Estimation of Extravascular Lung Water by Indicator-Dilution Techniques

By Francis P. Chinard

An abnormal increase in the volume of the extravascular fluid of the lungs can occur in cardiogenic pulmonary edema, the adult respiratory distress syndrome, and other situations such as the "shock lung" and the "wet lung." Knowledge of this volume can be important in assessing the threat to the patient and the efficacy of measures taken to alter hemodynamic pressures, solute concentrations, and water loads. Several extensive reviews of pulmonary edema have been published in the past few years (1-4), so the present review will focus on the measurement of extravascular lung water in vivo. Indicator-dilution techniques are emphasized, and the limitations and some possible extensions of these techniques are discussed. The clinical aspects of this measurement have recently been extensively reviewed by McCredie (5).

Because water is the major constituent of the lungs and the blood and because of the nature of the measurements, the amount of water rather than the amount of "fluid" in the lungs is considered. The total water content of the lungs includes the water in the vascular volume of the lungs. This volume, however, cannot be defined precisely and can vary without accompanying changes in lung tissue water. Accordingly, another measure of lung water, "extravascular lung water," has been devised. This measure is essentially a determination of the total water content of an operationally (not anatomically or functionally) defined region of the body. The water content of that portion of the vasculature included in the determination is subtracted from the total lung water content, and the difference is the extravascular lung water content.

THEORETICAL ASPECTS

The theoretical basis for the determination of extravascular lung water has been reviewed in a number of articles (6-10) and is presented in the appendix in condensed form.

The basic expression for the calculation of extravascular lung water, denoted in this paper as $\Delta V_{\text{weu}}$, is

$$\Delta V_{\text{weu}} = F_b \left( f_{p}(1 - Hct)(\bar{t}_w - \bar{t}_p) + f_r Hct(\bar{t}_w - \bar{t}_r) \right),$$

where $F_b$ is the flow of whole blood (g/sec), $Hct$ is the large-vessel hematocrit, $T$ is the mean transit time (seconds) calculated as it is in reference 11, $f_p$ is the volume/volume water fraction of plasma, $f_r$ is the volume/volume water fraction of red cells, and the subscripts $w$, $p$, and $r$ refer to water, plasma, and red cells, respectively. The quantity $\Delta V_{\text{weu}}$ is obtained in volumetric units (cm$^3$). This expression is equivalent to that proposed earlier by Goresky et al. (6) in which the mean transit time of a composite reference substance is used. Eq. 1 is accurate within limitations discussed later. Meier and Zierler (11) in their classic contribution demonstrated the necessity of using both red cell and plasma protein indicators to obtain true vascular volumes (as the sum of separately determined red cell and plasma volumes) and the organ hematocrit.

SOME APPROXIMATIONS

Under ordinary circumstances, the ratio of the mean transit times of plasma and red cells, $T_p/T_r$, is approximately 1.06 (9, 12). One could assume that this relationship obtains without determining $T_p$ and $T_r$ separately. However, in the special circumstances in which red cells are more rigid or aggregate to a greater degree than normal, the ratio can be unity or less than unity. Thus, in hyperma-
tremia, a ratio of 0.96 has been found (13), and retardation of cells relative to plasma has been noted when sickled cells have been tested in the pulmonary circulation in dogs (14). Experimentally, \( t_p \) is more conveniently obtained from T-1824 or indocyanine green data than \( t_r \) is from labeled red cell data. If desired, another approximation, denoted \( \Delta V' \), can be used in which \( t_r \) and \( t_p \) are assumed to be equal. Thus,

\[
\Delta V' = F_0 f_0 (t_w - t_p),
\]

where \( f_0 \), the volume/volume water fraction of whole blood, is given by \( f_0 = f_p (1 - Hct) + f_r Hct \). Values for \( f_0 \) probably sufficiently accurate for many purposes can be directly obtained experimentally without going through the separate determinations of \( f_p \) and \( f_r \) and \( Hct \). The difference between the values obtained for \( \Delta V \) and \( \Delta V' \) from the same set of data is about 5%. The whole blood equivalent volume, \( V \), is also often used; it is defined as

\[
\Delta V = \Delta V'/f_0 = F_0 (t_w - t_p). \tag{3}
\]

The difference between \( \Delta V \) and \( \Delta V' \) for the same set of data depends on the hematocrit. In an example cited in reference 7, \( \Delta V \) was 13% greater than \( \Delta V' \). Levine et al. (15) calculated \( \Delta V \). Corresponding values of \( \Delta V' \) calculated from their data differ by 12–18%. Determination of the necessary quantities to permit the use of Eq. 1 is urged: values should be obtained for the mean transit times and the flows of both red cells and plasma, particularly in situations which differ markedly from the normal resting state. If these values cannot be obtained, Eq. 2 should be used, particularly in those situations in which the hematocrit may be changing from one study to the next.

**RECIRCULATION OF INDICATORS**

The conventional extrapolation of the linear portion of the downslope of the indicator curve on a semilogarithmic plot may be an adequate procedure under ordinary circumstances. However, such a correction may be inadequate in heart failure or shock lung syndrome, since cardiac outputs may be quite low. Under such circumstances, there are several alternatives. The conventional correction can be used. If this procedure leads to the inclusion of too large an area under the curve, i.e., provides an underestimate of the extent of the recirculation, it will provide falsely lower flows and longer mean transit times than the actual ones. In a volume calculation of the type used in this paper, essentially \( V = FT \), such errors, being in opposite directions, might compensate for each other and give reasonably correct answers for the volume. However, with \( T \) being the first moment of the curve, errors in this quantity may be larger than errors in the area, i.e., in the flow. If the conventional correction leads to the inclusion of too small an area under the curve, i.e., provides an overestimate of the extent of the recirculation, the values for flow will be too large and those for the mean transit time will be too small. The correction for recirculation is apt to be particularly crucial in clinical situations in which, recirculation cannot be identified with certainty and may be occurring before much, if any, of a downslope has appeared (myocardial infarction, shock lung). The flow calculated from the area under the vascular indicator curve would presumably have less recirculation error than the flow calculated from the area under the water indicator curve and is in fact customarily used in expressions such as Eq. 1. However, this procedure leaves the error in \( t_w \), uncompensated. An alternative means of obtaining appropriately corrected data for the calculation of mean transit times has been reported by Knopp and Bassingthwaighte (16) and extended by Maseri et al. (17). In this approach, for each tracer transit time to be determined, a pair of multiple tracer outflow patterns which may be simultaneously or consecutively initiated is required and obtained from one sampling and two injection sites. One curve represents transit times from the pulmonary artery to the aorta and the other from the left atrium to the aorta. The two curves are deconvoluted one upon the other to provide the frequency distribution of transit times from the pulmonary artery to the left atrium. Pairs of tracers are required which are handled identically in the entire system. For studies of the vascular compartment, such a pair could be \(^{125}\text{I}-\text{albumin} \) and \(^{131}\text{I}-\text{albumin} \) or \(^{99m}\text{Tc}\)-albumin. For the water compartment, THO and DHO could be used. This requirement for identical handling was recognized by Maseri et al. (17). They did not, however, meet this requirement in that their albumin tracer pair was \(^{99m}\text{Tc}\)-albumin and indocyanine green, which disappears from the circulation much more rapidly than does \(^{99m}\text{Tc}\)-albumin.

Dr. K. B. Larson and Dr. W. Perl have pointed out (personal communication) that in such a system the mean transit time, \( \bar{t} \), of an indicator from the pulmonary artery to the left atrium can be obtained from the concentration, \( c_1(t) \), at the left atrium and the concentration, \( c_2(t) \), at the pulmonary artery. For an open system (losses of the
obvious. If the system is stationary (no change of the system with time), it is theoretically possible to determine the number of tracers to be determined are obvious. If the system is stationary (no change of the system with time), it is theoretically possible to carry out two successive injections of the same tracers and two successive samplings from the same sampling site. Stationarity must be maintained for the period during which the concentrations of tracers injected for the first sampling have decreased to a negligible or a constant level. A somewhat different approach, also a derivative of principles indicated by Stephenson (18) and directly related to Zierler’s (19) development of the theory of external monitoring or residue detection, has been proposed by Larson and Snyder (20). These authors used two injections of tracers, one an intra-arterial or an input injection and the second a venous or an outflow injection. Two residue curves are obtained from which the mean transit time through the system can be obtained without error due to recirculation. As in the procedure of Maseri et al. (17), pairs of tracers are required if the residue detection is to be carried out simultaneously for the two curves. However, if the system is stationary for the requisite period of time, two successive injections at the two sites can theoretically be used. Because residue detection requires tracers with appropriate radiation emission characteristics, neither spectrophotometrically determined substances nor low-energy beta emitters can be used. If pairs of tracers are used in the procedure of Larson and Snyder (20), differential tissue absorption of radiation may distort the recorded residue curves relative to each other because of tissue inhomogeneity. Thus, if one tracer for plasma proteins is 131I-albumin and the other is 99mTc, the geometry of the large vessels relative to the parenchyma of the lung can affect the detection of 99mTc at the hilum relative to the detection of 131I at the same site. Models and computers can correct for these differences. However, two successive injections of the same isotope bound to albumin eliminate the problem. Similarly, if this procedure is used to determine extravascular lung water, it is best if the same isotope is used to trace plasma proteins and water. Thus, two successive injections of 125I-albumin and two successive injections of 125I-antipyrine can be used. (See the following discussion on the use of iodoantipyrine as an indicator for water.) It is obvious that the use of tracers that do not recirculate to a significant extent is preferable, if achievable, to the more complicated procedures indicated earlier which also require a pair of tracers such as 51Cr and 42K for the red cells. Finally, stationarity of the system is an ideal that can only be approximated as pointed out by Bassingthwaighte et al. (21).

RECOVERY PROBLEMS

So far, it has been assumed that there is no loss of injected indicators on their transit through the lungs. In other words, complete recovery at the outflow has been assumed. Total outflow cannot be collected. Instead, completeness of recovery can be verified by determining the “recovery” of the water label relative to that of the vascular indicators. The recovery is the area inscribed by the indicator curve corrected for recirculation divided by the amount injected. Thus, with normalized concentrations,

$$\int_0^\infty c_1(t) \, dt = \int_0^\infty c_2(t) \, dt$$

(4)

and

$$\bar{I} = \int_0^\infty t[c_1(t) - c_2(t)] \, dt / \int_0^\infty c_1(t) \, dt.$$  

(5)

For closed recirculating systems (no loss of indicators to the outside) in which the dose-normalized concentrations $c_1(t)$ and $c_2(t)$ approach some constant nonzero value, $c_w$, when $t$ is very large (infinite),

$$\bar{I} = \int_0^\infty [c_1(t) - c_2(t)] \, dt/c_w.$$  

(6)

For an indicator limited in distribution to the whole body vascular volume, $c_w$ is determined by that volume. Similarly, for a tracer water indicator, $c_w$ is determined by total body water.

The experimental complexities in such a doubling of the number of tracers to be determined are obvious. If the system is stationary (no change of the system with time), it is theoretically possible to carry out two successive injections of the same tracers and two successive samplings from the same sampling site. Stationarity must be maintained for the period during which the concentrations of tracers injected for the first sampling have decreased to a negligible or a constant level. A somewhat different approach, also a derivative of principles indicated by Stephenson (18) and directly related to Zierler’s (19) development of the theory of external monitoring or residue detection, has been proposed by Larson and Snyder (20). These authors used two injections of tracers, one an intra-arterial or an input injection and the second a venous or an outflow injection. Two residue curves are obtained from which the mean transit time through the system can be obtained without error due to recirculation. As in the procedure of Maseri et al. (17), pairs of tracers are required if the residue detection is to be carried out simultaneously for the two curves. However, if the system is stationary for the requisite period of time, two successive injections at the two sites can theoretically be used. Because residue detection requires tracers with appropriate radiation emission characteristics, neither spectrophotometrically determined substances nor low-energy beta emitters can be used. If pairs of tracers are used in the procedure of Larson and Snyder (20), differential tissue absorption of radiation may distort the recorded residue curves relative to each other because of tissue inhomogeneity. Thus, if one tracer for plasma proteins is 131I-albumin and the other is 99mTc, the geometry of the large vessels relative to the parenchyma of the lung can affect the detection of 99mTc at the hilum relative to the detection of 131I at the same site. Models and computers can correct for these differences. However, two successive injections of the same isotope bound to albumin eliminate the problem. Similarly, if this procedure is used to determine extravascular lung water, it is best if the same isotope is used to trace plasma proteins and water. Thus, two successive injections of 125I-albumin and two successive injections of 125I-antipyrine can be used. (See the following discussion on the use of iodoantipyrine as an indicator for water.) It is obvious that the use of tracers that do not recirculate to a significant extent is preferable, if achievable, to the more complicated procedures indicated earlier which also require a pair of tracers such as 51Cr and 42K for the red cells. Finally, stationarity of the system is an ideal that can only be approximated as pointed out by Bassingthwaighte et al. (21).

RECOVERY PROBLEMS

So far, it has been assumed that there is no loss of injected indicators on their transit through the lungs. In other words, complete recovery at the outflow has been assumed. Total outflow cannot be collected. Instead, completeness of recovery can be verified by determining the “recovery” of the water label relative to that of the vascular indicators. The recovery is the area inscribed by the indicator curve corrected for recirculation divided by the amount injected. Thus, with normalized concentrations,

$$\int_0^\infty c_1(t) \, dt = \int_0^\infty c_2(t) \, dt = \int_0^\infty c_w(t) \, dt.$$  

(7)

In brief, it is assumed that there is conservation of the labels, or, what is equivalent, that there is a single exit, the bloodstream, for the labels. The required accuracy is difficult to attain in a system with recirculation. Because of the very high values of the blood flow through the system relative to the rate of net flux of water out of the vascular system into the tissues, it is unlikely that a significant fraction of either the red cell or the plasma label will be lost on a single pass through the heart-lung system in other than transient catastrophic situations. Accordingly, and because the recirculation problems are least for them, the vascular indicators are used as “refer-
ence" substances to which recoveries of other indicators are referred. The recovery of a water label or of other permeating indicators can be less or more than unity relative to the vascular reference substance for several reasons. There may be an exit from the system other than the arterial blood outflow. The correction for recirculation may be inappropriate. The additional exit may be the lymphatic drainage from the lung with a holdup or a pool in the lung tissues. However, lymph flow is so small relative to the volume flow of water through the lungs that this pathway is also probably not significant for the present purposes. The exit is unlikely to be the gas phase because of the insignificant mass of water in this phase of the lungs compared with the mass of water in the aqueous part of the system. For water tracers at least, it appears that incomplete recoveries indicate inappropriate corrections for recirculation unless some other reason can be established. Thus, if the tail is cut off, \( T_w \) will be underestimated as will \( \Delta V_{w,r} \). However, an indicator will have the same mean transit time as the water indicator if the shape of the curve is the same as that of the water indicator. The mean transit time is determined not by the recovery but by the relative frequency of distribution of traversal times. An indicator might not be suitable for measuring plasma flow, because of losses, but might still be suitable for the determination of the mean transit time of the plasma proteins if the losses are in the same proportion over all of the transit times. This situation is equivalent to assuming the existence of two nonoverlapping fractions of a permeative indicator: a fraction, \( \alpha \), with a distribution of traversal times identical to that of a simultaneously injected vascular indicator, and a fraction, \( 1-\alpha \), with traversal times sufficiently delayed that the investigator excludes this delayed fraction from the calculation of the mean transit time. (See the discussion of the use of sodium that follows.)

**PORTION OF TOTAL LUNG WATER DETECTED**

Apart from these problems, it is reasonably well established that this technique gives results that are smaller than the total lung water content obtained from the differences between wet and dry weights (4, 5). This discrepancy may reflect nonuniform perfusion of lung tissue. Recruitment and derecruitment with changes in pressures following changes in position have been dealt with by several investigators, and the effects on values obtained for extravascular lung water have been indicated elsewhere (1, 5, 7). Many of the clinical situations in which values of \( \Delta V_{w,e} \) would be helpful are associated with alterations from the usual ranges of both flow and hemodynamic relationships, and thus changes in \( \Delta V_{w,e} \) may reflect changes in tissue perfusion rather than changes in the amount of extravascular water about each perfused portion. At the least, it appears that 50% of the difference between wet and dry weight is detected by the multiple indicator-dilution technique (5, 7). Thus, one can be reasonably sure that the values of \( \Delta V_{w,e} \) in excess of twice the average values of about 3.0 cm\(^3\)/kg body weight (lean body mass and height might be more appropriate as bases for comparisons) do indeed represent absolute increases in \( \Delta V_{w,e} \) and accordingly can be considered to be significant and abnormal. Successive determinations in the same individual offer an internal base line from which small departures on the order of 1.0 ml/kg body weight or less may be significant. Pairs of successive determinations in anesthetized dogs in stable condition have shown variations of 10–15% (unpublished observations). In resting healthy human young adults Goresky (personal communication) has found values of \( \Delta V_{w,e} \) averaging 2.16 ± 0.47 (SD) g/kg; during low-level exercise, \( \Delta V_{w,e} \) averages 2.55 ± 0.47 g/kg. Reproducibility is less when significant blood losses or surgical procedures intervene between the successive determinations.

**LOCATION OF EXCESS EXTRAVASCULAR LUNG WATER**

Further cautions on the significance of increased values of \( \Delta V_{w,e} \) are in order. The anatomical locations of the excesses have not been determined. Any compartment or region that has substantial exchange with the vascular compartment is a possible site. Presumably the thinner portions of the alveolar-capillary barrier are included as are the supporting structures and the interstitium in the structural matrix. It is not known whether the increased \( \Delta V_{w,e} \) seen in clinically diagnosed pulmonary edema represents all or just some of the histologically detectable increase in water in the interstitium, in the alveoli, or about the larger vessels. Thus, it is not known whether perivascular cuffing is detected by the indicator-dilution technique. Peribronchial water is probably not included as pointed out by Goresky et al. (6). The amount of \( \Delta V_{w,e} \) per unit volume of capillary blood may vary from one region of the lung to another. Posture (erect or recumbent) affects the distribution of blood flow in the lungs and could affect the distribution of water in the extravascular compartment and the absolute amount as well.
INTERSTITIAL OR TOTAL EXTRAVASCULAR LUNG WATER?

Cell water and interstitial water are not differentiated in this type of measurement. Both are presumably included in the determination. There is substantial evidence from the osmotic bolus experiments of Effros (22) and from experiments in which weight changes are induced in isolated perfused lung preparations by changes in solute concentrations (23) that the total small-solute osmotic pressures as well as the protein osmotic pressure play a role in the transient distribution of water between the vascular and the extravascular regions of the lungs when changes over periods of seconds are considered. Whether total solute concentrations affect extravascular lung water in the development and correction of hypernatremia and hyponatremia and of hyperglycemic states is unknown. The extent to which the endothelial, epithelial, and interstitial cells participate in the excess water in pulmonary edema remains to be determined.

Sodium has been considered to be essentially extracellular in its distribution in lung tissue (22) but has not been used as a marker for the interstitial compartment of the lung in the manner that labeled water has been used for the total extravascular water compartment, because its apparent mean transit time is very close to that of simultaneously injected T-1824 (24). The shapes of the curves of sodium and T-1824 are, however, significantly different, at least on the upslpes, and these differences are the basis for the calculation of the permeability of the endothelium to sodium (7, 8, 25). If the mean transit times for sodium calculated with the conventional correction for recirculation are in fact the same as those for the plasma protein indicators, it does not necessarily follow that the volumes of distribution of sodium ions and plasma proteins must be the same, i.e., essentially vascular. That the recovery of tracer sodium in indicator-dilution experiments in the lungs is less than that of simultaneously injected T-1824 by about 5% (24) is interpreted as an indication that the volume of distribution accessible to sodium is larger than that accessible to plasma proteins. The flow of lymph from the lungs is quite small relative to the flow of blood through the lungs. It is unlikely, therefore, that the loss of sodium represents locally irreversible blood-to-tissue loss with delayed return by way of the lymph. Rather, it would seem that this "lost" 5% is distributing itself in the interstitium of the lungs and returning slowly to the circulation, well after the conventional downslope correction is applied. As pointed out earlier, there would be an underestimate of the mean transit time for tracer sodium, which, although involving only a small fraction of the total amount injected, could nonetheless have a substantial effect on the value obtained for the mean transit time. The recirculation problem is thus a major one, and the handling of experiments with tracer sodium would provide a suitable challenge of the procedure developed by Larson and Snyder (20). Hopefully, investigators will feel encouraged to attempt to identify and use a tracer for interstitial fluid rather than one for total extravascular lung water. The restrictions imposed on such a tracer (restriction to the extracellular compartment as well as rapid entry into that compartment) are formidable.

SUITABLE VASCULAR INDICATORS

The choice of vascular indicators or reference substance is necessarily related to the choice made for the indicator to be used for water for analytical reasons. For red cells, labeling with 51Cr has been customary, although 32P and 42K have also been used. For plasma proteins, the most widely used indicators are T-1824 and indocyanine green, which can be determined spectrophotometrically and which depend, with respect to their suitability as plasma protein indicators, on their binding to the plasma proteins and particularly to albumin. Radioactive labels chemically bound to albumin also provide suitable indicators, e.g., 125I-albumin, 131I-albumin, and 99mTc albumin. These substances require that the labeling be done ex vivo. 51CrCl3 can be injected as such and thus label the plasma proteins in vivo.

Indicators that leave and return to the circulation during the transit from injection to sampling sites can be used as substitutes for the conventional types of indicators just mentioned provided the losses are negligible. Such substitute indicators might be 22Na and 44Na, which have mean transit times nearly identical to that of simultaneously injected T-1824 (24) after the conventional recirculation correction. Some other characteristics of radioactive sodium as an indicator have been considered earlier. It is appropriate to emphasize that, although a sodium indicator-dilution curve might provide data adequate for the purpose of obtaining a mean transit time to be used like that of plasma proteins, the curve should not be used to evaluate blood or plasma flow because of the losses to the extravascular compartment. As shown by Pearce (26), the sodium losses from edematous lungs can substantially exceed the 5% losses found normally. It would have to be demonstrated that
the mean transit times of sodium and a conventional vascular reference substance are indeed identical in the abnormal situation despite the increased losses. The contributions of Caubarrère et al. (27) should be noted in this connection. These authors determined flow from an indocyanine curve and vascular protein mean transit times with a radioactive ion, such as $^{131}$I, used as a substitute indicator. Simultaneously, the mean transit time of $^{125}$I-iodoantipyrine was obtained. Thus, the appropriate quantities for the calculation of the values of extravascular lung water can be obtained without the usually required precise determination of the amounts of radioactive indicators that are injected. The technique requires that there be no significant difference between the mean transit time of the substitute indicator, whether or not losses occur in the traversal, and the mean transit time of suitable plasma protein indicators.

Strictly, it appears that labeled red cells are the only appropriate vascular reference available. A fraction of the perfusing albumin does leave the circulation in the transit through the lungs and does distribute itself in the interstitium (4). However, the amounts of albumin lost are so small in a single passage that little effect is to be expected on the calculated value of the mean transit time. Nonetheless, the fact of the distribution of albumin in the lungs suggests that a sufficiently accurate determination of the mean transit of labeled albumin should reflect this phenomenon. In brief, the use of labeled albumin as a marker for the plasma components of the vasculature is an approximation. The situation is analogous to that of sodium as an indicator for interstitial volume. The resultant error may be of no practical significance in many situations but is a potential source of uncertainties in conditions such as the capillary leak syndrome and shock lung.

**SUITABLE WATER INDICATORS**

The number of substances suitable for use as indicators or tracers for water is limited, and not all have been tested under an adequate variety of conditions. The single most important criterion for suitability is that the curve of frequency of distribution of traversal times not be significantly different from that for simultaneously injected tracer water (i.e., DHO or THO). A requirement that the mean transit times be identical is contained in this condition. It should be noted, however, that the mean transit times could be identical without the shapes of the curves being identical. The requirement of identity of curve shape is in fact a sufficient condition, since it is the mean transit time, $T_m$, and not just the area under the outflow curve that enters into the calculations of $\Delta V_{ext}$. Suitable substances are THO, DHO, and H$_2^{18}$O, and probably $^{14}$C-antipyrine and $^3$H-antipyrine. Distribution of the labeled oxygen in the carbon dioxide pool of the body may be rapid but is not significant quantitatively in view of the relative concentrations of water (55 M) and carbon dioxide (25 mM). Distribution of hydrogen elsewhere than in water can be ignored for similar reasons. Substances that show relatively minor differences of curve shape but nearly identical mean transit times are $^{14}$C-valeramide, $^{14}$C-benzamide, $^{14}$C-heptane-1, 7-diol, $^{14}$C-octane-1, 8-diol, $^{14}$C-methanol, $^{14}$C-ethanol, and $^{14}$C-propanol. Two substances that show somewhat greater differences of mean transit time from water are $^{131}$I-iodoantipyrine and $^{125}$I-iodoantipyrine. Iodoantipyrine and antipyrine are chemically different and have different oil-water distribution coefficients. Nonetheless, these substances have been used by some investigators as tracers for water, because they offer considerable analytical convenience over the use of more suitable labels. These transit time differences have been attributed to the distribution of the iodoantipyrines into lipid phases in the lungs (10). The differences are small but do raise some uncertainties concerning the validity of studies carried out with these materials. They are not necessarily invariant in different situations.

Special mention must be made of the use of heat as an indicator because of its ready adaptability to clinical problems (28). From published data on the simultaneous use of heat and THO, it appears that the mean transit time of the heat bolus as calculated is larger than that of THO in similar situations (28). Errors from heat exchanges in the large vessels and heart chambers and losses to the gas phase may be substantial. Heat measures a larger fraction of the total lung water than does THO. A particular advantage of the use of heat as an indicator is that repeated determinations can be made without loss of blood from the patient in contrast to the repeated samplings required when THO, for example, is used. In conjunction with heat as an indicator for water, the use of NaCl as an indicator for the plasma component of blood offers the possibility of intravascular measurement of its concentration through conductivity changes (28, 29). The use of NaCl depends on the usually low permeability of the pulmonary vasculature to sodium (7, 8, 25). Thus, there is the possibility of rapid, repetitive measurement of extravascular
lung water through the use of NaCl for the vascular component (plasma) to provide both mean transit time and flow values combined with the use of heat as a substitute indicator to provide mean transit time values for water, both indicators being measured intravascularly without blood sampling. Crosbie et al. (30) have reported that the permeability to sodium in the blood-to-tissue direction is increased in patients with renal failure. In such situations, the use of sodium ions as a substitute indicator for plasma proteins is of uncertain validity, since their mean transit time may differ significantly from that of a more appropriate plasma protein tracer. A technique which involves the inhalation of C15O2 and depends on the randomization of the oxygen in the water has been developed by Jones et al. (31). Other techniques and procedures are under investigation or being developed such as that of Severinghaus et al. (32), which is based on a focusing electrode impedance bridge.

Finally, with regard to the choice of a substitute indicator for water, attention should be given to the equilibration rate of the indicator between plasma and red cells, since the rate may affect the indicator's mean transit time (33, 34).

REGIONAL DISTRIBUTION OF LUNG WATER

All of the techniques described in this paper have the potential of providing the information on the regional distribution of water. The conventional multiple indicator technique can be applied by injecting different indicators for water along with suitably different vascular indicators simultaneously as several boluses into several branches of the pulmonary artery with sampling from appropriate outflows. Or, sampling catheters can be introduced into different branches of the pulmonary vein, and the injection of a single bolus can be made into the pulmonary artery. External detection techniques can provide, at least theoretically, regional information more simply and, in clinical situations, may prove to be the most accurate. An outline of such a technique has recently been reported by Prichard and Lee (35).

In conclusion, the measurement of extravascular lung water can produce useful information not only for investigational purposes but also in clinical situations. The techniques that are currently readily available have substantial limitations in large part owing to the problem in disease or abnormal states of assessment of the recirculation of the two or more tracers or indicators that are required. In clinical situations in which repeated estimates of extravascular lung water are to be made, the choice of indicators or tracers and of procedures is limited and consideration should be given to those indicators whose “concentrations” can be determined in situ in the arterial blood (e.g., NaCl by conductivity and heat by thermistor) or in blood flowing through a catheter system that provides for the return of the diverted blood to the subject’s circulation. Indicators whose concentrations are measurable by spectrophotometric methods or by radiation measurements can be used in this situation. With such indicators and with appropriate measurement and computer instrumentation, the delay between the initiation of the test and the delivery of results will be on the order of minutes. Indicators that require sampling and handling of a large series of individual blood specimens, as do the original procedures, are by and large not suitable for use in clinical situations. Progress appears likely with the adoption of external residue detection rather than outflow detection techniques. Since pulmonary edema probably involves largely extracellular excess water accumulation, it would seem appropriate to put some emphasis on the development of techniques to obtain data on the interstitial water content of the lungs rather than just on the total extravascular lung water.

Appendix

Consider the lungs in the following very simplified manner which ignores the gas compartment. Under ordinary circumstances, there is a single input of water to the lungs at a rate of \( I_w \) (g/sec) and a single output of water at a rate of \( J_w \) (g/sec). Thus, when there is neither an increase nor a decrease in the lung water content, \( M_w \) (g), \( I_w \) must equal \( J_w \). From other considerations, it can be shown that

\[
M_w = I_w t_w = J_w t_w. \tag{A1}
\]

where \( t_w \) (seconds) denotes the mean transit time of a suitable indicator for ordinary water, such as deuterium, tritium, or \(^{18}O\) or \(^{15}O\)-labeled water. The mean transit time in a bolus injection, outflow detection experiment is calculated from the concentration-time relationship at the exit of the tracer or label as given by

\[
I_w = \int_0^t c(t) \, dt = \int_0^t \frac{c(t) \, dt}{\int_0^t c(t) \, dt}, \tag{A2}
\]

where \( c(t) \) denotes the concentration of a tracer in effluent blood at time \( t \) after injection. The mean transit time obtained in this manner or from a step-input function relates to the transit from the site of injection of the bolus to the end of the sampling catheter or to the detector of the indicator.

The experiment will provide the total water content between the point of injection of the tracer and the site at
which concentrations are determined. The total water content, \( M_w \), is resolved into the following components:

\[
M_w = M_{wev} + M_{wr} + M_{wp},
\]

(A3)

where \( M_{wev} \) denotes extravascular lung water, \( M_{wr} \) water in red cells, and \( M_{wp} \) water in plasma. Thus,

\[
M_{wev} = M_w - (M_{wr} + M_{wp}).
\]

(A4)

Note that \( M_{wev} \) is not resolved into cellular and interstitial components. Then, by analogy with Eq. A1,

\[
M_{wev} = I_{wr}T_w = (I_{wr}T_r + I_{wp}T_p),
\]

(A5)

where \( T_r \) and \( T_p \) denote the mean transit times of red cells and plasma, respectively, and \( I_{wr} \) and \( I_{wp} \) denote the fluxes of red cell water and plasma water, respectively. Since \( I_w = I_{wr} + I_{wp} \),

\[
M_{wev} = I_{wp}(T_w - T_p) = I_{wr}(T_w - T_r).
\]

(A6)

To determine \( I_{wp} \) and \( I_{wr} \) requires knowledge of the flow of red cells and plasma through the system and of the volume fraction of water in cells and plasma, \( f_r \) and \( f_p \) respectively. Eq. A6 can be recast in terms of volumes and flows to yield Eq. 1 given in the text by dividing both sides of Eq. A6 by the density of water (1 g/cm\(^3\)).

Acknowledgment

I thank Dr. William Perl for critical review of this manuscript.

References

31. Severinghaus JW, Catron C, Noble W: A focusing elec-


34. PERL W: Red cell permeability effect on mean transit time of an indicator transported through an organ by red cells and plasma. Circ Res 36:352-357, 1975

Estimation of extravascular lung water by indicator-dilution techniques.
F P Chinard

Circ Res. 1975;37:137-145
doi: 10.1161/01.RES.37.2.137

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/37/2/137.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/