Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter

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Isakow, Warren, and Daniel P. Schuster. 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 291: L1118–L1131, 2006. First published August 4, 2006; doi:10.1152/ajplung.00277.2006.—The recently completed Fluid and Catheter Treatment Trial conducted by the National Institutes of Health ARDSNetwork casts doubt on the value of routine pulmonary artery catheterization for hemodynamic management of the critically ill. Several alternatives are available, and, in this review, we evaluate the theoretical, validation, and empirical databases for two of these: transpulmonary thermodilution measurements (yielding estimates of cardiac output, intrathoracic blood volume, and extravascular lung water) that do not require a pulmonary artery catheter, and hemodynamic measurements (including estimates of cardiac output and ejection time, a variable sensitive to intravascular volume) obtained by esophageal Doppler analysis of blood flow through the descending aorta. We conclude that both deserve serious consideration as a means of acquiring useful hemodynamic data for managing shock and fluid resuscitation in the critically ill, especially in those with acute lung injury and pulmonary edema, but that additional study, including carefully performed, prospective clinical trials demonstrating outcome benefit, is needed.

esophageal Doppler

SINCE THE INTRODUCTION of the balloon flotation-assisted pulmonary artery catheter (PAC) in the 1970s, hemodynamic monitoring has been considered part of the standard of care in managing critically ill patients with shock and/or acute lung injury (111). In 1996, Connors et al. (20) made the disturbing observation that mortality might actually be higher among patients whose therapy was guided by the data obtained from hemodynamic monitoring with a PAC than in matched controls. This study, along with others that raised similar concerns (22, 64), became the principal incentive for launching the recently completed Fluid and Catheter Treatment Trial (FACTT) conducted by the National Heart, Lung, and Blood Institute’s ARDSNetwork (76, 77). The results of the FACTT study should be quite sobering to those who assumed that hemodynamic monitoring benefits the critically ill.

There were two principal conclusions to the FACTT study: 1) hemodynamic monitoring with a PAC [in which cardiac output (CO) and pulmonary artery occlusion pressure (PAOP; otherwise known as “wedge” pressure) measurements were obtained] provided no outcome benefit compared with management based on the more readily obtained (and more limited) central venous pressure (CVP) measurement, and 2) gas exchange, radiographic improvement, ventilator dependency, and intensive care unit (ICU) and hospital time were all improved by a treatment strategy that emphasized fluid restriction and diuresis when possible (a favorable trend in reduced mortality was also present but did not reach statistical significance). Thus intensivists and others caring for patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) now find themselves in a rather paradoxical position: strong theoretical (92) and empirical (32, 73, 76, 91) evidence for a treatment strategy based, at least in part, on its hemodynamic effects (lowering hydrostatic pressures within the pulmonary capillaries while maintaining a physiologically adequate CO) but no outcome benefit when therapy is guided by direct measurement of these same hydrostatic pressures (i.e., PAOP and CO over therapy guided simply by the CVP (at best, only indirectly related to PAOP). As a result, whereas treatment algorithms in other fields of medicine employ ever increasingly sophisticated biomarkers, the use of hemodynamic monitoring to guide the management of the critically ill has just taken a 35-year step backward.

The implications of the FACTT studies have yet to be fully digested by the clinical and scientific medical communities, but one obvious question is this: if the information provided by the PAC is not useful, are there alternative monitoring strategies that are? The answer, of course, is that we do not know. However, several reasonable alternatives do exist, are commercially available, and could be incorporated into new management algorithms that build on the lessons offered by the FACTT study. The purpose of this review is to assess the theoretical and empirical basis for two of these technologies in particular: hemodynamic (and other) measurements obtained by a transpulmonary thermodilution method that do not require a PAC, and hemodynamic measurements obtained by esophageal Doppler analysis of blood flow through the descending aorta.
At present, only a limited number of devices are commercially available to make these measurements. Thus any discussion about the methods upon which these instruments are based is necessarily influenced by technical decisions incorporated into machine and/or software design, not all of which may be readily or easily identifiable from publicly available literature. Technology has typically evolved from systems that were built by the investigators themselves to commercially produced machines that are no longer in use to currently available commercial devices. Therefore, studies of validity in an older literature may or may not have relevance for how the technology might be deployed at present, as few direct comparisons are available. Even when such comparisons have been undertaken, interpretation has been plagued at times by just such technical factors (5, 94). Accordingly, we will focus where possible on the types of data that can be generated by currently available instrumentation, and we will emphasize studies conducted in humans. In addition, however, we wish to make explicit here rather than in a footnote that neither of us have any connection, commercial or otherwise, to the manufacturers of any of the devices mentioned in this review.

The evaluation of cardiac function and intravascular volume by either transthoracic or transesophageal echocardiography (as opposed to Doppler flow analysis) is not included as a bedside alternative in this review although others have provided a convincing case that such monitoring might indeed be useful in general intensive care (4, 107, 108).

**Data Derived From Thermodilution Measurements**

**Measurements of flow.** CO measurements, obtained via a PAC or the transpulmonary method, are based on the principle of indicator dilution. Excellent reviews of the theory and underlying assumptions of this approach have been published previously and are only summarized briefly here (1, 45, 101).

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.

In practical terms, with currently available technology, the indicator is injected into the circulation at one point, and its concentration in blood is measured at some other point downstream from the injection site. Since the method was originally introduced, a variety of indicators has been employed for flow measurements. When CO is measured in the critically ill, however, the injected indicator is usually saline that is cold relative to body temperature (i.e., the indicator is temperature). With current technology that is designed to measure other variables besides CO (to be described later), injections of 15–20 ml of cold (<8°C) are made via a central venous catheter (inserted into the internal jugular or subclavian veins) for indicator injection, and the indicator is then detected at an arterial site using a 4–5 Fr thermistor-tipped catheter (inserted into the radial, axillary, or femoral arteries).

If flow between these two points is high, then the concentration of the injected substance (e.g., “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 more quickly.

If the quantity of the indicator is known, and if it can be assumed that there is no loss or gain of indicator between the injection and detection sites, then by conservation of mass

\[
Q = A \int_0^t c(t) \, dt
\]

(1)

where \( Q \) is flow, \( A \) is the quantity of the indicator, and the integral represents the area under the concentration-time curve.

Stewart (102) first, and then Kinsman and colleagues (53), established principles for the ideal indicator: stable, non-toxic, uniformly distributed, completely mixed before arriving at the detection site, confined to the intravascular compartment between the injection and detection sites, but is completely cleared from the circulation before returning to the site of injection to avoid recirculation artifacts in the analysis of the concentration-time curves. Indocyanine green dye, although not meeting all of these criteria, was the accepted standard indicator for decades, and many studies have validated the use of indocyanine green dye for indicator dilution measurements of CO (reviewed in Ref. 101).

Fegler (35), and separately Chinard and Enns (18), modified the method so that temperature could be used as the indicator. The appropriate modifications to Eq. 1 result in the following equation (still often referred to as the “Stewart-Hamilton equation”):

\[
CO = \frac{(T_b - T_i) \times V_i \times K}{\int_0^\infty \Delta T_i \, dt}
\]

(2)

where \( T_b \) is blood temperature at the time of injection and \( T_i \) is injectate temperature after taking into account such factors as the intracorporeal fraction of the injection catheter dead space, dead space of the injection catheter, injector set, any extension tubing, and temperature of both the blood before injection and of the extracorporeal dead space before injection. \( V_i \) is intended injectate volume, \( \int_0^\infty T_b \times dt \) is area under the thermodilution curve, and \( K \) is a correction constant that accounts for differences between the specific gravity and specific heat capacity of blood vs. saline [reported as 1.08–1.10 (48, 82)] and such factors as the dead space of the intravascular portion of the injecting catheter (caliber, length, and thermal conductance of the catheter material) (80).

As with other indicators, when temperature is used as the indicator, method accuracy assumes complete mixing with the circulating blood, no loss or gain of indicator, constant blood
flow during the period of measurement, no recirculation of the indicator (i.e., the injected indicator passes the detection site only once), and in the specific case of thermodilution, a constant blood temperature during the period of measurement (82). Also, technically, Eq. 2 is only valid for constant, not pulsatile, flow, but the error is small if the cardiac cycle length is much less than the indicator transit time, which is certainly the case for transpulmonary thermodilution measurements of CO given the very long transit times by this method. Of note, however, any errors that do result in a misestimate of CO will propagate similarly to the calculation of extravascular lung water (EVLW) because the CO measurement is integral to the EVLW calculation (see below).

Differential emptying of blood from the superior and inferior vena cavae during the respiratory cycle, the respiratory rate, the timing of injection, and baseline drift in the thermal signal can each affect the thermodilution curve. In patients requiring mechanical ventilation, respiratory variation in Ti may be exacerbated by changes in respiratory gas temperature, humidity, and the flow rate of inspired gas (80). These factors can affect the thermal signal in both positive and negative ways, so the summative effect is difficult to predict. Most modern CO computers compensate for such thermal noise via a variety of electronic averaging or signal processing strategies.

Thermodilution measurements of CO can be made by measuring the temperature-time curve in the pulmonary artery (COpa, using a PAC) or in the aorta (COap, the “transpulmonary” method). For technical reasons (outlined below), these methods have different sensitivities to various potential artifacts.

Factors that can affect the measured change in temperature during an indicator dilution measurement with the PAC (other than CO itself) include valvular regurgitation and left-to-right shunts (and others) because they distort the time-temperature curve. These are much less likely to affect the temperature-time curve as detected in the descending aorta during transpulmonary measurements of CO.

On the other hand, the assumption that there is no unaccounted loss of thermal indicator is more likely to be in error during transpulmonary measurements of CO in the presence of extrapulmonary “sinks” for the thermal indicator (such as pericardial or pleural effusions) (13).

The temperature-time curves obtained during transpulmonary thermodilution measurements are broader and lower in magnitude than when obtained via a PAC (Fig. 1). Thus transpulmonary thermodilution measurements are more vulnerable to errors caused by baseline drift and miscorrections for indicator recirculation. On the other hand, 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 15–20 ml rather than the 10 ml of room temperature saline often used for thermodilution measurements via a PAC).

Errors in the calculation of CO due to recirculation artifact are minimized by assuming that the decay in the temperature-time curve, in the absence of recirculation, would be monoexponential. Given the broader shape of the curve during a transpulmonary thermodilution measurement than during a measurement with the PAC, recirculation effects may be present before monoexponential decay can be reliably established (10). Overcorrection for recirculation has the same effect as an unaccounted loss of indicator: both will result in a smaller than expected area under the thermodilution curve (Eq. 2), resulting in an overestimate of CO. These twin sources of error (unaccounted loss of indicator and inaccurate correction for recirculation) are the most likely reasons for an approximate 10% systematic difference between COpa and COap (9, 48, 62).

In currently available equipment, the decay of the thermal-time curve is assumed to be monoexponential without recirculation artifact between 80 and 50% of the peak change in temperature, after corrections for baseline drift (82). A computer then fits a line to the data in this region of the curve by logarithmic regression and computes a correlation coefficient, followed by successive additional correlations as data beyond the 50% of the peak temperature change. It is assumed that when recirculation of the thermal indicator reaches the thermistor, the correlation coefficient will begin to decline in value. The data between 80% of the peak value and the lowest value before the correlation coefficient begins to decline is then extended to infinity to define the final portion of the thermal-time curve that is free of recirculation artifact.

A high degree of correlation between COpa and COap has been established in multiple experimental and clinical settings including cardiac surgery patients, intensive care patients, septic patients, and burn victims (7, 14, 26, 29, 38, 50, 57, 89, 113). For instance, Sakka et al. (89) studied 37 surgical ICU patients, 34 of whom had sepsis. They found that COpa correlated strongly with COap (R2 = 0.94) (Fig. 2), with a bias2 of 0.68 l/min (COpa was consistently higher than COap) and with a SD for the difference between the two methods of 0.62 l/min (8).

2 In many studies in this field, in which different methods are measuring the same putative entity (e.g., CO), 3 types of data are reported: the “coefficient of determination” (which is the square of the correlation coefficient obtained during linear regression of data from one method against the other), “bias” (which is the mean difference between the estimates of the variable in question), and the “limits of agreement” (conventionally, 2 SD about the estimate of bias) (8).
In a more recent comparison using current technology, Della Rocca et al. (29) compared COpa to COtp measurements in 62 patients undergoing liver transplantation at various stages of the procedure and found a bias of only 0.15 l/min and a limit of agreement of ± 1.74 l/min.

In children, measurements of COtp have been compared with calculations based on the Fick principle, often considered the gold standard for estimating CO (79, 103). For instance, in a study by Pauli et al. (79), the two methods were highly correlated ($R^2 = 0.99$), with a bias of only $0.036 \text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and a limit of agreement of ± 0.44 l/min$^{-1} \cdot \text{m}^{-2}$ (Fig. 3).

**Measurements of intrathoracic thermal volume.** Indicator-dilution methods (including thermodilution) can be used not only to measure flow but also to measure the volume through which flow is measured (i.e., from the point of injection to the point of detection):

$$V = CO \times MTt$$

where $V$ is the distribution volume for the indicator, and $MTt$ is the mean transit time for the indicator.

The $MTt$ is calculated as the ratio of two integrals obtained from analysis of the indicator dilution curve:

$$MTt = ATT + \frac{\int c(t) \times (t - AT) \, dt}{\int c(t) \, dt}$$  \hspace{1cm} (4)

where $AT$ is the appearance time before the indicator is detected after injection and $c$ is the concentration of the indicator. Obviously, by this approach, the estimates of volume, being a function of the integrals (1 for CO and 2 for the $MTt$), are vulnerable to errors when measuring both CO and $MTt$ (1).

The distribution volume for a thermal indicator during a transpulmonary measurement of CO includes the blood volume between these points, a portion of the water volumes of the vessel walls, a portion of the walls of the heart chambers, and the water volume of the lungs, i.e., it is an “intrathoracic thermal volume” (ITTV) (Fig. 4).

Low COs and high EVLW lower the peak value of temperature change and greatly lengthen the $MTt$ during transpulmonary measurements. The total change in temperature may only be 0.25°C; therefore, failure to account for baseline temperature drift during the measurement time (perhaps as long as 1 min when CO is low and/or EVLW is truly high) will, as in the CO measurement, cause significant errors in the measurement of $MTt$, and thus of EVLW.

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3 As the methodology associated with indicator dilution methods has evolved over the last 85 years, the acronyms associated with the developing techniques have multiplied. Many, such as “intrathoracic thermal volume,” “lung thermal volume,” and “pulmonary thermal volume,” represent the same or overlapping entities. In an attempt to minimize confusion, we attempt to limit our use of these acronyms to those employed by the PiCCO system, as it is currently the only commercially available equipment to measure COtp or EVLW.

4 Strictly speaking, ITTV also includes the water volume of the blood and a portion of the aortic wall in the intra-abdominal descending aorta until the point of detection at the thermistor tip of the femorally placed catheter. Also, the distribution volume of the thermal indicator is related to the heat capacity of the volume, which also includes tissue (non-water) components as well as the specific heat of each component. Ignoring these factors may account for a 2–3% error in the estimate of ITTV (1).
The thermal indicator, being blood borne, gains access to the extravascular compartment of ITTV via the diffusion of heat. The exact distance over which such diffusion can take place during a typical measurement period is not clear (the diffusion coefficient of heat in water is estimated at $1.5 \times 10^{-3}$ cm$^2$/s (55)), but factors such as vascular obstruction caused by embolism (2, 6) or by physiological hypoperfusion [from positive end-expiratory pressure (PEEP) (1, 17), hypovolemia, or hypoxic vasoconstriction (16, 44)] result in an underestimation of EVLW as measured by gold standard gravimetric methods. The underestimates due to PEEP are less likely to occur if pulmonary artery pressures are significantly higher than PEEP levels (11), which clinically is almost always the case. Despite the hypoxic vasoconstriction associated with atelectasis, this type of lung pathology has not been shown to cause underestimates of ITTV, at least at the level of whole lung atelectasis (6). Theoretically, high flows (high CO, reducing the time for diffusion) could cause the extravascular component of lung water to be underestimated, but in general this has not been observed experimentally with the thermodilution method (1, 44). [Reports that EVLW measurements are dependent on CO appear to be related more to previous instrumentation than to the method itself (11).]

A common misconception about ITTV, and by extension EVLW as measured by the indicator dilution method, is that it is equivalent to a measure of pulmonary edema, if by that term one means extravascular, extracellular, water. EVLW may well be equivalent to pulmonary edema when caused by cardiac failure or volume overload, as the semipermeable alveolocapillary membrane remains intact. However, most cases of non-cardiogenic pulmonary edema are associated with an extensive infiltration of inflammatory cells. These cells, be they in the interstitium or in the alveolar space, are, like all soft tissue cells, >80% water, and constitute a large potential sink for the thermal indicator. Thus thermodilution measurements of EVLW may not be responsive to treatments designed to reduce pulmonary edema by decreasing hydrostatic pressures if a significant fraction of EVLW represents inflammatory cell water. To our knowledge, the quantitative influence of extravascular (inflammatory) cellular water on EVLW measurements by the thermodilution method has not been evaluated.

**Measurements of intrathoracic blood volume.** Since ITTV reflects both intravascular as well as extravascular volume, a separate estimate of the intravascular component is needed to calculate EVLW. The distribution volume for an indicator that is confined to the vascular space (such as indocyanine green dye) will be smaller (and therefore, the MT$_{gd}$ shorter) than for an indicator with a larger distribution volume (such as a diffusible indicator like heat). Since most of the volume in this intravascular space, when measured by the transpulmonary method, is within the thorax, it has been referred to as the intrathoracic blood volume, ITBV (Fig. 4).

Thus

$$\text{ITBV} = \text{CO} \times \text{MT}_{gd} \tag{5}$$

where MT$_{gd}$ is the mean transit time for a non-diffusible indicator like indocyanine green dye.

An alternative to measuring ITBV via the “mean transit time” method is derived from a theory first presented by Newman et al. (78), although earlier versions had been suggested (45). The Newman method subsequently has been characterized as the “slope-volume” method. On the basis of Newman’s principles, it is possible to estimate ITBV during the same injection of cold saline that is used to measure CO and ITTV (see below). Thus all three measurements can be made with a single indicator, and it is this method that has been incorporated into currently available instrumentation.

The logic behind the slope-volume method is as follows. First, assume that a given amount of an indicator, A, is injected into a chamber of volume, $V$. At any point in time, $t$, the rate of change in A will depend on its concentration, $c$, and flow, Q, through the chamber. Next, proceed with the following assumptions: 1) the volume of the chamber is constant, 2) the indicator is completely mixed within the chamber’s volume, 3) the injection of the indicator into the chamber is instantaneous, 4) there is no recirculation of the indicator back into the chamber, and 5) flow is constant. Accordingly, in this case, with no additional indicator coming into the chamber, initially $c = A/V$, and the rate of change in the amount of the indicator is given by

$$\frac{dA}{dt} = -\frac{QA}{V} = -Qc \tag{6}$$

Dividing both sides of this equation by $V$ gives the rate of change in the concentration of the indicator as...
downslope at the downstream detection site must represent the
Therefore, of the various chambers connected in series, the
(Q/V) will be greater, i.e., the decay will be faster (Fig. 6).
individual chamber. Thus, with smaller volumes, the slope
time curves (after semi-log transformation) that would be
is the same by definition, then the downslope of concentration-
time curves obtained at a point distal to the 2 chambers would be
slowest decay of the indicator concentration-time curve from
the largest volume. Newman et al. (78) also showed that this
was the case regardless of the order in which the chambers
were connected or even if the chamber volumes of the smaller
chambers change during the measurement (as long as they
remain smaller than the volume of the largest chamber).
The mixing volume for the thermal indicator (ITTV) can be
thought of as a set of chambers in series, namely the right heart,
the lungs, and the left heart (and vessels leaving the heart to the
point of detection) (Fig. 4). Whereas MTt represents the mean
transit time for the thermal indicator through this entire volume
(ITTV), the downslope time (DSr) is determined only by the
largest of these three chambers, namely the lungs (78, 85).
(If the volumes of the smaller chambers can therefore change, as
with the beating heart, without affecting the fact that the lungs
determine DSr.) This lung thermal volume is referred to as the
pulmonary thermal volume (PTV) when measured using currently
available equipment.
Accordingly
\[
\text{ITTV} = \text{CO} \times \text{MTt}
\]
and
\[
\text{PTV} = \text{CO} \times \text{DSr}
\]
Although there is no dispute that PTV < ITTV, the actual
anatomic volume represented by PTV has been questioned
(45). The criticisms focus on the assumption that each chamber
in the Newman model functions as a “mixing volume” (does
“mixing” occur as the indicator traverses the lungs?) and
discrepancies between theory and experimental data (45).
However, the questions raised by these analyses have not been
reassessed in terms of modern instrumentation or the use of
“heat” as the diffusible indicator.
The difference between ITTV and PTV is (approximately)
the thermal volume of the nonpulmonary chambers in series
between the point of injection and the point of detection. Since
this consists primarily of the blood volume of the cardiac
chambers, and since these volumes are greatest at end-diastole,
this difference has been called the global end-diastolic volume (GEDV).

Accordingly

\[ \text{GEDV} = \text{ITTV} - \text{PTV} \quad (11) \]

Recall from Eq. 5 that ITBV can be measured by indocyanine green dye dilution (ITBV\(_{gd}\)). ITBV\(_{gd}\), like GEDV, represents the blood volume component of ITTV, but should be larger because it includes the blood volume of the lungs as part of its relevant mixing volume, whereas GEDV does not (Fig. 4).

Empirically, Sakka et al. (90)\(^4\) found, in 57 critically ill adult patients (most of whom had sepsis or ARDS), that indeed ITBV\(_{gd}\) was routinely greater than GEDV, as follows (Fig. 7):

\[ \text{ITBV}_{gd} = 1.25 \text{ GEDV} - 28.4 \text{ (ml)} \quad (12) \]

They then validated this relationship in 209 additional critically ill patients (about one-half of whom had sepsis or ARDS) by using this regression equation to calculate ITBV from the measured GEDV (ITBV\(_{th}\)) and compared these calculations to separate measurements of ITBV\(_{gd}\). The two estimates of ITBV were highly correlated \((R^2 = 0.92\) with little bias \(<8 \text{ ml/m}^2\) body surface area). Commercially available equipment has simplified this relationship slightly so that ITBV is calculated as just

\[ \text{ITBV}_{th} = 1.25 \text{ GEDV} \quad (13) \]

Only a few studies have been done subsequently to evaluate the validity of Eq. 12 for calculating ITBV. Kuntscher et al. (58) studied 18 burn patients and reported an \(R^2\) for ITBV\(_{gd}\) vs. ITBV\(_{th}\) of only 0.59 but unfortunately did not report the actual regression equation for ITBV\(_{gd}\) vs. GEDV.

Rossi et al. (87) examined the relationship between ITBV\(_{gd}\) and GEDV in pigs given either intravenous endotoxin or, separately, manipulated to change lung perfusion or ventilation by inflating balloon catheters in the vena cava, a distal pulmonary artery, or a bronchus. They found slightly different coefficients for the regression of ITBV\(_{gd}\) vs. GEDV.

The ITBV vs. GEDV relationship may not be as robust as the Sakka (90) study implies and should be verified in more patients with a broad range of cardiopulmonary pathology and pathophysiology. Whether any variance from Eq. 12 or 13 will affect the clinical utility of using Eqs. 12 or 13 to estimate ITBV should also be studied.

ITBV as an index of preload. A number of studies have examined the value of ITBV\(_{th}\) as a predictor of responses to hemodynamic interventions (e.g., an intravascular volume fluid challenge). The idea is that GEDV and ITBV\(_{th}\) are directly related to the end-diastolic volume of the cardiac chambers. Thus they should function as an index of cardiac “preload.”

\(^4\) To derive this relationship, Sakka et al. (90) used a form of regression analysis they referred to as “structural linear regression.” We speculate they resorted to this strategy because of a non-normal distribution of their data, but details are lacking in the report. The impact of this statistical strategy on the value of the coefficients used to estimate ITBV\(_{th}\) from GEDV data is therefore unclear, and comparisons to subsequent studies by others who employed standard linear regression may also be affected.

\(^5\) Several studies (e.g., Ref. 63) have evaluated specifically ITBV\(_{gd}\), instead of ITBV\(_{th}\), as a predictor of cardiac performance. The equipment required to make the ITBV\(_{gd}\) measurement, however, is no longer commercially available. Even so, the results of these earlier studies are qualitatively similar to those discussed in the text regarding ITBV\(_{th}\).

\[ \text{Although GEDV and ITBV could vary independently of one another if the pulmonary blood volume varied independently of GEDV (refer to Fig. 4), Eq. 12, which is used to calculate ITBV}_{th} \text{ in commercially available equipment, mandates that the two variables have a constant relationship to one another even though the database upon which the ITBV}_{th} \text{ calculation is based (Eq. 12) is still meager. The data from studies that examine GEDV or ITBV}_{th} \text{ as predictors of hemodynamic responses, however, do serve as a type of validation of the ITBV calculation. It is easy to be critical of such work until one realizes that the database upon which the scientific and clinical communities accepted the use of PAOP for so many years as a predictor of hemodynamic responses is at least as weak, if not more so (7, 15, 41, 42, 46, 47, 56, 63, 83, 88, 110, 112).] \]

In several studies, ITBV\(_{th}\) has been compared directly with PAOP as a predictor of hemodynamic function (25, 28, 49, 88). An example of data from one of these studies is shown in Fig. 8.

Michard et al. (70) studied 36 patients with septic shock. Measurements of GEDV and CVP were made in 27 patients before and after fluid challenge and in 9 patients before and after dobutamine infusion. They found that changes in GEDV correlated with changes in stroke volume \((SV; R^2 = 0.52\) but that CVP did not. Dobutamine increased CO without changing GEDV, as would be expected. This observation is important because GEDV and CO share a common variable \(\text{CO}\), (from Eqs. 10 and 11), and an artifactual correlation between GEDV and \(\text{CO}\) (“mathematical coupling”) could have been observed during the dobutamine infusion for this reason alone, but was not (69).

Combes et al. (19) also found that ITBV\(_{th}\) was a useful predictor of hemodynamic responses in 33 mechanically ventilated patients with no right ventricular dysfunction. However, in three patients with right ventricular dysfunction, left ventricular systolic function was underestimated because GEDV reflects the blood volume of all four cardiac chambers, not just those of the right heart. The important principle here is that ITBV\(_{th}\) (or GEDV) may only be reliable predictors of cardiac preload with a normally functioning heart or during global ventricular dysfunction.

In evaluating these various correlation studies, it should be noted that although ITBV is routinely a better predictor of cardiac performance than PAOP, the coefficients of determination typically are only of moderate strength \((-0.4-0.5),\)
indicating a significant fraction of the variability in cardiac performance (~50%) must be accounted for by other variables.

Measurements of EVLW. Once ITBV is known, the calculation of EVLW is straightforward. For the double-indicator dilution approach,

\[ \text{EVLW} = \text{ITTV} - \text{ITBV}_{gd} = (\text{CO} \times \text{MT}_{th}) - (\text{CO} \times \text{MT}_{th} - \text{MT}_{gd}) \]  
(14)

For the single-indicator dilution method,

\[ \text{EVLW} = \text{ITTV} - \text{ITBV}_{th} = (\text{CO} \times \text{MT}_{th}) - 1.25(\text{CO} \times \text{MT}_{th} - \text{CO} \times \text{DSt}) \]  
(15)

The “normal” value for EVLW is reported to be ~5–7 ml/kg with values as high as 30 ml/kg during severe pulmonary edema (11). In experimental animal studies, the double-indicator dilution method can detect changes of as little as 20–33% increases in EVLW (11, 44), significantly below the level usually associated with alveolar flooding (~100% increase) (12). The coefficient of variation for repeat measurements is <10% (11).

Interestingly, whereas all of the caveats noted previously regarding the measurement of CO are relevant to the measurement of EVLW as well, some (such as baseline drift) affect \( C_{op} \) and the measurement of \( MT_{th} \) in opposite, and therefore self-canceling, directions (33).

An extensive amount of literature documents the validity of the double-indicator dilution method to measure mean transit times for the calculation of EVLW (1, 11, 62, 71, 72), including a review of the literature to that time in reference (1). In general, the method slightly overestimates EVLW in normal lungs (5–10%), primarily due to equilibration of the heat indicator with nonpulmonary tissues such as the myocardium and vessel walls and other unaccounted for losses of the indicator between the point of injection and the point of detection) and variously underestimates EVLW during pulmonary edema (depending primarily on the severity and extensiveness of associated perfusion defects) (11). Although correlation studies in the clinical setting tend to support the overall accuracy of thermodilution estimates of EVLW (by either double- or single-indicator dilution approaches), the fact is that the severity and extensiveness of perfusion defects cannot be predicted [although some evidence suggests that such perfusion defects may not be common in humans (93)]. It is for this reason more than any other that some experts continue to discount the validity of the method in the clinical setting (31).

The validity, specifically, of the slope-volume method of estimating EVLW has also been evaluated in a variety of studies, across the different technologies that have been used to make the measurements. For instance, Ramsey et al. (85), using the double-indicator dilution method, and Elings and Lewis (33), using both the double- and single-indicator dilution methods, showed an excellent correlation of the slope-volume method of calculating EVLW with gravimetric measurements. The latter study of the single-indicator method included nearly 2,000 measurements, but the pulmonary blood volume was estimated from a thermodilution curve obtained via a PAC, and thus represented a direct measurement of “right heart mixing volume” instead of the \( ITBV_{th} \) as described above. However, initial attempts to commercialize the single-indicator slope-volume method produced disparate results regarding accuracy, probably due to technical issues regarding the instrumentation (5, 94).

More recently, Katzenelson et al. (52) found a very close correlation in dog models of ALI and hydrostatic pulmonary edema \( (R^2 = 0.94) \) between \( EVLW_{th} \) and EVLW measured by gravimetry (EVLW\(_{grav}\)), the accepted gold standard method of quantifying pulmonary edema. The strength of the correlation was not dependent on the type of pulmonary edema, but \( EVLW_{th} \) was consistently higher than EVLW\(_{grav} \) (by 3.1 ± 1.3 ml/kg) across the different subgroups. Thus, as in earlier studies with the double-indicator dilution technique, the overestimation was relatively greater in normal animals (~30% normals) than in animals with pulmonary edema (~11%). Both thermal losses to nonpulmonary tissues and the use of Eq. 12 to estimate \( ITBV_{th} \), which is based on regression coefficients derived from human data (90), were offered as possible explanations for the discrepancy.

A similar study has been done by Kirov et al. (54) comparing \( EVLW_{th} \) to EVLW\(_{grav} \) in sheep with lung injury induced by intravenous Escherichia coli lipopolysaccharide or intravenous oleic acid. The coefficient of determination, \( R^2 \), was 0.72. These investigators also found that \( EVLW_{th} \) was consistently
higher than EVLW_{grav}, but in this study, the degree of overestimation increased with the severity of ALI.

Studies have previously been conducted comparing pre-mortem double-indicator dilution measurements of EVLW (EVLW_{gdth}) to gravimetric measurements performed on lung tissue from humans obtained at autopsy ($R^2 = 0.86$–0.94) (11, 71). A comparable study using single-indicator, transpulmonary measurements of EVLW has not been reported.

Several studies have been conducted comparing EVLW_{th} to EVLW_{gdth}. In the study that is the primary basis for the algorithm incorporated in currently available instrumentation (90), EVLW_{th} = 0.83 EVLW_{gdth} + 1.6 ml/kg ($R^2 = 0.92$). Thus, both methods tend to overestimate EVLW_{grav} in the normal range, but EVLW_{th} underestimates EVLW measured by the double-indicator dilution method. Since both measurements calculate ITTV in the same manner, any discrepancy must be due to differences in estimating ITBV. Given the five- to sixfold range in EVLW measured in normals vs. patients with severe pulmonary edema, it is not clear that the magnitude of these discrepancies would be important clinically.

**EVLW as a surrogate outcome marker.** Despite the means for measuring EVLW in humans for over 85 years, the role of making such measurements (by any method) in patient management of the critically ill still remains unclear. A hemodynamic management algorithm that incorporates measurements of CO, ITBV, and EVLW, is available on the website of one equipment manufacturer $^7$ but has never been subjected to formal prospective testing. It is possible that the EVLW measurements could be used as an aid to early diagnosis, to determine the natural history of ALI and to provide prognostic estimates of possible recovery, to determine the etiology of pulmonary edema (see below), to quantify the severity of injury, as a marker of treatment effectiveness, and to guide therapy by being incorporated into a fluid management algorithm. Several studies have used EVLW measurements as the primary outcome variable for prospective trials testing fluid management strategies in ALI (32, 67, 73, 91). Two of these studies (73, 91) provided some of the strongest evidence justifying the conservative fluid management arm of the FACTT study (76).

Several studies have reported a poor correlation between EVLW and routine chest radiography, with instances of increased EVLW_{th} despite a normal chest radiograph appearance and normal EVLW_{th} even in the presence of radiographic “infiltrates” (32, 59, 67). Whereas such discrepancies often raise concern about the validity of the EVLW measurement in the clinical setting, another interpretation is that EVLW may be more accurate or more sensitive than chest radiography, a definite possibility given the known greater sensitivity of other methods, such as chest X-ray-computed tomography, over routine chest radiography (especially when the latter is obtained by portable methods, as is often the case in critically ill patients). To our knowledge, there has been no direct comparison between X-ray-computed tomographic assessments of pulmonary edema and transpulmonary thermodilution measurements of EVLW.

**Other variables.** The primary data collected during a transpulmonary thermodilution measurement include the area under the thermodilution curve to calculate CO (as in Eq. 1), and the mean transit and downslope times to calculate ITTV and PTV (as in Eq. 10). GEDV, ITBV, and EVLW are derived from these data (Eqs. 11, 12, and 15). Since heart rate is known, it is also possible to calculate SV. Since the catheter used for indicator detection is in a systemic artery, the mean arterial pressure and systemic vascular resistance can be computed (the CVP value used in the calculation of systemic vascular resistance is obtained via the central venous catheter used for indicator injection). Combining the calculation of stroke volume with GEDV, a global ejection fraction (GEF) can be further calculated (GEF = SV/GEDV). With continuous measurement of arterial pressure via the arterial catheter, the maximum rate of pressure increase (dP/dt\_max) can be calculated. Both GEF and dP/dt\_max might be considered indexes of ventricular “contractility” (19), but such indexes are also known to be sensitive to changes in ventricular afterload. Furthermore, it can be anticipated that instances of isolated (right vs. left) depressed ventricular contractility (during myocardial infarction, pulmonary embolism, increased pulmonary vascular resistance associated with ARDS, etc.) would not be accurately reflected by such “global” indexes.

Katzenelson et al. (52) calculated a “pulmonary vascular permeability index” as EVLW/ITBV, reasoning that ITBV would be increased in cases of increased hydrostatic pressure pulmonary edema but should be normal or low during instances of increased permeability pulmonary edema. In their study, this index was able to accurately separate out patients with these two types of pulmonary edema, as judged by clinical criteria.

The continuous measurement of arterial pressure via the arterial catheter can be used to estimate CO on a beat-by-beat basis by so-called “pulse contour analysis” (27, 29, 43, 110) after a calibration step that incorporates a thermodilution measurement of CO. The theory, justification, and empirical evidence supporting the accuracy of this approach to monitoring CO are beyond the scope of this review.

All of these derived variables could arguably provide valuable information to guide patient care in the appropriate circumstances, but none have, to our knowledge, been tested in formal management algorithms.

**Data Derived From Esophageal Doppler Measurements**

Hemodynamic evaluation via esophageal Doppler monitoring (EDM) has become another attractive alternative to PAC in recent years because it is less invasive than methods that require vascular catheterization, easier to initiate [can be entirely managed by nursing personnel (68, 104)], and easier to interpret (if one understands certain cardinal assumptions and limitations). The concepts behind the technique were first introduced by Side and Gosling (95) and later refined by Singer et al. (100).

The ease of insertion and rapid retrieval of hemodynamic data are key advantages of EDM. The EDM probe is inserted through the mouth like an orogastric tube and usually requires only a few minutes for proper positioning (39, 86, 97, 100). Because the probe is relatively stiff, most patients (but not all) require at least moderate sedation if they are to tolerate probe insertion (3). Since the most common indication is shock, most patients are already sedated while receiving mechanical ventilatory support. [A new probe that can be inserted nasally in awake patients has been reported recently (109).]

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The probe is gently advanced ~35–40 cm from the teeth until the tip is in the midthorax. The probe is then rotated posteriorly until the transducer faces the aorta, and the aortic velocity waveform is visualized on a dedicated monitor and Doppler flow is audible. Signal optimization occurs by slowly rotating the probe; small changes in the depth of insertion along with adjustments to the noise filter and gain setting are made to obtain the highest peak velocity and best outline of the waveform. An optimal signal produces a waveform with minimal spectral dispersion and the loudest auditory signal. The probe can move within the esophagus between serial measurements and therefore needs to be repositioned before each measurement. The technique of probe insertion is relatively easy to learn with low inter- and intra-observer variability, and most operators become proficient after 10–12 probe insertions (37, 61, 105). Despite the theoretical concern of esophageal injury with the probe, the procedure appears to be relatively safe, as we have been unable to identify any literature reporting complications associated with placement of the probe. Recommended absolute contraindications include recent esophageal surgery or the presence of congenital or acquired esophageal abnormalities (strictures, varices, or fistulae).

**Measurements of flow.** CO is measured during EDM by first estimating cardiac stroke volume from Doppler blood flow velocity measurements in the descending aorta. Originally, Huntsman et al. (51) measured velocity in the aortic outflow tract using a suprasternal Doppler probe. However, this approach was abandoned because the position of a handheld probe is difficult to stabilize and standardize, especially for repeat measurements, and because this location provides a relatively poor ultrasound window. Instead, with EDM, the aortic blood velocity measurements are obtained via a Doppler transducer secured to the tip of a probe placed in the middle esophagus, optimally at the level of the left atrium (23, 95). The frequency of the Doppler pulsed wave depends on the probe manufacturer but is normally between 4–5 MHz.

Blood velocity \( v \) is computed from the Doppler relationship

\[
v = \frac{f_A c}{2f_0 \cos \Theta}
\]  

(16)

where \( v \) is velocity of erythrocytes, \( f_A \) is Doppler shift frequency, \( f_0 \) is transmitted frequency, \( c \) is velocity of sound in blood, and \( \Theta \) is the angle between the ultrasound beam and the blood flow vector (the so-called “angle of insonation”).

The area under each waveform (the integral of velocity during the ejection time) is called the “stroke distance” (SD) (Fig. 9), i.e., the distance traveled by blood in the descending aorta during each systole (cm). SV is then computed simply as

\[
SV (\text{cm}^3 = \text{ml}) = SD \times CSA (\text{cm}^2)
\]  

(17)

where CSA is cross-sectional area of the aortic lumen. In practice, the conversion of SD to SV is performed using a nomogram to compute the CSA based on the patient’s age, weight, and height, as well as the proportion of blood flow distributed between the descending aorta vs. branches of the aortic arch. We have not been able to find a published version of the nomogram, and the only validation we have encountered is the assertion by Dark and Singer (24) in their meta-analysis that the strong overall correlation observed for CO obtained by EDM vs. thermodilution measurements of CO (COth) in the studies included in that analysis should serve as, essentially, a validation of the nomogram.

For Eq. 17 to be valid, the velocity flow profile within the aorta should be “flat” (i.e., the velocity should be the same at any given point across the aortic lumen), and CSA should be constant during systole. Whereas flow in the descending aorta may be somewhat parabolic, with faster flow at the center of the vessel compared with the periphery (34), the differences, in the absence of aortic pathology that would create turbulent flow, are unlikely to be significant (98).

Errors in the angle of insonation (assumed to be 45° in Eq. 16) will be magnified in the calculation of SV because of the effect that taking the cosine has on the angle term in the equation. Although the magnitude of error would be less if the true angle was <45° (again, a function of the cosine), a smaller angle would also result in less signal transmitted back to the probe from blood flowing in the nearby aorta. Thus the 45° angle represents a compromise between the need for signal quality and the potential for producing error if the true angle is a value other than 45°. As long as the aorta and esophagus are parallel to one another, it can be reasonably assumed that this angle will be maintained when measuring CO by EDM. However, with a tortuous aorta or deforming chest wall pathologies (e.g., scoliosis), this assumption will not be valid. The most likely outcome will be for the Doppler velocity to be underestimated. The frequency of this problem in using EDM in the ICU has not been studied.

The estimate of SV based on Doppler flow measurements in the distal aorta obviously does not take into account that portion of cardiac SV that is delivered to the head and upper
extremities. The most common solution\(^8\) simply assumes a constant distribution of blood flow between the brachiocephalic and coronary arteries (30%) vs. the descending aorta (70%). This artificial partitioning of flow can be affected by multiple clinical situations [e.g., cardiac surgery (66, 81)], but the extent to which this partitioning of CO is altered by or during critical illness has not been studied.

An alternative approach\(^9\) incorporates an M-mode echo transducer into the esophageal probe, allowing aortic diameter to be measured at the same time as flow velocity. Although commercially available, there are very few studies of the accuracy of this device at present.

CO, as measured by EDM, has been compared with CO\(_th\) in multiple clinical settings, including the operating room and the medical/surgical ICU. Laupland and Bands (60) reviewed such comparison studies performed as early as 1985 and found that they varied considerably in quality, including inadequate blinding. Nevertheless, they identified a good overall correlation between CO determined by the two techniques (\(R^2 = 0.79\), range 0.25–0.96), minimal bias (median \(-0.01\), range \(-1.38\) to 2 l/min), and fair precision, as assessed by Bland-Altman limits of agreement (24). Their analysis identified the utility of detecting trends in CO by EDM with low intra- and inter-observer variation. The analysis included 558 patients, and a successful probe insertion was achieved in 97% of subjects.

Dark and Singer (24) published a more recent meta-analysis of studies between 1989 and 2003, comparing EDM estimates of CO with those derived from simultaneous measurement of CO\(_th\). Twenty-one validation studies for EDM were identified involving 314 patients and 2,400 paired measurements. An example of the correlations from one of these studies is shown in Fig. 10. The pooled median bias for CO\(_th\) vs. EDM was only 0.19 l/min (range \(-0.69\) to 2.00 l/min) for absolute measurements of CO and 0.6% for detecting changes in CO. The pooled median percentage of clinical agreement for CO\(_th\) vs. EDM was only 52% (interquartile range 42–69%) for CO and a more robust 86% (interquartile range 55–93%) for changes in CO. Like Laupland and Bands (60), these authors also concluded that EDM has high validity (minimal bias and high clinical agreement with CO\(_th\)) for monitoring changes and trends in CO during patient management but has limited clinical agreement with any single thermodilution measurement of CO.

Estimates of intravascular volume. The width of the Doppler waveform base corresponds to the systolic ejection time; when corrected for the patient’s heart rate (in a manner similar to correcting the electrocardiographic QT interval for differences in heart rate), it has been labeled as the corrected flow time (FTc)

\[\text{FTc} = \frac{\text{flow time}}{\sqrt{\text{cycle time}}}\]  

(18)

The FTc has been shown to vary inversely with systemic vascular resistance (SVR; Ref. 100). One reason for an increased SVR, of course, is hypovolemia, and indeed a narrow waveform base (short ejection time) would be expected with small stroke volumes, as might occur during hypovolemia. In such a case, a fluid challenge should increase circulating blood volume, increase SV, and prolong FTc, widening the waveform base. Accordingly, a number of studies have compared FTc with PAOP, pulmonary artery diastolic pressure, or echocardiographic measures of left ventricular size, either directly to one another or as predictors of CO.

For instance, Singer and Bennett (99) compared changes in PAOP and FTc in 43 ventilated ICU patients. They found that in hypovolemic patients, there was a matched increase in PAOP and FTc.

DiCorte et al. (30) compared the FTc and PA diastolic pressure (PAD) in 20 patients undergoing coronary artery bypass grafting. They correlated these measurements to the end-diastolic short-axis area (EDA) measured by transesophageal echocardiography and found that the FTc correlated better (\(R^2 = 0.24\)) with the EDA than did PAD. A small trial by Madan et al. (65) in 14 surgical ICU patients, using 118 matched data sets, found that the FTc correlated better with CO\(_th\) than did PAOP.

Other studies have evaluated incorporating FTc into management algorithms for fluid therapy (21, 36, 40, 74, 75, 96, 106). Virtually all of these studies have been performed in surgical or postoperative settings. For instance, Monnet et al. (74) studied the response to a 500-ml normal saline fluid challenge, given over 10 min, in 38 ventilated patients, in sinus rhythm, with no spontaneous breathing activity. An FTc below 277 ms predicted a response of >15% increase in CO with a sensitivity of 55% and a specificity of 94%.

Thus overall, the evidence that incorporating EDM measurements of CO and FTc into management algorithms in the operative or perioperative setting improves outcome is robust. Evidence that FTc is a better predictor of improved cardiac performance than PAOP is also strong. However, the coefficients of determination between FTc and measures of cardiac performance are not nearly as good as with ITBV as a predictor. Thus, at this point, it would appear that when both technologies are available, the clinician must choose between the ease of use of the EDM vs. the greater predictive power of...
measuring ITBV, which requires both central venous and arterial cannulation.

Other variables. Information other than CO and FTc can be derived from the analysis of the Doppler velocity-time curve, including peak velocity and mean acceleration of flow. These variables are related to cardiac contractility but are also affected by changes in systemic vascular resistance (“afterload”). To our knowledge, there have been no studies of how this additional information might affect management or outcome in critically ill patients.

Summary and Conclusions

The theory underlying the measurement of flow and volume via thermal indicator dilution methods is well established. Likewise, the empirical validation of the estimates of flow and volume against gold standards such as the Fick measurement of CO or gravimetric measurements of lung water are also robust in that multiple studies using a variety of instruments have repeatedly reported good-to-excellent correlations in both animals and humans. This empirical database, however, is less extensive for the downslope method of estimating volume, especially in instances of disease.

The theoretical foundation for estimates of CO via the Doppler method is also sound, and the empirical database supports a strong correlation between Doppler estimates and thermodilution or Fick measurements of CO. Whereas there is little systematic bias, the limits of agreement for differences between the Doppler estimates of flow and the reference method are significant. The empirical database supporting the use of FTc as a marker of intravascular volume is encouraging but still relatively limited. When using FTc for such a purpose, its sensitivity to differences in systemic vascular resistance (afterload) must be kept in mind.

The weakest set of data concerns the clinical utility of both transpulmonary thermodilution and esophageal Doppler measurements, including the plethora of variables that can be derived from the primary data. As Pinsky has noted (84), preload is not the same thing as “preload responsiveness.” In other words, simply making a hemodynamically relevant measurement, regardless of accuracy, does not necessarily predict how the patient will respond to a therapeutic intervention based on that measurement or how that response will translate into a desired patient outcome. The FACTT study could easily, and in fact, would suffocate attempts to advance patient care through the conduct of appropriate clinical studies that will allow clinicians to choose which of these most recent types of hemodynamic measurements will help them improve the outcome of their patients.

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