Indicator dilution measurements of extravascular lung water: basic assumptions and observations

Richard M. Effros, Prapaporn Pornsuriyasak, Janos Porszasz, and Richard Casaburi
Los Angeles Biomedical Institute at Harbor-UCLA Medical Center, Torrance, California

Effros RM, Pornsuriyasak P, Porszasz J, Casaburi R. Indicator dilution measurements of extravascular lung water: basic assumptions and observations. Am J Physiol Lung Cell Mol Physiol 294: L1023–L1031, 2008. First published March 21, 2008; doi:10.1152/ajplung.00533.2007.—Since they were introduced more than five decades ago, a variety of single-pass indicator, thermal, and osmotic dilution approaches have been developed for detecting and measuring excess fluid in the lungs. This brief review discusses why studies of the extravascular lung water (EVLW) continue to intrigue physiologists and clinicians and the likelihood that they will become sufficiently reliable for more widespread use. Emphasis is placed on the basic assumptions that underlie these measurements and limitations imposed by the nature of the data that are collected. A distinction is made between approaches that are based on compartmental models of solute and water exchange and those that represent extensions of more conventional washout procedures, which have been utilized extensively for measurements of gas volumes in the lungs.

Although the compartmental approach has been used to simplify indicator dilution studies by eliminating the need for a vascular indicator, it is based on assumptions that may not be realistic. Early recirculation inevitably limits the period in which observations can be made and impairs detection of those portions of the lungs with decreased perfusion. These general principles are also used to develop a new method of analyzing osmotic transient studies. A short account is given of EVLW observations that have been made in animals and humans. Both the sensitivity and specificity of EVLW measurements in humans are uncertain, and the normal clinical range of EVLW remains in doubt.

acute lung injury; adult respiratory distress syndrome; pulmonary edema; dye dilution techniques

THE PERENNIAL QUEST to find a practical and reliable method for detecting and measuring excess water in the lungs of patients with transudative and/or exudative pulmonary edema has recently grown more urgent because of concerns regarding the safety of pulmonary artery catheterization in critically ill patients (8, 56). Although measurements of pulmonary artery occlusion pressures do not provide a direct measurement of the amount of fluid in the lungs, they can indicate the presence of elevated left atrial pressures, which tend to promote edema formation. Nor have conventional measurements of gas exchange or pulmonary mechanics proven either specific or sensitive for following the progress of lung injury in patients with pulmonary edema due to diffuse lung damage. Routine chest X-rays can be useful but do not provide quantitative information. In theory, advanced imaging approaches could provide valuable information, but these are difficult to use in an intensive care environment.

It is therefore not surprising that efforts have been made to resuscitate and perfect older techniques that were designed for bedside measurements of extravascular lung water (EVLW), including single-pass indicator dilution procedures (33, 50, 78). Most of these approaches are based on simultaneous intravenous injections of indicators that rapidly exchange with lung water (e.g., labeled water, ethanol, osmotic transients, or heat) and those that remain in the vasculature (usually labeled plasma proteins and/or red blood cells). Estimates of lung water are made from the manner in which these indicators subsequently emerge in the systemic arterial blood. In more recent studies, a single thermal or osmotic indicator has been used to estimate the EVLW.

Although many studies of EVLW have been reported (see below), controversy persists regarding the reliability and usefulness of these approaches. Justification for these measurements must be based in part on conceptual analysis and consideration of the assumptions that are made.

Early Procedures

Chinard and Enns (14) were the first to use bolus injections of solutions containing a dye bound to serum protein (Evans blue) and labeled water to study exchange between the blood and tissues of canine lungs (Fig. 1). They noted that the emergence of labeled water from the lungs was delayed compared with Evans blue dye. Because initial concentrations of labeled water were lower than those of dye, they concluded that much of the injected tritiated water had left the pulmonary circulation during a single transit through the lungs.

Lillienfield et al. (44) and Anthonisen and Crone (3) subsequently used a similar approach to show that the water content
of the lungs was increased in patients with congestive heart failure. Following bolus injections into the pulmonary inflow, concentrations of the water indicator (e.g., D₂O or alcohol) are initially less than those of the vascular indicator, indicating loss into the tissues (Fig. 1, area A). The subsequent return of the water label into the vasculature is indicated by the later increase in its concentration above those of the vascular indicator (Fig. 1, area B). These investigators assumed that concentrations of the water indicator were the same in the lung tissues and blood at the time of the crossover (t_{equil}, indicated by an asterisk). They calculated the net quantity (m) of the water indicator that had entered the tissue at t_{equil} from the product of the area A and the cardiac output (Q)

\[ m = Q \int_{t_0}^{t_{equil}} (c_{vasc} - c_{water})\,dt \]  

where t₀ indicates the time at which the intravascular indicator appears in the outflow and c_{vasc} and c_{water} designate the concentrations of the vascular and water indicators at time t. The EVLW was then calculated from the equation

\[ \text{EVLW} = m/c_{water,\text{equil}} \]  

where c_{water,\text{equil}} designates the concentration of the water indicator at t_{equil}.

This approach makes the unnecessary assumption that concentrations of water indicator in the tissues and blood are the same at t_{equil}. There are a number of reasons for doubting that concentrations of any label ever become uniform throughout the lungs after a transient injection. Because there is considerable variability in the transit times of indicators through the lungs, it can be anticipated that the injected indicators reach the pulmonary vessels at different times and that some of the labeled water may be leaving some of the exchange vessels and returning to others at the very same time. Furthermore, the ratio between the extravascular-to-vascular volumes may differ in various regions of the lungs, thereby altering concentrations of D₂O relative to those of the vascular indicator in blood emerging from these areas. Instantaneous equilibration of labeled water throughout the lung tissues would result in the emergence of this indicator before the vascular indicator, which must be delivered to the pulmonary veins by convection within vessels rather than diffusion across cell membranes. Since this has never been seen, this model of exchange has been abandoned, although a comparable analysis has been revived in recent osmotic studies (see below).

Steady-State Infusions and the Mean Transit Time Approach

Equilibration of indicator concentrations between the blood and tissues can only be expected when the indicators are infused at a constant rate over a sufficiently long interval. Under these circumstances, outflow concentrations of the indicators reach maximal values that equal those in the inflow and the compartmental volume. This approach is analogous to the conventional nitrogen washout approach used to measure the volume of gas in the lungs at the functional residual capacity. Because they are analogous, it is useful to compare the similarities and differences in these procedures.

In nitrogen washout studies, patients inhale pure oxygen from functional residual capacity, and measurements are made of the total volume of nitrogen (V_{N₂}) recovered in the exhaled air over a period of 7 min or more. This approach is very "robust" since it only assumes that nitrogen represents ~80% of the gas in all portions of the lungs before washout and that all of the nitrogen that was in the lungs is recovered. The amount of gas in unventilated regions consequently remains unmeasured. The rate of washout and the relative roles of diffusion and convection can vary during washout. Even the lung volume can change during washout since the volume calculated represents the volume at the beginning of the washout procedure. The volume of air in the lung (plus the volume in the dead space of the equipment) at the start of washout is calculated as V_{N₂}/0.8.

In an analogous fashion, all of the unlabeled blood in isolated lungs could be flushed out of the lungs by pumping saline or "labeled" blood into the pulmonary artery and collecting the entire pulmonary venous outflow. Under these circumstances, the intrathoracic blood volume (ITBV) would be measured (Fig. 1). It is assumed that all of the unlabeled blood is collected, but the rate at which the lung is perfused with the new fluid does not have to be constant. Nor is it assumed that the volume of the pulmonary vascular volume remains constant. However, it is assumed that there is no recirculation of the fluid used to perfuse the lungs during the period of the study. The volume of unlabeled blood recovered indicates the pulmonary vascular volume when the infusion began. A similar method could be used to replace unlabeled water in the central blood volume and lung tissues by perfusing the lungs with an appropriate water indicator.

Rather than replacing the entire cardiac output with vascular and water indicators (for example, indocyanine green and labeled water), these indicators are usually injected as a bolus into a systemic vein, and concentrations are monitored in the arterial blood (Fig. 1). It is assumed that the cardiac output and the vascular and water content remains constant during the study and that the indicator bolus becomes well mixed with the inflow. It is also assumed that the distribution of transit times
of the indicators remains unchanged between the sites of injection and collection and that this function is not influenced by the concentration of indicators.

Although labeled water was originally used as the water indicator, this was subsequently replaced with a thermal signal, which avoids isotopic exposure and is readily measured in the pulmonary outflow. In a typical study, a 20-ml bolus of a cold (4°C) isotonic solution (0.9% NaCl) containing a dye (indo- cyanine green) is rapidly injected into a central venous catheter, and concentrations of the dye and the temperature of blood in a peripheral artery or aorta are measured and plotted against time (63). An advantage of a thermal signal is that it is ~100 times more diffusible than labeled water in aqueous solutions and can presumably reach some poorly perfused regions of the lung. As reviewed by Lewis et al. (43), early studies showed that the thermal signal reached a distribution volume that approached the weight of water in the lungs, whereas the volume of distribution calculated for labeled water was generally between 50 and 70% of the water content of the lungs.

Both the vascular and extravascular volumes of the lungs can be calculated from the products of the cardiac output and the mean transit times (\( t \)) of the vascular and extravascular indicators.

\[
\begin{align*}
\text{ITBV} &= \dot{Q} \bar{t}_{\text{vasc}} \\
\text{ITVV} &= \dot{Q} \bar{t}_{\text{water}} \\
\text{EVLW} &= \text{ITTV} - \text{ITBV} = \dot{Q}(\bar{t}_{\text{water}} - \bar{t}_{\text{vasc}})
\end{align*}
\]

Where ITBV is the intrathoracic blood, ITTV is the intrathoracic thermal volume. (See Supplemental data for this article, available online at the AJP-Lung web site, and Refs. 49, 42, and 80 for derivation of these equations and calculation of \( \dot{Q} \).)

It should be emphasized that these equations do not assume any model of indicator transport, which can include a complex mixture of diffusional and convective processes. This analysis can be extended to indicators that are distributed heterogeneously between organ compartments, and this approach has been used to determine tissue pH (16).

Meier and Zierler’s analysis (49) of mean transit times following bolus injections was originally applied to intravascular compartments, in which it was assumed that the intravascular indicator labeled convectional movements of fluid in the blood. Extension of this approach to indicators that diffuse into extravascular compartments was accomplished more than a decade later, when it was used to estimate both lung compartmental volumes and the concentrations of extravascular and intracellular indicators that would prevail during constant infusions (13, 16). Although various “labels” are used in these studies, they need not behave in the same manner as any unlabeled constituents already present in the blood.

Osmotic Volume of Distribution

Injections of hypertonic solutions have also been used as an alternative indicator for estimating the EVLW volume. The effect of these solutions to dehydrate the lungs has been monitored in the pulmonary outflow by either measuring 1) the dilution of intravascular indicators (19, 2) the gravimetric density of this blood (35, 37), or 3) the velocity of sound through the blood (24, 45). We originally injected small volumes of hypertonic saline, sucrose, or urea into the jugular veins of anesthetized dogs and collected serial samples of blood from the carotid artery (18, 19). Extraction of water from the pulmonary parenchyma was followed by monitoring dilution of blood emerging from the lungs. By measuring concentrations of hemoglobin, plasma protein, osmolality, labeled red cells, and plasma, Na⁺, and Cl⁻, it was possible to show that bolus injections of hypertonic solutions result in the extraction of water from the lungs that was relatively free of electrolytes and other small solutes. This observation was consistent with the assumption that these hypertonic solutions rapidly dehydrate the cellular compartments of the lung, which allow rapid flow of water across cell membranes but resist the movement of electrolytes and other lipophobic solutes. It has subsequently been shown that much of the water that crosses cell membranes passes through aquaporin channels (1, 11, 17, 38).

In a recent clinical study, estimates of lung water were made using injections of hypertonic saline (5 g/dl) in patients undergoing dialysis (45). The venous and arterial catheters provided convenient access for injections and analysis of arterial blood. Since fluid overload with pulmonary edema is a frequent consequence of renal insufficiency, this is an important group to study. Rather than directly measuring concentrations in the pulmonary outflow (i.e., the arterial blood), the investigators monitored the velocity of sound through the catheters, which decreases when protein and red blood cell concentrations fall. The expected effects of such injections on serum osmolality and protein concentrations are shown in Fig. 2. Sequential injections are made of isotonic and hypertonic saline. It is assumed that the passage of the hypertonic bolus through the pulmonary circulation remains about the same as that of the isotonic bolus and that the osmolality of the blood emerging in the arterial catheter following the hypertonic injection can be calculated from the isotonic curve. As indicated in Fig. 2, the movement of hypertonic saline though the circulation results in a flow of water from the tissue to the blood and a correspond-
indicating fall in the velocity of sound in the blood entering the arterial catheter. This is presumably associated with contraction of the extravascular volume with an increase in the osmolality of the pulmonary tissues. Once the hypertonic solution has left the pulmonary circulation, water returns to the hypertonic tissues, resulting in an increase in blood protein concentrations and sound velocity. The osmolality of the tissues fall and the EVLW is restored to its original volume.

As in early studies of labeled water exchange (3, 44), the authors have inappropriately assumed that equilibration of the osmotic transient occurred at some time during the transient study. Equilibration of osmolality in the lungs can only be expected during constant infusions. In theory, the response of the osmotic and protein concentrations emerging from the lungs during a constant hypertonic infusion can be calculated from the transient injections by integrating both the protein (sound velocity) and osmotic pressure curves (estimated from the isoosmotic injections). This could be readily accomplished by summing successive points along the putative osmotic and protein curves derived from successive injections of isotonic and hypertonic saline.

The maximal osmolality ($c_{\text{osm, max}}$) that the blood would reach after a constant infusion of hypertonic saline can be calculated by integrating the osmolalities observed following a bolus injection

$$c_{\text{osm, max}} = c_{\text{osm,0}} + \int_0^t (c_{\text{osm,t}} - c_{\text{osm,0}}) dt$$

where $c_{\text{osm,0}}$ is the osmolality of the blood before the hypertonic saline injection and $c_{\text{osm,t}}$ is the osmolality at time $t$. As indicated above, $c_{\text{osm,0}}$ is estimated from the response to an initial injection of isotonic saline but would be better estimated by including an intravascular dye such as indocyanine green in the injections solution and measuring dye concentrations as well as those of protein in the blood emerging from the lungs.

After a prolonged infusion of the hypertonic saline, the amount of fluid removed from the lung ($\Delta$EVLW) can be calculated by integrating the fall in serum protein concentrations observed after a bolus injection

$$\Delta\text{EVLW} = \frac{\int_0^t (c_{\text{prot,t}} - c_{\text{prot,0}}) dt}{Q}$$

where $c_{\text{prot,0}}$ indicates the baseline protein concentration and $c_{\text{prot,t}}$ designates the protein concentration at time $t$. For the sake of simplicity, the cardiac output is assumed approximately constant.

If the total quantity of osmoles in the EVLW remains constant, then:

$$c_{\text{osm,0}} \Delta\text{EVLW} = c_{\text{osm, max}}(\text{EVLW} + \Delta\text{EVLW})$$

$$\text{EVLW} = \frac{c_{\text{osm, max}}}{c_{\text{osm,0}} - c_{\text{osm, max}}} \Delta\text{EVLW}$$

Although integration of osmotic bolus studies to estimate lung water has not been reported, constant infusions of hypertonic solutions have been used to estimate the total amount of water in the lungs in isolated dog lungs suspended from a weight transducer (66). Only half of the lung water was detected. This discrepancy can be attributed to heterogeneous perfusion of the lungs and to the likelihood that the reflection coefficients of the tissue membranes to sodium chloride are less than 1.0. A low reflection coefficient would indicate that sodium chloride leaks into the tissues, thereby reducing its osmotic efficiency. There is evidence that hypertonic injections selectively dehydrate the parenchymal cells rather than the pulmonary interstitium (19, 88). Estimates of lung water using osmotic challenges may exclude the extracellular fluid in the interstitial and alveolar compartments from estimates of the EVLW. Since accumulation of fluid in the interstitium and alveolar compartments is more likely to interfere with gas exchange in the lungs than cellular edema, this could diminish the usefulness of osmotic measurements of EVLW.

Other problems with the osmotic bolus approach should also be kept in mind. Injections of hypertonic solutions (including radioopaque dyes) are associated with transient hypotension and reduced lung perfusion related in part to decreases in deformability of red blood cells (18, 71). Since injections of hypertonic saline are associated with transient changes in blood flow and the hematocrit of blood emerging from the lungs, the assumption that the outflow patterns of isotonic and hypertonic saline remain the same may therefore be unjustified.

### Intrinsic Limitations of Indicator Dilution Measurements of Lung Water

The most serious problem associated with any indicator dilution measurements of compartmental volumes is the potential failure of the injected indicators to reach all portions of the organ during the observation period. Since heat diffuses more rapidly than labeled water, it was hoped that thermal signals would reach more remote areas of the lungs. However, it can be calculated that the mean transit time of the thermal signal with a sphere 1 cm in diameter would be nearly 39 s, which is about twice the time at which recirculation of indicators occurs (20). Furthermore, heat can exchange with adjacent tissues such as the walls of the heart and vessels, the pleura, and even the gas phase in the air spaces and nonaqueous tissue constituents. Evidence for equilibration with the cardiac walls has been described (61), although this was not always detected in another report (9).

A second and related problem of indicator dilution measurements of vascular and water volumes in the lungs is the method used to correct for recirculation of indicators. Following injection into a systemic vein, recirculating indicators can be detected in the systemic arterial blood within 20–30 s in resting subjects (20) and sooner when cardiac output increases. To remove recirculation from the indicator dilution curves, it is generally assumed that the concentrations of these indicators fall monoeXponentially. These extrapolations are usually graphed on semilogarithmic coordinates, and the downslopes are calculated between the times when concentrations have fallen from 85 to 45% of peak values (33). Justification for this procedure is based on the assumption that the central vascular and total lung water volumes can be modeled as single compartments that empty monoeXponentially. There is, however, relatively little evidence for this premise. If lung perfusion is heterogeneous, multiexponential washout patterns would be expected. It is not possible to distinguish between recirculation and a multiexponential outflow pattern on the basis of the indicator dilution curves.
Even in normal lungs, pulmonary vascular perfusion is distinctly heterogeneous, in part because of gravitational forces, and perfusion is influenced by position and cardiac output (89). Increased perfusion of the upper lobes probably plays an important role in the observation that estimated values of lung water increase in normal animals and humans with exercise (27, 29, 30). Pulmonary perfusion becomes further disturbed in patients with lung disease: pulmonary emboli were evident in 20 of 21 patients with ARDS, and fibrocellular intimal obliteration of arteries and veins is common in those surviving beyond 10 days (26, 84). Other factors that can reduce perfusion to injured areas of the lungs include pneumonia, pleural effusions, atelectasis, reduced cardiac output due to shock, increased bronchial artery flow, and increased airway pressures related to the mode of ventilation (7, 15, 26, 68, 69). A variety of studies have shown that acute obstruction of the pulmonary vasculature with PEEP, emboli, and vascular occlusion is usually associated with a reduction in the measured EVLW (2, 4, 76, 85).

It should be noted that if one area of the lung is poorly perfused, the error in calculating the lung water volume can be considerable, even though the calculation of cardiac output is only slightly affected. An extreme but not improbable example is instructive: if 95% of the cardiac output goes to half of the total lung tissue, and 5% perfuses the remainder, the error in calculating the cardiac output will be only 5%, but the error regarding the total extravascular water volume will be 50%. Indicators in blood leaving the underperfused lung would tend to arrive late, after recirculation has occurred and would not be accounted for by the assumption of a monoexponential downslope. Much information regarding regions of the lung with slower perfusion is presumably lost by the arbitrary practice of deleting data after indicator concentrations fall to 45% of peak values.

It is particularly instructive to compare the efficiency with which nitrogen is washed from the air spaces in measurements of functional residual capacity with that of flushing unlabeled water from the lungs. Patients inhale 100% oxygen for 7 min or longer to ensure that nitrogen concentrations have fallen to <2% before collection of the exhaled gas is terminated. The pattern of nitrogen washout is not monoexponential and may be very complex in patients with lung disease. In contrast, concentrations of the thermal gas is terminated. The pattern of nitrogen washout is not monoexponential and may be very complex in patients with lung disease. In contrast, concentrations of the thermal water label remain at ~45% peak levels when recirculation occurs, and the subsequent washout of this signal remains undefined, and the assumption of a monoexponential decline remains unproven.

A correction can in theory be made for recirculation if blood is sampled at a site proximal to the site of injection (Fig. 1) or in the pulmonary artery. Using this approach, evidence has been obtained that the outflow curves of neither vascular nor thermal indicators are monoexponential (7, 47). These “deconvolution” procedures are probably too difficult for routine measurements, and measurements of lung water will always be difficult because the EVLW normally represents only ~30% of the total amount of water between the sites of indicator injection and collection after labeled water injections (16), although perhaps somewhat more after thermal injections.

Single Indicator Dilution Studies of Lung Water

To facilitate indicator dilution measurements of EVLW, recent studies have been conducted using only the thermal transients without intravascular indicators. These studies are based on a very early theoretical approach of Newman et al. (58), who developed a monoexponential compartmental model to calculate the volume of the pulmonary vasculature.

The simplest compartmental model (Fig. 3) is a single, well-mixed chamber with a volume, V, in which mixing is instantaneous, and concentrations, c, of an indicator, M, are uniform throughout the chamber. M is delivered to the chamber in the blood flow at one inflow site (e.g., the pulmonary artery) and leaves at an outflow site (e.g., the aorta). If the concentration of m entering the compartment in the inflow blood is \( \theta \) and that in the outflow is c, then

\[
\frac{dm}{dt} = -Qc \tag{9}
\]

where \( m \) designates the quantity of M remaining in the exchange volume.

Since concentrations of M are assumed to be uniform,

\[
m = cV \tag{10}
\]

\[
dc/dt = -(Q/V)c \tag{11}
\]

Solution of equation (12) yields

\[
c = c_0e^{-kt} = c_0e^{-(Q/V)t} \tag{12}
\]

where \( k \) is the rate constant, c is the outflow concentration at time \( t \), and \( c_0 \) is the initial outflow concentration. Since \( V/Q = t \) (see above and Fig. 3), \( r \) can be readily derived from the inverse of the downslope \( k \) of the indicator outflow curve plotted on semilogarithmic coordinates (Fig. 3). This relation-
ship can also be shown by substituting Eq. 13 into the mean transit time equation, see Supplement.) The value of \( t \) is governed by the ratio of the volume of distribution (e.g., the volume of water in the vascular space for an intravascular dye or the volume of water in the vascular plus the lung water space for the thermal transient) to the blood flow.

Newman et al. (58) assumed that following injection through a central venous catheter, the vascular indicator traverses a series of three well-mixed compartments: the right side of the heart, the pulmonary vasculature, and the left side of the heart and arteries up to the point of collection in a peripheral artery or aorta. They also assumed that the pulmonary blood volume (PBV; see Fig. 4) represents by far the largest of these compartments and is primarily responsible for determining the downslope in the outflow curve.

This compartmental analysis of the manner in which vascular indicators are washed out of the lungs has been criticized on several important grounds (31, 87). There is little reason to believe that 1) the pulmonary vascular compartment represents most of the intrathoracic vascular volume, particularly when there is distention of the cardiac chambers, or that 2) it empties as a single well-mixed compartment. Using Newman’s published data, Grodins (31) calculated that the volume of blood between the pulmonary veins and the carotid artery averaged 60% of the volume between the right atrium and carotid artery, arguing against the assumption that the pulmonary vasculature is the largest compartment. Although the Newman approach is based on an analysis of series compartments, it does not consider the possibility of parallel compartments, which are associated with multieponential washout patterns.

These considerations, as well as the development of the mean transit time approach, led to the general abandonment of the Newman technique for nearly five decades. However, in a recent reincarnation of the Newman model, the downslope of the thermal rather than the intravascular indicator curve is used to calculate what is referred to as a pulmonary thermal volume (PTV) (33, 40, 73, 75). It is assumed that the PTV comprises the intravascular volume plus the exchangeable water volume of the lungs (Fig. 4). In contrast, the total intrathoracic thermal volume (ITTV) is determined from the product of \( Q \) and the mean transit time of the thermal signal (Fig. 4). The difference ITTV-PTV purportedly represents all of the blood in the central circulation except for the pulmonary vascular volume and is referred to as the “global-end diastolic (blood) volume,” GEDV (Fig. 4).

Sakka et al. (75) compared the GEDV with the entire vascular volume (ITBV) calculated from the product of \( Q \) and the mean transit time of indocyanine green. They found that

\[
\text{ITBV} = 1.25 \times \text{GEDV} - 28.4 \text{ ml} \quad (13)
\]

in a study of more than 200 critically ill patients. However, it is usually assumed that

\[
\text{ITBV} = 1.25 \times \text{GEDV} \quad (14)
\]

Sakka et al. postulated that the ITBV exceeded the GEDV because the former includes the PBV, whereas the latter does not

\[
\text{PBV} = \text{ITBV} - \text{GEDV} = \text{ITBV} - (\text{ITBV}/1.25) = 0.2 \times \text{ITBV} \quad (15)
\]

Equation 15 indicates that the PBV constitutes only 20% of the total ITBV. This is contrary to the key assumption of Newman et al. (58) that the pulmonary vasculature represents the predominant mixing volume in the central circulation. It also seems very unlikely that this presumed anatomical relationship between the vascular volume within the lungs (GEDV) and the total central blood volume remains nearly the same in their entire population. Independent differences in pulmonary vascular and/or cardiac chamber volumes would be expected in patients in an intensive care environment. Since the stroke output from the right heart distends the pulmonary vasculature during systole, it is difficult to tell how much of the downslope of the thermal curve is determined by mixing in the PTV rather than the heart. Nor is it obvious how much of the larger pulmonary vessels contribute to mixing in the PTV. In view of uncertainty regarding the portions of the pulmonary circulation and lung tissue that effectively contribute to the PTV, the assumption that the PBV, PTV, and GEDV values represent what their names imply must also remain in doubt.

It has also been suggested that an increase in the ratio between GEDV and ITTV can be used to distinguish patients with congestive failure from those with noncardiac pulmonary edema (55). Aside from uncertainty concerning the interpretation of GEDV, this hypothesis ignores the fact that many patients with congestive heart failure have diastolic dysfunction with normal intracardiac blood volumes.

Two points (circles in Fig. 3) are used to draw the downslopes of each indicator for calculation of \( t_{\text{downslope}} = F/V_{\text{downslope}} \) in the monoexponential models. Similarly, two points (squares in Fig. 3) must be selected for extrapolation of the indicator dilution curves beyond the time that recirculation appears in the washout (noncompartmental) calculation of \( t_{\text{washout}} = F/V_{\text{washout}} \). These frequently use the same exponen-

\[
\begin{align*}
\text{MEAN TRANSIT TIME VOLUMES} & \quad \text{DOWNSLOPE VOLUMES} \\
\text{ITBV} & \quad \text{Dye Injections} \\
\text{Injection} & \quad \text{EVLW} \\
\text{SV RA RV PA} & \quad \text{Collection} \\
\text{ITTV} & \quad \text{ITTV} \\
\text{Thermal Injections} & \quad \text{PTV} \\
\text{EVLW} = \text{ITTV} - \text{ITBV} & \quad \text{Derived Volumes} \\
\text{GEDV} = \text{ITTV} - \text{PTV}
\end{align*}
\]
tial downslope (55). Under these circumstances, the only difference between the two curves is the upslope, which is incorporated in the \( t_{\text{washout}} \) calculation but is excluded in the \( t_{\text{downslope}} \) model. Because the upslope values of the curves are less than those of the downslope during the upslope interval, the overall curve is flatter, yielding a value for \( t_{\text{washout}} \) that is greater than that calculated for \( t_{\text{downslope}} \). The upslope values presumably reflect the heterogeneous manner in which the indicators traverse the pulmonary circulation.

At best, thermal indicator estimates of vascular volumes can only be considered convenient approximations for the intravascular volume that presumably would be more accurately calculated with an intravascular dye, such as indocyanine green.

Experience With Indicator Dilution Measurements of Lung Water

Despite these conceptual reservations concerning indicator dilution measurements of lung water, evidence has been reported suggesting that they may prove useful in the management of patients with various forms of pulmonary edema (see excellent reviews of Isakov and Schuster and Michael) (33, 50). Increases in EVLW have been described in cardiogenic pulmonary edema and ALI/ARDS, and EVLW appeared to fall with clinical improvement in many of these studies (5, 21, 22, 23, 30, 39, 41, 46, 48, 50, 53, 54, 55, 59, 67, 73, 77, 81, 83). A correlation between EVLW was seen with X-rays and CT examinations in some studies (46, 64, 83). A reduction in EVLW was seen in response to systemic \( \beta \)-agonists (65), and EVLW seemed to be useful in planning fluid administration (2, 54).

Although the approach retains much of its popularity, reports have appeared that question the reliability of EVLW measurements. EVLW tends to exceed gravimetric measurements when a thermal signal is used, especially when no vascular indicator is used (21, 36, 52, 57, 73, 75, 79). In one study, the volume of distribution of the thermal indicator averaged 76% more than that measured gravimetrically (86). Of particular concern was the observation that EVLW was in the normal range in 35% of patients with clinical ARDS/ALI (51). Nor were EVLW studies found useful in patients with burns (40), and calculated EVLW failed to increase in some forms of experimental edema (10, 34, 72). These observations suggest that measurement of EVLW may not be sensitive. Furthermore, there appears to be very little data available concerning the range of values EVLW determined with thermal injections in normal human subjects or patients with other disorders. Thus the specificity of EVLW measurements is also in doubt. It is generally accepted that the EVLW is normally below 7 ml/kg in humans, but this value appears to be based on limited data collected in animals (43), which might not be applicable to human studies. A recent study suggests that EVLW measurements should be indexed with ideal rather than observed body weight (64).

The Clinical Role of Indicator Dilution Studies of Lung Water

Although the introduction of procedures that can measure EVLW could be of some importance in patients with excess lung water, EVLW data can be very misleading (12, 20, 33, 82). A decrease in EVLW among individuals or groups of patients could either represent clinical improvement related to reabsorption of lung water or deterioration due to reduced perfusion of the pulmonary vasculature that might not be obvious from changes in vascular volumes. Equivocal data of this nature could put patients at some risk.

Validation of indicator dilution approaches must ultimately be based on comparison with gravimetric measurements, which can only be obtained in animal models or postmortem lungs. Although generally considered to be a “gold standard,” wet/dry ratios were originally used to detect transudative edema fluid, which contains relatively low protein concentrations and therefore has a high wet/dry ratio. Exudative fluid contains higher protein concentrations, and even inflammatory cells, which have less of an effect on the wet/dry weight ratio as transudates. In contrast, exudates should increase the measured volume of the EVLW nearly as much as transudates.

Reported correlations between gravimetric and indicator measurements in EVLW may partially reflect the fact that measurements of flow are much more accurate than those of mean transit time (see above). Since cardiac output is greater in larger subjects, the apparent agreement in these parameters can be related to differences in flow rather than EVLW. These studies should report whether there is any correlation of gravimetric measurements with mean transit time differences of the water and vascular indicators.

It can also be argued that it would be more useful to measure the extracellular volumes of the lung than the entire water volume, since fluid accumulation in the interstitial and alveolar compartments would be more likely to interfere with gas exchange than changes in the cellular compartment. Unfortunately, relatively little of conventional extracellular indicators (e.g., salts and sugars) diffuse out of the pulmonary vasculature during a single circulation. In any case, measurements of endothelial and/or epithelial permeability would provide more direct evidence for lung injury than any measurement of compartmental volumes.

From a clinical point of view, the sites of fluid accumulation may be as important as the volume of water that has entered the lungs. Characteristically, early fluid accumulation is restricted to the interstitial compartment. This generally has a relatively modest effect on gas exchange. In contrast, alveolar and airway flooding can rapidly lead to asphyxiation. Only radiologic approaches can make this distinction (25, 27). Furthermore, radiologic procedures can detect lung water in regions that are poorly perfused or ventilated. Whether advanced imaging techniques can be adapted to an intensive care environment remains uncertain.

REFERENCES


