the heart, peripheral pressure represents blood pressure obtained in smaller, distal arteries. The relationship between central and peripheral arterial pressure can be altered by vasoactive agents, anesthetics, core temperature, and cardiopulmonary bypass.

1. Radial artery: The radial waveform is subject to inaccuracy inherent to the distal location. Radial catheters may produce an attenuated waveform with an exaggerated pulse pressure in states of hypovolemia and vasoconstriction.[120] Urzua et al[121] prospectively studied the effects of thermoregulatory vasoconstriction and concluded that the combination of more forceful cardiac ejection, stiffer arteries, and locally increased arteriolar resistance produced marked radial waveform distortion, artificially increasing peak systolic pressure. Finally, Dorman et al[36] studied the adequacy of radial pressure monitoring by using a prospective observational study during high-dose vasopressor administration and concluded that radial pressure underestimated central pressure and resulted in excessive vassopressor administration.
2. Axillary artery: Axillary artery cannulation reflects central pressure and provides more reliable waveform morphology than of peripheral catheters; it more accurately reflects systolic blood pressure, and proximity to the aortic arch affords accurate pressure and waveform, even during profound vasoconstriction. It may be used during extended monitoring, owing to a large intraluminal bore. Van Beck et al[122] concluded that the axillary artery was the most distal site in upper extremity at which arterial pressure consistently and accurately estimated central aortic pressure postcardiopulmonary bypass.

3. Femoral artery: Femoral cannulation affords access to central pressure, a morphologically reliable waveform, and an accurate reflection of systolic blood pressure. It provides accurate estimation of central pressure in hypovolemic, vasoconstricted, and central shunting states, with waveform changes less than those observed in radial artery during vasoconstriction.[121] Femoral systolic pressure exceeding radial systolic pressure by more than 50 mm Hg has been described.[36] Similar to axillary cannulation, the large intravascular lumen of the femoral artery allows for extended monitoring.[123]

This restriction raises concern among many clinicians. Although the placement of a radial arterial catheter is perceived as safest, this notion is not supported in the available literature published to date.

Radial Artery The radial artery is the most common site for arterial cannulation for hemodynamic monitoring.[36,124,125] In a clinical review of complications and risk factors of peripheral arterial cannulation, Scheer et al[124] found that the most common complication from radial arterial cannulation was temporary occlusion of the artery, the incidence of which ranged from 1.5%[126] to 35%.[127] Although temporary occlusion of the artery has no serious sequela, permanent occlusion can lead to devastating outcome. Thankfully, this seems to be rare with mean incidence of 0.09%.[124] This review included 19,617 arterial cannulations.

Another serious complication described in this review was pseudoaneurysm, with a reported mean incidence of 0.09%. Pseudoaneurysm poses a risk for infection, sepsis, rupture,[128–130] and formation of an extracorporeal pseudoaneurysm.[131] Radial catheterization was associated with sepsis with mean incidence of 0.13%, whereas local infection at the cannulation site was reported with mean incidence of 0.72%. Other complications include abscess, cellulitis, paralysis of the median nerve, suppurative thromboarteritis, air embolism, compartment syndrome, and carpal tunnel syndrome.[124]

Femoral Artery The review included 3899 femoral cannulations. Temporary occlusion of the femoral artery was reported with a mean incidence of 1.45%, and serious ischemic complications requiring extremity amputation was reported with a mean incidence of 0.18%.[132] Pseudoaneurysm formation occurred with mean incidence of 0.3%, sepsis was observed with a mean incidence of 0.44% and local infection was reported with a mean incidence of 0.78%. Bleeding (generally minor) was observed with a mean incidence of 1.58%, and hematoma formation was observed with a mean incidence of 6.1%.[124]

Axillary Artery In this review, the axillary artery was cannulated in a total of 1989 reported cases. Serious complications included permanent ischemic damage with a mean incidence of 0.20%, pseudoaneurysm

formation with a mean incidence of 0.1%, and sepsis with a mean incidence of 0.51%. Paresthesia of the hand due to pressure on the brachial nerve plexus was also described.[124]

This systematic review concluded that "Incidence rates for major complications such as permanent ischemic damage, sepsis and pseudoaneurysm formation are low and similar for the radial, femoral, and axillary arteries. They occur in fewer than 1% of cases."[124]

These data suggest that radial artery cannulation is not safer than axillary or femoral cannulation. Although the most commonly used cannulation site, the radial artery should probably be used for shorter period of time and in a state of relative hemodynamic stability. However, when patients become hemodynamically unstable and for a longer period (eg, a septic shock patient in the ICU), cannulation of the axillary or femoral arteries may be beneficial. These arteries better reflect central blood pressure, may decrease the amount of vasopressors administered, and the catheter may last longer in comparison with radial cannulation.

■ Conclusions

The PiCCO monitor is an "all inclusive" hemodynamic monitor. It allows for assessment of fluid responsiveness using the well-established dynamic parameters. The PPV and SVV are measured and presented on the monitor and provides the clinician a continuous assessment of fluid status.

CO is measured by 2 techniques; the transpulmonary thermodilution allows for intermittent CO measurement, and the pulse contour analysis technique allows continuous CO measurement, using the transpulmonary thermodilution measurement to calibrate the pulse contour method for better accuracy.

Finally, the transpulmonary thermodilution curve is used to calculate volumes in the thoracic cavity, the EVLW being one of the most important ones. Management algorithm based on the EVLW—a surrogate marker for pulmonary edema—may help clinicians in the management of fluid status and may help improve outcome.

■ References

1. Sandham JDHR, Brant RF. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348:5–14.
2. Osman DRC, Ray P. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med*. 2007;35:64–68.
3. Lichtwarck-Aschoff MZJ, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med*. 1992;18:137–138.

4. Reuse CVJ, Pinsky MR. Measurement of right ventricular volumes during fluid challenge. *Chest*. 1990;98:1450–1454.
5. Michard FBS, Chemla D. 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.
6. Calvin JEDA, Sibbald WJ. The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery*. 1981;90:61–76.
7. Tousignant CPWF, Mazer CD. The use of transesophageal echocardiography for preload assessment in critically ill patients. *Anesth Analg*. 2000;90:351–355.
8. Diebel LNWR, Tagett MG. End-diastolic volume. A better indicator of preload in the critically ill. *Arch Surg*. 1992;127:817–821.
9. Diebel LWR, Heins J. End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. *J Trauma*. 1994;37: 950–955.
10. Tavernier BMOLG. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*. 1998;89:1313–1321.
11. van Daele META, van Woerkens LC. Transesophageal echocardiographic monitoring of preoperative acute hypervolemic hemodilution. *Anesthesiology*. 1994;81:602–609.
12. Greim CARN, Apfel C. Relation of echocardiographic preload indices to stroke volume in critically ill patients with normal and low cardiac index. *Intensive Care Med*. 1997;23:411–416.
13. Feissel MMF, Mangin I. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest*. 2001;119:867–873.
14. Mrarx GCT, McCrossan L. Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. *Eur J Anaesthesiol*. 2004;21: 132–138.
15. Sander MSC, Berger K. Prediction of volume response under open chest conditions during coronary artery bypass surgery. *Crit Care*. 2007;11:1–24.
16. Bendjelid KRJ. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. *Intensive Care Med*. 2003;29:352–360.
17. Chemla DHJ, Coirault C. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol*. 1998;274:H500–H505.
18. Kramer AZD, Hawes H. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest*. 2004;126:1563–1568.
19. Michard FCD, Richard C. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effect of PEEP. *J Respir Crit Care Med*. 1999;159:935–939.
20. Berkenstadt HMN, Hadani M. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg*. 2001;92:984–989.
21. Reuter DAKA, Felbinger TW. Usefulness of left ventricular stroke volume variations to assess fluid responsiveness in patients with reduced left ventricular function. *Crit Care Med*. 2003;31:1399–1404.
22. Rex SBS, Metzelder S. Prediction of fluid responsiveness in patients during cardiac surgery. *Br J Anaesth*. 2004;93:782–788.
23. Reuter DAFT, Schmidt C. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med*. 2002;28:392–398.
24. Reuter DAKA, Felbinger TW. Optimising fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations: a comparison to aortic systolic pressure variations. *Br J Anesth*. 2005;88: 124–126.
25. Kress JPPA, O'Connor MF. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342:1471–1477.

26. Girard TDKJ, Fuchs BD. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371: 126–134.
27. The 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.
28. Tavernier BMO, Lebuffe G, et al. Systolic pressure variation to guide fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*. 1998;89:1313–1321.
29. Reuter DABJ, Goepfert MS. Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Med*. 2003;29:476–481.
30. Szold APR, Segal E. The effect of tidal volume and intravascular volume state on systolic pressure variation in ventilated dogs. *Intensive Care Med*. 1989;15: 368–371.
31. Pizov RYaY, Perel A. The arterial pressure waveform during acute ventricular failure and synchronized external chest compression. *Anesth Analg*. 1989;68: 150–156.
32. Tournadre JPAB, Cayrel V. Estimation of cardiac preload changes by systolic pressure variation in pigs undergoing pneumoperitoneum. *Acta Anaesthesiol Scand*. 2000;44:231–235.
33. Reuter DAGT, Goepfert MS. Effects of mid-line thoracotomy on the interaction between mechanical ventilation and cardiac filling during cardiac surgery. *Br J Anaesth*. 2004;92:808–813.
34. Gardner RM. Direct blood pressure measurement: dynamic response requirements. *Anesthesiology*. 1981;54:227–236.
35. Smulyan HSM. Systolic blood pressure revisited. *J Am Coll Cardiol*. 1997;29: 1407–1413.
36. Dorman TBM, Lipsett PA. Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients. *Crit Care Med*. 1998;26:1646–1649.
37. Stern DHGJ, Allen FB. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass?. *Anesthesiology*. 1985;62:557–561.
38. Stewart GN. Researches on the circulation time and on influences which affect it. *J Physiol*. 1897;22:159–183.
39. Hamilton WFMJ, Kinsman JI. Studies on the Circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. *Am J Physiol*. 1932;99:534–551.
40. Meier PZK. On the theory of the indicator-dilution method for measurement of blood flow and volume. *J Appl Physiol*. 1954;6:731–744.
41. Hamilton WFRR, Attyah AM. Comparison of the Fick and dye injection methods of measuring the cardiac output in man. *Am J Physiol*. 1948;153:309–321.
42. Michard F. Looking at transpulmonary thermodilution curves: the cross-talk phenomenon. *Chest*. 2004;126:656–657.
43. Isakow WSD. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol*. 2006;291:L1118–L1131.
44. Breukers RBJJ. Pulmonary artery thermodilution cardiac output vs. transpulmonary thermodilution cardiac output in two patients with intrathoracic pathology. *Acta Anaesthesiol Scand*. 2004;48:658–661.
45. Goedje OHK, Lichtwarck-Aschoff M. Continuous cardiac output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution. *Crit Care Med*. 1999;27:2407–2412.

46. Buhre WWA, Kazmaier S. Comparison of cardiac output assessed by pulse-contour analysis and thermodilution in patients undergoing minimally invasive direct coronary artery bypass grafting. *J Cardiothorac Vasc Anesth.* 1999;13:437–440.
47. Marx GST, Siimpelmann R. Comparison of cardiac output measurements by arterial trans-cardiopulmonary and pulmonary arterial thermodilution with direct Fick in septic shock. *Eur J Anaesthesiol.* 2005;22:129–134.
48. Della Rocca GCM, Coccia C. Cardiac output monitoring: aortic transpulmonary thermodilution and pulse contour analysis agree with standard thermodilution methods in patients undergoing lung transplantation. *Can J Anaesth.* 2003;50: 707–711.
49. Funk DJME, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. *Anesth Analg.* 2009;108:887–897.
50. Wesseling KHPR, Smith NT. A computer module for the continuous monitoring of cardiac output in the operating theatre and the ICU. *Acta Anaesthesiol Belg.* 1976;27(suppl):327–341.
51. Wesseling KHdWB, Weber JAP. A simple device for the continuous measurement of cardiac output. *Adv Cardiovasc Phys.* 1983;5:16–52.
52. Wesseling KHSN, Nichols WW. Beat to beat cardiac output from the arterial pressure pulse contour. In: *Course on Measurement in Anaesthesia*. Leiden: University of Leiden Press; 1974.
53. Wesseling KHJJ, Settels JJ. Computation of aortic flow from pressure in humans using a nonlinear three-element model. *J Appl Physiol.* 1984;74:2566–2573.
54. Godje OHK, Goetz AE. Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. *Crit Care Med.* 2002;30:52–58.
55. Jansen JRSJ, Mulier JP. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth.* 2001;87.
56. Zollner CBJ, Kilger E. Retrospective analysis of transpulmonary and pulmonary arterial measurement of cardiac output in ARDS patients. *Anaesthesist.* 1998;47:912–917.
57. Zollner CHM, Weis M. Beat-to-beat measurement of cardiac output by intravascular pulse contour analysis: a prospective criterion standard study in patients after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2000;14:125–129.
58. Bein BWF, Tonner P. Comparison of esophageal Doppler, pulse contour analysis, and real-time pulmonary artery thermodilution for the continuous measurement of cardiac output. *J Cardiothorac Vasc Anesth.* 2004;18:185–189.
59. Felbinger TWRD, Eltzschig HK. Cardiac index measurements during rapid preload changes: a comparison of pulmonary artery thermodilution with arterial pulse contour analysis. *J Clin Anesth.* 2005;17:241–248.
60. Tannenbaum GAMD, Weissman C. Pulse contour cardiac output in surgical intensive care unit patients. *J Clin Anaesth.* 1993;5:471–478.
61. Rodig GPC, Keyl C. Continuous cardiac output measurement: pulse contour analysis vs. thermodilution technique in cardiac surgical patients. *Br J Anaesth.* 1999;82:525–530.
62. Gödje OTC, Reichenspurner H. Less invasive, continuous beat-to-beat hemodynamic monitoring during minimally invasive coronary surgery. *Ann Thorac Surg.* 1999;68:1532–1536.
63. Jellema WWK, Groenevald ABJ. Continuous cardiac output in septic shock by simulating a model of the aortic input impedance—a comparison with bolus injection thermodilution. *Anaesthesiology.* 1999;90:1317–1328.
64. Sakka SGRK, Wegscheider K. Is the placement of a pulmonary artery catheter still justified solely for the measurement of cardiac output? *J Cardiothorac Vasc Anesth.* 2000;14:119–124.

65. Genahr AMA. Transpulmonary thermodilution in the critically ill. *Brit J Int Care*. 2004;Spring:6–10.
66. Mitchell JPSD, Calandrino FS. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis*. 1992;145:990–998.
67. Eisenberg PRHJ, Anderson D. A prospective study of lung water measurements during patient management in an intensive care unit. *Am Rev Respir Dis*. 1987; 136:662–668.
68. Chinard FPET. Transcapillary pulmonary exchange of water in the dog. *Am J Physiol*. 1954;178:197–202.
69. Lewis FREV, Hill SL. The Measurement of extravascular lung water by thermal-green dye indicator dilution. *Ann New York Acad Sci*. 1982;394–410.
70. Gee MHMP, Stage AF. Estimation of pulmonary extravascular fluid volume by use of thermodilution. *Fed Proc*. 1971;30:379.
71. Bock JLF. Clinical relevance of lung water measurement with the thermal-dye dilution technique. *J Surg Res*. 1990;48:254–265.
72. Mihm FGFT, Jamieson SW. Thermal dye double indicator dilution measurement of lung water in man: comparison with gravimetric measurements. *Thorax*. 1987;42: 72–76.
73. Sturm JA. *Development and Significance of Lung Water Measurement in Clinical and Experimental Practice*. Berlin: Springer; 1990:129–139.
74. Gödje OPM, Seebauer T. Reproducibility of double-indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. *Chest*. 1998;113:1070–1077.
75. Sakka SGRC, Pfeiffer UJ. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med*. 2000;26:180–187.
76. Michard FSA, Toens C. Factors influencing the estimation of extravascular lung water by transpulmonary thermodilution in critically ill patients. *Crit Care Med*. 2005;33:1243–1247.
77. Kirov MYKV, Kuklin VN. Extravascular lung water assessed by transpulmonary single thermodilution and postmortem gravimetry in sheep. *Crit Care*. 2004;8:451–458.
78. Katzenelson RPA, Berkenstadt H. Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water. *Crit Care Med*. 2004;32:1550–1554.
79. Nirmalan MNM, Willard T. Estimation of errors in determining intrathoracic blood volume using thermal dilution in pigs with acute lung injury and haemorrhage. *Br J Anaesth*. 2004;93:546–551.
80. Nirmalan MWT, Edwards DJ. Estimation of errors in determining intrathoracic blood volume using the single transpulmonary thermal dilution technique in hypovolemic shock. *Anesthesiology*. 2005;103:805–812.
81. Neumann P. Extravascular lung water and intrathoracic blood volume: double versus single indicator dilution. *Intensive Care Med*. 1999;25:216–219.
82. Pearce MLBJ. The measurement of pulmonary parenchymal volume by thermal indicator dilution. *Clin Res*. 1966;14:182.
83. Meier PZK. On the theory of indicator-dilution method of measurement of blood flow and volume. *J Appl Physiol*. 1954;6:731–744.
84. Newman EVMM, Genecin A. The dye dilution method for describing the central circulation. An analysis of factors shaping the time-concentration curve. *Circulation*. 1951;4:735–746.
85. Stewart GN. Research on the circulation time in organs and on the influences which affect it. *J Physiol*. 1897;15:1–89.
86. Effros RM. Lung water measurements with the mean transit time approach. *J Appl Physiol*. 1985;59:673–683.

87. Allison RCCPJ, Gray BA. Thermodilution measurement of lung water. *Clin Chest Med*. 1985;6:439–457.
88. Schreiber THL, Schwarzkopf K. Lung perfusion affects preload assessment and lung water calculation with the transpulmonary double indicator method. *Intensive Care Med*. 2001;27:1814–1818.
89. Beckett RCGB. Effects of atelectasis and embolization on extravascular thermal volume of the lung. *J Appl Physiol*. 1982;53:1614–1619.
90. Michard F. Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls. *Crit Care Med*. 2007;35:1–7.
91. Myers JCRT, Cloutier CT. Effect of positive end-expiratory pressure on extravascular lung water in porcine acute respiratory failure. *Crit Care Med*. 1988;16:52–54.
92. Carlile PVLD, Gray BA. Effect of PEEP and type of injury on thermal-dye estimation of pulmonary edema. *J Appl Physiol*. 1986;60:22–31.
93. Colmero-Ruiz MF-ME, Fernandez-Sacristan MA. PEEP and low tidal volume ventilation reduce lung water in porcine pulmonary edema. *Am J Respir Crit Care Med*. 1997;155:964–970.
94. Ruiz-Bailen MF-ME, Hurtado-Ruiz B. Immediate application of positive end expiratory pressure is more effective than delayed positive end expiratory pressure to reduce extravascular lung water. *Crit Care Med*. 1999;27:380–384.
95. Demling RHSN, Edmunds LH Jr. Effect of end-expiratory airway pressure on accumulation of extravascular lung water. *J Appl Physiol*. 1975;38:907–912.
96. Patroniti NBG, Maggioni E. Measurement of pulmonary edema in patients with acute respiratory distress syndrome. *Crit Care Med*. 2005;33:2547–2554.
97. Prien TTL, Herndon DN. Pulmonary edema with smoke inhalation, undetected by indicator-dilution technique. *J Appl Physiol*. 1987;63:907–911.
98. Roch AMP, Lambert D. Accuracy of the double indicator method for measurement of extravascular lung water depends on the type of acute lung injury. *Crit Care Med*. 2004;32:811–817.
99. Groeneveld ABJVJ. Is pulmonary edema associated with a high extravascular thermal volume? *Crit Care Med*. 2004;32:899–901.
100. Carlile PVGB. Type of lung injury influences the thermal-dye estimation of extravascular lung water. *J Appl Physiol*. 1984;57:680–685.
101. Schuster DPAC, Kozlowski J. Regional pulmonary perfusion in patients with acute pulmonary edema. *J Nucl Med*. 2002;43:863–870.
102. Sakka SGKM, Reinhart K. Prognostic value of extravascular lung water in critically ill patients. *Chest*. 2002;122:2080–2086.
103. Zeravik JPU. Efficacy of high frequency ventilation combined with volume controlled ventilation in dependency of extravascular lung water. *Acta Anaesthesiol Scand*. 1989;33:568–574.
104. Zevarik JBU, Pfeiffer UJ. Efficacy of pressure support ventilation dependent on extravascular lung water. *Chest*. 1990;97:1412–1419.
105. Lichtenstein DGI, Mourgeon E. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology*. 2004;100:9–15.
106. Sivak EDRB, O'Donovan PB. Value of extravascular lung water measurement versus portable chest x-ray in the management of pulmonary edema. *Crit Care Med*. 1983;11:498–501.
107. Fernandez-Mondejar ER-FR, Garcia-Delgado M. Small increases in extravascular lung water are accurately detected by transpulmonary thermodilution. *J Trauma*. 2005;59:1420–1424.
108. Verheij JvLA, Raijmakers PG. Pulmonary abnormalities after cardiac surgery are better explained by atelectasis than by increased permeability oedema. *Acta Anaesthesiol Scand*. 2005;49:1302–1310.

109. Groeneveld ABVJ, van den Berg FG. Increased pulmonary capillary permeability and extravascular lung water after major vascular surgery: effect on radiography and ventilatory variables. *Eur J Anaesthesiol.* 2006;23:36–41.
110. Michard FZV, Alaya S. Better characterization of acute lung injury/ARDS using lung water. *Chest.* 2004;125:1166–1167.
111. Martin GES, Mealer M. Extravascular lung water in patients with severe sepsis: a prospective cohort study. *Crit Care.* 2005;9:R74–R82.
112. Groeneveld ABJPK. Acute lung injury, overhydration or both? *Crit Care.* 2005;9: 136–137.
113. Meade MOCR, Guyatt GH. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2000;161:85–90.
114. Matthay MA. Clinical measurement of pulmonary edema. *Chest.* 2002;122: 1877–1879.
115. Schuster DP. Identifying patients with ARDS: time for a different approach. *Intensive Care Med.* 1997;23:1197–1203.
116. Monnet XAN, Osman D. Assessing pulmonary permeability by transpulmonary thermodilution allows differentiation of hydrostatic pulmonary edema from ALI/ ARDS. *Intensive Care Med.* 2007;33:448–453.
117. Rivers EP. Fluid-management strategies in acute lung injury—liberal, conservative, or both? *N Engl J Med.* 2006;354:2598–2600.
118. Schuster DP. Fluid management in ARDS: "keep them dry" or does it matter? *Intensive Care Med.* 1995;21:101–103.
119. 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.* 20006;354:2564–2575.
120. Bryan-Brown CWKK, Lumb PD. The axillary artery catheter. *Heart Lung.* 1983;12: 492–497.
121. Urzua JSD, Meneses G. Thermoregulatory vasoconstriction increases the difference between femoral and radial arterial pressures. *J Clin Monit.* 1994;10:229–236.
122. Van Beck JOWR, Abenstein JP. Thermoregulatory vasoconstriction increases the difference between femoral and radial arterial pressure. *J Clin Monit.* 1993;10: 229–236.
123. Cousins TRODJ. Arterial cannulation: a critical review. *AANA J.* 2004;72:267–271.
124. Scheer BVPA, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care.* 2002;6:198–204.
125. Durbin CG Jr. Radial arterial lines and sticks: what are the risks? *Respir Care.* 2001;46:229–230.
126. Soderstrom CAWD, Dunham CM. Superiority of the femoral artery for monitoring. A prospective study. *Am J Surg.* 1982;144:309–312.
127. Bedford RF. Wrist circumference predicts the risk of radial-arterial occlusion after cannulation. *Anesthesiology.* 1978;48:77–378.
128. Wolf SMD. Pseudoaneurysm: a late complication of radial-artery catheterization. *Anesthesiology.* 1980;52:80–81.
129. Fraile JRCJ, Gilsanz F. Postpuncture pseudoaneurysm of the radial artery [in Spanish]. *Rev Esp Anestesiol Reanim.* 1989;36:126–127.
130. McEllistrem RFOTD, Keane P. Post-cannulation radial artery aneurysm: a rare complication. *Can J Anaesth.* 1990;37:907–909.
131. Arrowsmith JE. Extracorporeal pseudoaneurysm: an unusual complication of radial artery cannulation. *Anesthesia.* 1991;46:894–895.
132. Riker AIGR. Vascular complications and femoral artery catheterization in burn patients. *J Trauma.* 1996;41:904–905.