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Underestimation of thermal lung water volume in patients with high cardiac output

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When utilizing the intravascular double-indicator dilution technique to measure extravascular lung water, blood flow may be so high that diffusion equilibrium of the diffusible indicator fails to occur and the water distribution space is underestimated during the first 7 days after thermal injury. We serially measured cardiac index and lung water in five severely burned patients (mean age 24 years, range 18 to 33 years; mean burn size 56% total body surface, range 43% to 80%) by a rebreathing method utilizing two gases of differing solubility and by the thermal–indocyanine green dye (ICG) double-indicator dilution technique. Rebreathing lung water, determined by a time- and blood flow–insensitive method, increased significantly over the study period, from 6.6 ml/kg on admission to the hospital 11.3 ml/kg on postburn day 6 (+70%, $P < 0.01$). Thermal-ICG lung water decreased slightly as blood flow rose. Rebreathing lung water correlated with clinical data in a patient with pulmonary edema, while thermal-ICG lung water changed in the opposite direction. Our data suggest that the thermal-ICG technique may be diffusion limited by short transit times at the high flows characteristic of burned and other critically ill patients with hyperdynamic circulations. Additionally, segmented redistribution of pulmonary blood flow known to occur in burn patients may contribute to underestimation of lung water.

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SUBSEQUENT TO massive thermal injury, the lung participates in the pathophysiologic response associated with large plasma volume loss and administration of large resuscitation volumes—that is, the formation of tissue edema in the area of injury and probably in noninjured tissues.[2] Because most pulmonary dysfunction during the early phase of burn injury results either directly or indirectly from abnormal distribution and accumulation of lung tissue water, the ability to measure extravascular lung water (EVLW) serially not only would help elucidate the magnitude and direction of acute fluid shifts and the effects of hypoproteinemia but also would help identify the optimal volume and composition of the resuscitation fluid. Several preliminary studies of diverse groups of burned patients have indicated that passive lung water changes are related to coexisting pulmonary injury or sepsis and are not directly dependent on plasma oncotic forces.[20, 23, 33] Furthermore, the addition of colloid to balanced electrolyte solutions during resuscitation to maintain normal plasma oncotic pressures does not appear to limit the accumulations of excess lung water and may, in fact, produce the opposite effect.[15]

Chinard et al.[8-10, 12] laid the theoretical basis and introduced the first practical method for the in vivo measurement of EVLW. In principle, after bolus injection of a solution containing a nondiffusing intravascular tracer (e.g., labeled red blood cells) and a diffusible water tracer (e.g., tritiated water) into the arterial inflow of the lungs, the venous concentration-time curves of the tracers reflect the individual distribution spaces of the two tracers. The volume of each distribution space is equal to the flow through the lungs and the mean transit time of each tracer. The use of an isotope of water as the water tracer has been found to underestimate EVLW, especially when used in the presence of lung edema, because of the lack of equilibrium of such tracers with all tissue water within one passage through the lung. The use of a thermal indicator with in-stream thermistor-tipped catheters has been shown by concomitant gravimetric analysis to measure EVLW more accurately.[1, 14, 26]

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Table I. Patient characteristics and summary of selected clinical data during initial postburn week*

Patient	*Age (yr)*	*TBS/3° burn (%)*	*Resuscitation (ml/kg/% TBS)*	*Preburn weight (kg)*	*Maximal weight gain (%)*	*Lowest room air Pa_{O_2} (torr)*	*Outcome*
1	33	50/17	4.12	66	19(2)†	90	Survived
2	18	80/55	2.80	95	12(2)	79	Survived
3	20	43/28	4.36	66	12(2)	92	Survived
4	19	55/46	2.96	66	4(1)	89	Survived
5	28	53/39	3.01	80	8(1)	‡	Died of sepsis PBD 29

Legend: TBS, total body surface; 3°, third degree; PBD, postburn day.

*All patients were men, all had normal chest roentgenograms, and none had inhalation injury.

†Postburn day in parenthesis.

‡Pa_{O_2} was measured in this patient with face mask and humidified oxygen at $FI_{O_2} = 0.30$; the lowest Pa_{O_2} under these conditions was 134 torr.

Lung water also can be measured by a rebreathing method utilizing two gases of differing solubility. Tissue volume determinations have been shown to reflect lung water changes with reliability in animals with normal and edematous lungs.[29] The theoretical basis and original breath-holding technique were described by Cander and Forster.[6] Subsequent modifications to allow rebreathing of the tracer gases facilitate clinical application of this technique. When an insoluble gas is inspired into the lungs, equilibration between the alveolar gas and the surrounding lung tissue volume occurs within approximately 10 msec. The dissolution of soluble gas into the lung tissue volume results in an initial fall in gas concentration, and its magnitude is a direct function of the tissue solubility of the gas and the volume of lung tissue.

The principal advantage of the rebreathing method is that it is noninvasive. In addition, with suitable gases, additional physiologic indices of pulmonary function can be calculated from the gas measurements. However, the rebreathing method requires very expensive equipment, complicated data reduction, and, in our hands, alert and spontaneously breathing patients. Although the intravascular double-indicator dilution method requires access both to the pulmonary artery and to a systemic artery, current hardware allows sterile sampling without loss of blood from the patient. In addition, serial measurements are quite easy to perform in all patients, including those being treated with mechanical ventilators. This study evaluates the utility of these two independent methods for quantification of EVLW and defines the limitations of each in patients with massive thermal injuries.

MATERIAL AND METHODS

Subjects. Five thermally injured patients who required hemodynamic monitoring with pulmonary arterial and systemic arterial catheters were studied serially after informed consent was obtained for participation in a research protocol approved by institutional review (Table I). All were admitted to the study within 12 hours of injury; mean age was 24 years (range 18 to 33 years) and mean burn size was 56% of the total body surface (range 43% to 80%). During the first 24 hours, the patients received lactated Ringer's solution at a rate sufficient to stabilize vital signs and to achieve a urinary output of 30 to 60 ml/hr. Utilizing these guidelines, the mean resuscitation volume in the 24 hours after injury was 3.45 ml/kg weight/% body surface burn (range 2.80 to 4.36 ml/kg/% burn). No patients had accompanying inhalation injury or other pulmonary disease based on clinical evaluation and on normal xenon ventilation-perfusion lung scan, fiberoptic bronchoscopy, chest roentgenogram, and arterial blood gases. None of the patients developed positive blood cultures or demonstrated microbiologic or clinical evidence of pulmonary infection during the 7 days of the study. An additional patient, who sustained an inhalation injury and subsequently developed early pulmonary edema, was studied under a separate protocol and is discussed to illustrate water changes in injured lungs.

Study design. Studies were carried out every 12 hours (6 A.M. and 6 P.M.) for the first 3 postburn days and daily (6 A.M.) on postburn days 5, 6, and 7. Patients were studied in a semirecumbent position to which they had acclimated for several hours prior to study. EVLW was measured by two independent methods—a rebreathing method utilizing two gases of differing solubility and an intravascular double-indicator dilution technique. The order in which the two methods were employed was randomized for each study.

Rebreathing lung water. The distribution of each test gas (helium and dimethyl ether) was measured by a time of flight medical mass spectrometer (MGA 1100A, Perkin-Elmer Corp.). A bag-in-box with a

Table II. Serial changes in cardiac output and lung water subsequent to thermal injury

	Postburn day								
	0.5	*1*	*1.5*	*2*	*2.5*	*3*	*5*	*6*	*7*
CI (L/min/M²)	3.44 ± 0.23	3.12 ± 0.47	4.75 ± 0.55	4.71 ± 0.20	4.99 ± 0.52	5.66 ± 0.75	6.55 ± 0.44	7.15 ± 0.43	6.75 ± 0.46
RBLW (ml/kg)	6.55 ± 0.87	7.16 ± 0.91	7.87 ± 0.58	7.76 ± 0.65	7.17 ± 0.61	8.24 ± 1.14	8.84 ± 1.06	11.25 ± 1.65	10.39 ± 0.62
TGLW (ml/kg)	5.32 ± 0.82	4.95 ± 0.67	4.81 ± 0.61	4.44 ± 0.55	4.68 ± 0.62	4.76 ± 0.58	3.86 ± 0.34	4.10 ± 0.44	4.53 ± 0.46
MTT_1 (sec)	4.18 ± 0.33	4.33 ± 0.22	3.52 ± 0.22	3.55 ± 0.22	3.37 ± 0.27	3.19 ± 0.19	3.05 ± 0.14	3.06 ± 0.22	3.36 ± 0.23
MTT_2 (sec)	8.07 ± 0.51	7.69 ± 0.32	6.00 ± 0.04	5.81 ± 0.37	5.40 ± 0.58	5.52 ± 0.61	4.44 ± 0.15	4.48 ± 0.23	4.92 ± 0.23

Legend: CI, Cardiac index; RBLW, rebreathing lung water; TGLW, thermal-ICG lung water; MTT_1, mean transit time for ICG; MTT_2, mean transit time for thermal indicator. Values represent mean ± SE.

16-inch, spring-loaded, gas-impermeable, low-compliance reservoir bag (Calibrated Instruments, Inc.) was connected with large-bore tubing to a previously calibrated data acquisition dry spirometer (model 843, Ohio Instrument Co.) for a volume signal output. The subject was instructed to exhale to residual volume, the valve was turned into the rebreathing bag, and verbally directed consecutive maximal rebreathing maneuvers were carried out for 15 to 20 seconds. Calculated values include lung tissue volume (lung water), residual lung volume, alveolar volume, pulmonary capillary blood flow (cardiac output), and rebreathing dead space. Rebreathing lung water results are expressed as milliliters per kilogram of preburn weight. All measurements were made in duplicate.

Thermal–indocyanine green dye lung water. Ten milliliters of iced 5% dextrose solution containing 10 mg of ICG (Hynson, Westcott, and Dunning, Inc., lot 386) were injected by a CO_2 gas injector (model 37200, USCI Cardiology Products, Inc.) through the proximal port of the pulmonary artery catheter into the right atrium. ICG concentration was measured by withdrawing blood by sterile technique through the thermistor-tipped femoral artery catheter (model 96-020-5F, Edwards Laboratories, Inc.) and a disposable cuvette (model 9602, Edwards Laboratories, Inc.) connected to an ICG densitometer (DCR-702, Waters Instruments, Inc.). The ICG and the femoral artery thermal signal were detected and digitized automatically by a portable microprocessor (model 9310, Edwards Laboratories, Inc.).

Statistical analysis. A one-way analysis of variance was used to examine serial changes within each technique group. A two-way analysis of variance was utilized to detect differences between the two technique groups. Statistical differences with $P < 0.05$ were accepted as significant. Values are reported as mean ± standard error.

RESULTS

Table II summarizes the changes during the 7-day study in rebreathing lung water, thermal-ICG lung water, cardiac index, and the mean transit times for the ICG and thermal indicators. Lung water measured by the rebreathing technique increased significantly by completion of the study, with a maximal increase of +70% on postburn day 6 ($F = 3.55$, $P < 0.01$) (Fig. 1).

Lung water measured by the thermal-green dye technique decreased slightly by postburn day 7 (−20%), but this change was not statistically significant ($F = 1.498$, $P > 0.05$). The two technique groups were statistically distinct from one another ($F = 35.6$, $P < 0.001$); however, since each method measures a physically different distribution property, the statistical comparisons of the results of each method may be artificial.

The cardiac index rose progressively in all patients as postburn hypermetabolism developed during the first postburn week ($F = 8.927$, $P < 0.001$). The rising flow was reflected by shortening of the mean transit times of the intravascular ICG and diffusible thermal indicators.

In a patient who sustained inhalation injury (not included with the data of the study patients), lung water levels measured by each method changed in opposite directions during an episode of fluid overload and acute pulmonary edema in the presence of an elevated cardiac output (Fig. 2). When pulmonary edema became clinically evident, lung water determined by the thermal-ICG technique decreased, while that measured by the rebreathing method increased.

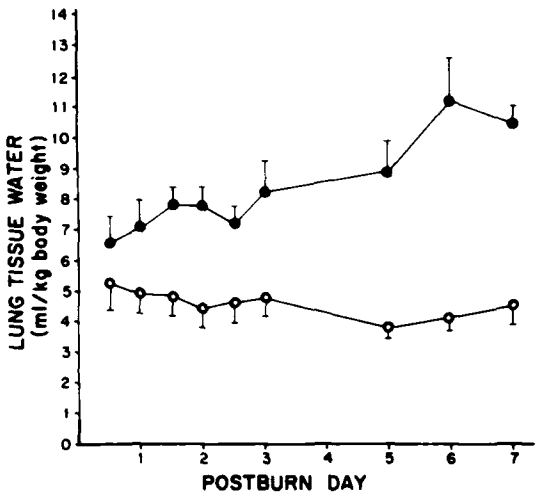

Fig. 1. Time course of changes in lung water measured by the rebreathing method (solid circles) and the thermal-ICG method (open circles). Values are normalized to preburn weight.

These changes were paralleled by a moderate increase in pulmonary shunt and roentgenographic evidence of pulmonary fluid overload. With fluid restriction and diuretics, all measurements changed in the opposite direction: thermal-ICG lung water increased, rebreathing lung water decreased, pulmonary shunting lessened, and the chest roentgenogram cleared.

DISCUSSION

During the first week after large thermal injuries, EVLW determined by a well-standardized rebreathing method increased significantly in our patients. This increase in lung water was modest during the first 3 postburn days, a period when intravascular volume deficits were being corrected and injured tissue accumulated large volumes of edema fluid. During the subsequent 4 days, the increase in EVLW became much more pronounced and was associated in time with decreased fluid requirements and mobilization of the massive quantity of burn wound edema. By contrast, EVLW as measured by the intravascular double-indicator dilution (thermal-ICG) technique did not change significantly during the 7-day study period and, if anything, demonstrated a tendency to decrease during that interval. In large reported series, clinical pulmonary edema in the early postburn period occurs most frequently between the third and seventh postburn days and this pattern corresponds with the period of greatest lung water accumulation detected by the rebreathing technique in our patients, who had no evidence of acute pulmonary injury. In an additional patient with inhalation injury (not included in the main study group) who was evaluated by both measurement techniques, the clinical, physiologic, and roentgenographic evidence of pulmonary edema correlated directly with the rebreathing lung water and inversely with lung water determined by the intravascular method. The greatest divergence of the two techniques occurred during the latter half of the study interval, when cardiac output was markedly elevated and the mean transit times for the indicators were quite shortened. These physiologic conditions may impose limitations on the intravascular method when utilized in patients with hyperdynamic circulations.

The validity of the rebreathing method for estimating lung water deserves careful examination. Strictly speaking, the volume in which the soluble gas tracer distributes during breathing measures lung tissue volume, *not water volume, which can be truly measured* only with water as the tracer molecule. However, water comprises more than 80% of the lung tissue volume,[6] and thus most of the tissue volume measured reflects lung water content. More importantly, during serial studies over several days, the solid tissue structures of the lung can be assumed to remain constant, and any change in measured lung tissue volume likely represents change in that organ's water content. The accuracy of measurements of lung tissue volume as a reliable indicator of water content has been verified in animal studies. Gravimetric analysis of lung water correlates closely with rebreathing measurements until lung weight increases in excess of 250% of control values.[13, 29, 31] Beyond this point, alveolar flooding occurs, with massive obliteration of alveolar air spaces and restriction of soluble gas distribution.[3]

The major criticism of the rebreathing method is that it measures not only the water in the pulmonary interstitial tissues but also that in the capillaries. In our study, we did not independently measure pulmonary capillary blood volume, as can be done while determining carbon monoxide diffusing capacity.[22] However, we can indirectly assess the contribution of pulmonary capillary blood volume to the estimates of lung water in our patients. Central blood volume can be calculated from the cardiac outputs and the mean transit times of the intravascular indicator. In our patients, the increase in central blood volume from the time of intravascular volume restitution (postburn day 3) to time of maximal lung water (postburn day 6), at most, can account for 50% of the approximate 375 ml mean increase in lung water of each patient. However,

CO (L/min)	12.30	14.40	13.20
TDLW(ml/kg)	6.81	5.81	6.45
RBLW(ml/kg)	10.58	13.41	8.57
Q_S/Q_T (%)	10.00	18.00	8.00

Fig. 2. Changes in blood flow, intrapulmonary shunt, and lung water on postburn days 5, 6, and 7 in a 27-year-old patient with a 60% total body surface burn and inhalation injury. *CO*, Cardiac output; *TDLW*, thermal-ICG lung water; *RBLW*, rebreathing lung water; Q/Q, shunt.

central blood volume includes all the blood between the tip of the injection catheter and the densitometer, not only the pulmonary capillary blood volume but that in the right ventricle, pulmonary arteries and veins, left side of the heart, and aorta. This calculated blood volume greatly overestimates the contribution of the pulmonary capillary blood volume.

The pulmonary capillaries of adults contain 80 to 100 ml of blood under normal conditions.[6, 24, 30] Calculated central blood volumes increased as cardiac output rose in our patients. Serial measurements of lung tissue volume, capillary blood volume, and cardiac output with graded exercise in human subjects have demonstrated that a near doubling of cardiac output was associated with an increase of pulmonary blood volume from 101 to 123 ml.[31] Moreover, pulmonary tissue volume measurements were not correlated with blood flow. In animal studies, large-vessel blood volume was found to increase massively when acute pulmonary edema was induced by elevating left atrial pressure, while pulmonary capillary blood volume, measured by carbon monoxide diffusion, increased only transiently and returned to baseline within a few hours.[11] From the above considerations, it is unlikely that an increased pulmonary capillary blood volume contributed significantly to the increased tissue volume measured in our patients. Thus, assuming the capillary volume remained unchanged at 100 ml, lung tissue volume increased 90% and most likely represents water accumulation. If a "worst case" is considered—that is, a doubling of lung capillary blood volume, lung tissue volume still increased 65%.

As with the rebreathing method, the diffusible thermal indicator of the intravascular-indicator dilution method does not detect lung water volume. Rather, the thermal tracer detects a thermal volume, which includes not only parenchymal lung tissue structures and water content but also the thermal distribution of the left side of the heart, the bronchi, pulmonary arteries and veins, and possibly a small portion of the chest wall.[25] These components may contribute as much as 30% to 35% of the measured tissue volume under basal conditions. The degree to which thermal volume measurements correspond to EVLW depends in part on the intravascular reference indicator. When hypertonic saline is employed, lung thermal volume overestimates gravimetric lung water 4% to 20%.[1, 26] Albumin labeled with ICG, currently the most widely used reference tracer, yields lung water measurements that either moderately underestimate or correlate quite closely with those obtained from gravimetric analysis. This close correlation holds true not only under normal conditions but also in the presence of pulmonary edema, emboli, and sepsis.[17-19, 21, 27]

The reasons why the thermal-ICG technique may have underestimated lung water in our patients are not clear. Immediately after burn injury, before large resuscitation volumes had been administered, we measured a mean thermal volume of 5.3 ml/kg. This value is entirely consistent with thermal-ICG lung water of 5.7 ml/kg measured in similar patients without pulmonary pathology in other studies. However, in the ensuing 6 days, thermal-ICG lung water fell to a mean of 3.9 ml/kg on postburn day 5 in our patients, with values of less than 3 ml/kg in some patients. This small quantity of lung water is physiologically untenable, and we have examined potential sources of error in the technique that may explain these circumstances.

The use of albumin alone as the reference tracer for the intravascular distribution of water can result in sizable underestimation of EVLW.[5] The reflection coefficient of albumin is not unity, and any leak of albumin out of the circulation and into the interstitial spaces will alter the distribution of its transit times and will increase its mean transit time and, thus, its apparent intravascular volume of distribution. In addition, plasma separates from red cells in small vessels, creating an intravascular plasma space that is accessible to albumin but not to red cells.[16] This separation becomes more pronounced with increased blood flow and with edema.[4] However, since water distributes in both red cells and in plasma, the intravascular transit time used for EVLW calculations must take this into account. To use only the albumin transit time will lead to overestimation of the intravascular water volume and underestimation of EVLW. This discrepancy increases with rising cardiac output and with large changes in hematocrit, both of which occur during the first postburn week.

Heat is advanced as a more ideal tracer than labeled water for determining EVLW because its diffusivity is 100 times greater than that of water.[28] However, this very quality may limit its use in the indicator dilution measurements. Because it does not distribute by the same mechanisms as molecular tracers, the use of blood flow as the flow factor for the thermal tracer may not be applicable. Thermal volume calculated from blood flow is not synonymous with that calculated from heat flow. As volume and velocity of blood flow increase, the relationship between blood flow, heat flow, and thermal volume may change and may explain the very short thermal mean transit times and small thermal volumes in our patients.[7] Higher heat flows relative to blood flow may explain why the thermal curves preceded the ICG curves, especially at lower flows, in our patients. Finally, like tritiated water, heat capacity may be diffusion limited at higher blood flows.[32]

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DISCUSSION

Dr. Frank R. Lewis (San Francisco, Calif.). The authors have carried out a study that is extremely difficult, using two sophisticated methods. I do, however, disagree with their conclusions, and would like to raise four points to illustrate the reasons why an alternative interpretation is possible. First, in terms of documentation of lung water, they have, effectively, used the rebreathing technique as the standard against which to compare thermal dye, and they have concluded that the rebreathing technique is the more accurate method. Available gravimetric data in the literature do not support that. In two studies the rebreathing technique was evaluated against postmortem gravimetrics, which does not make it a real gold standard, and the discrepancies were both on the high and the low side. This raises significant questions about the technique. And most recently, in a study regarding the rebreathing technique, the data emphasized that the method did not work well when fluid starts to accumulate and that it depends on the alveolar ventilation level—another element that it is impossible to correct for. Conversely, more than 10 studies concerned with the dye technique over a wide range of lung water values have indicated that its accuracy extends from the normal range, or subnormal, up to about 25 to 30 ml/kg.

Second, a direct comparison of the two techniques is not entirely valid. As Dr. Goodwin has pointed out, the difference between the two is pulmonary capillary blood volume, and in the comparison of the inhaled gas technique, the best correlation was found with total lung weight rather than with extravascular lung water. Since pulmonary blood volume normally accounts for about 40% of total lung weight, one would expect the rebreathing technique to give results 70% to 120% greater than the thermal dye technique. This is what they found, and without gravimetric confirmation that must remain unknown.

Third, cardiac output effects are difficult to evaluate at best, because they are relatively subtle, and I believe that if one is going to evaluate this, one must use an experimental method in which the cardiac output change is induced quite rapidly—so rapidly that no true change in lung water could occur. One could do this, for example, by creating an arteriovenous fistula experimentally, and if one measures lung water by either technique with a low cardiac output, opens the fistula, and remeasures it within 5 minutes, one can assume that true lung water has not changed but cardiac output has, with incredible results. We have done that in 46 observations and find that there is a very slight cardiac output effect, but it is much, much smaller than has been suggested in this study. Basically, for a cardiac output change of about 50%, the lung water changes by a small percentage—perhaps 5% or 6%.

Finally, I think even from the authors' own data an alternative interpretation is possible. They presented nine data points, nine observations at different times in their patients. If indeed their hypothesis is correct, one should be able to show that with cardiac output changes between each of those data points, the lung water changes, in fact, were in inverse direction. I have plotted eight data points, which correspond to the eight intervals between their measurements, with cardiac output changes represented on the horizontal axis and measured lung water on the vertical axis. If their hypothesis were correct, then all of their data points should fall either in the upper left or bottom right quadrant. In actuality, five of these eight points fall in upper right and lower left quadrants, indicating a conclusion opposite that of the authors. What one really sees from these data is that with cardiac output changes there is almost no effect on lung water. Since the lung water scale here is +2 at the top and −3 at the bottom, and the expected error is +1, one can really see that these are not true effects.

Dr. Herbert Ben Hechtman (Boston, Mass.). Drs. Goodwin and Pruitt are to be congratulated for putting in perspective a very difficult technique that requires extraordinarily careful interpretation. I have never really believed that one could, using a double-tracer method, interpret the results of the measurement, because there are so many stagnant pools and spaces in the lung. You have used tracer methods to show that there is a discrepancy between the techniques, as I might have predicted, and that common-sense interpretation of your thermal indocyanin green measures does not follow the patient's clinical course.

The perfusion method would seem to be very sensitive to areas of the lung that are being ventilated but not perfused—that is, in absence of the tracer seeing those areas of lung water. On the other hand, despite the fact that you have a diffusable tracer, the ventilation technique would be very sensitive to so-called physiologic dead space. I am not at all surprised that there is a discrepancy between the two techniques, or between the expected clinical findings.

Dr. Cleon W. Goodwin *(closing).* I think we can find as many gravimetric studies that support our technique as you can find for yours. I am aware of the studies to which you refer; some overestimate and some underestimate the true gravimetric lung water, but I think this is true for the thermal, or at least the intravascular double indicator dilution technique also. With your use of the albumin as the intravascular reference tracer, you find a considerably smaller thermal volume than do some of the other authors who use other intravascular reference tracers, such as conductivity. However, most reports agree that both techniques correlate fairly well in situations where lung water is normal or moderately increased. Once albumin flooding occurs, probably neither technique is very good.

You have hit the nail on the head as far as the main weakness in our technique, which is pulmonary capillary blood volume, measured by the rebreathing method. On the other hand, most of the studies on changes of pulmonary capillary blood volume with increased cardiac output, increased left atrial pressure, and so forth, document only a transient change in pulmonary capillary blood volume, and that change is quite small. These increases in lung water—or lung thermal volume—are from 450 to about 800 or 850 ml. Normal pulmonary capillary blood volume is about 100 ml, and if we assume that there is no change in this volume, then what we have found accounts for about a 90% increase in lung water.

If we assume a very bad case, for example if the pulmonary capillary blood volume has doubled (this has never been reported, to my knowledge), an approximate 60% increase in lung water, or lung thermal volume, must still be accounted for, and I think most of this is probably lung water. We are quite confident with the technique.

The problem that Dr. Hechtman mentioned regarding the maldistribution of the tracers, both with the intravascular and rebreathing methods, is certainly true. We normalized our data in this study to the patient's body weight—not our usual technique. We usually normalize these measurements to the patient's measured lung volume. This, in part, offsets the problem with maldistributions of the ventilation and the tracer gases, and we find even a higher correlation and a higher increase, a more predictable increase, using this technique. So, Dr. Hechtman, you are quite right that this will cause a mismeasurement. We purposely chose patients with no known lung disease to study in our comparison of these two techniques.

The problem with cardiac output is obviously the weak point of the indicator dilution technique. Using slides we analyze the transfer function from the pulmonary artery trace and the femoral artery trace to look at the effect of diffusion, and by mathematical manipulation we can tell whether a diffusion limitation has occurred. Over a wide range of changes in blood flow the transfer function tracers should be superimposable if there is no diffusion limitation. In fact, when we studied the transfer functions from the patients as their blood flow increased, they were all superimposable from cardiac outputs of around 3 to 4 L/min up to greater outputs of around 8 to 10 L/min. However, beginning with cardiac outputs over 11 L/min and certainly when cardiac outputs went up to 16 or 17 L/min, these curves began to widely separate, and the only reasonable explanation for the separation would be the diffusion limitation. This information convinced us that the method may require some modification.

Dr. Lewis, your comment regarding arteriovenous shunts and the increase in cardiac output is certainly pertinent. The increases in cardiac output that you found were upwards of 50% or 60%, as I recall you saying, and I think this may be too low. We did not see it in our patients until cardiac outputs were at least twice normal, and they became more pronounced when they were two to two and one half times normal. So there may be a threshold at which this occurs. Certainly, in discussions of the theory of indicator dilution technique, for all diffusable tracers there is a flow above which there will be diffusion limitation. The scatter diagram with the two apogees that you presented may reflect a threshold effect—that is, there was not much of a diffusion limitation until cardiac outputs rose above a certain level.