

LABORATORY REPORTS

Anesthesiology
57:116-122, 1982

Measurement of Extravascular Lung Water in Dogs Using the Thermal-Green Dye Indicator Dilution Method

Frederick G. Mihm, M.D.,* Thomas W. Feeley, M.D.,† Myer H. Rosenthal, M.D.,‡ Frank Lewis, M.D.§

The measurement of extravascular lung water by a double-indicator dilution technique using cold indocyanine green dye was evaluated in dogs. Pulmonary edema was induced in 11 animals by volume overload; 12 animals served as controls. For each measurement, the two indicators (cold dye) were injected into the superior vena cava and detected in the femoral artery. The extravascular thermal volume was calculated using the mean transit times of the two indicator curves. Pretermination measurements of extravascular thermal volume correlated closely with standard gravimetric analysis of pulmonary extravascular tissue weight (EVTV = $1.15 \text{ PEW} + 2.1 \text{ ml/kg}$, $n = 21$, $r = 0.97$, $P < 0.001$; where EVTV = extravascular thermal volume and PEW = pulmonary extravascular tissue weight).

Throughout the experiment, the arterial oxygen tension and alveolar-arterial oxygen tension gradient, correlated poorly with EVTV (linear correlation: $r = 0.47$, 0.45 , respectively). The intrapulmonary shunt correlated better with EVTV ($r = 0.72$). Nonlinear correlation of EVTV with intravascular pressures (left ventricular filling pressures, colloid oncotic pressures, and the pulmonary artery occlusion pressure-colloid oncotic pressure gradient) were more significant than linear relationships. The critical pressures at which lung water rapidly increased in this model occurred at left ventricular filling pressures of 22-27 mmHg and at pulmonary artery occlusion pressure-colloid oncotic pressure gradients of 25-30 mmHg. The thermal dye technique appears to provide an accurate measurement of lung water changes in this high pressure edema model. (Key words: Lung; edema. Measurement techniques: dye dilution; lung water; thermodilution.)

PRESENT CLINICAL TECHNIQUES of monitoring the development and resolution of pulmonary edema are slow and nonspecific. Fishman has estimated that a three- to fourfold increase in extravascular lung water must occur before clinical recognition of the disease is possible.¹ Recently, a modification of the double-indicator dilution technique by Lewis and Elings has been combined with

a small computer which calculates lung water volume immediately following central venous injection of cold indocyanine green dye.^{2,3} Their studies demonstrated good correlation with gravimetric lung water determinations in animals with pulmonary edema. However, they examined animals with only moderate increases in lung water; no animals developed airway flooding. They also did not examine the relationship between the lung water measurement and commonly used physiologic indices of acute pulmonary edema. Therefore, we sought to compare lung water determinations made using the new method with standard gravimetric analysis in dogs with normal lungs, in animals with moderate edema, and in animals with airway flooding produced by volume overload. In addition, the *in vivo* measurement of lung water was then compared to commonly used indices of pulmonary edema.

Materials and Methods

Twenty-three mongrel dogs weighing 15-30 kg were anesthetized with intravenous pentobarbital (25 mg/kg). The trachea was intubated and all animals ventilated with tidal volumes of 15 ml/kg and rates of 6-10/min. The inspired concentration of oxygen (FI_{O_2}) was 1.0 in all but three control animals who were ventilated with air. A 7F, 4-lumen, flow-directed catheter was advanced from the femoral vein into the pulmonary artery and a 5F thermistor-tipped arterial catheter (17.5 cm long) was placed in the femoral artery. A central venous catheter was placed via the right jugular vein. In 14 of the animals a balloon-tipped catheter was placed in the left atrium. This was done under fluoroscopic control in four of the edema animals. Due to difficulties encountered in keeping a balloon placed retrograde in the atrium, in the remaining 10 animals a catheter (10F) was placed by thoracotomy (three control and seven edema). Following thoracotomy the lung was reexpanded and the chest closed. The electrocardiogram, femoral arterial, pulmonary arterial, and either left atrial (LAP) or central venous pressures (CVP) were recorded continuously (HP-1064A stripchart recorder). The animals were divided into two groups: a control group and a pulmonary edema group where lung water was increased by inflating the left atrial balloon and infusing physiologic

* Assistant Professor of Anesthesia.

† Associate Professor of Anesthesia.

‡ Associate Professor of Anesthesia, Surgery and Medicine.

§ Associate Professor of Surgery.

Received from the Department of Anesthesia, Stanford University Medical School, Stanford, California 94305 and the Department of Surgery, University of California, San Francisco, San Francisco, California 94143. Accepted for publication February 25, 1982. Supported in part by a grant (162-L-818-2HVA-473-61600) from the National Institutes of Health and by a grant from American-Edwards Laboratories, Santa Ana, California. Presented in part at the annual meeting of the American Society of Anesthesiologists in St. Louis, October 1979.

Address reprint requests to Dr. Mihm: Department of Anesthesia, Room S278, Stanford University Medical Center, Stanford, California 94305.

saline intravenously to increase the LAP and lower the colloid oncotic pressure.⁴

CONTROL ANIMALS (n = 12)

Following the placement of monitoring catheters the following determinations were performed hourly during the 2- to 5-h experiment: (1) Multiple extravascular thermal volume (EVTV) measurements were made and the result reported as the mean of these determinations. The EVTV was measured by injecting 10 ml of cold (0° C) indocyanine green dye (2 mg) rapidly into the superior vena cava. Blood was withdrawn through the thermistor-tipped femoral arterial catheter connected to a dye densitometer (Waters D-402A). The densitometer cuvette analyzed withdrawn blood through lumen tubing attached directly to the end of the femoral arterial catheter. Curves of both femoral blood temperature and dye concentration versus time were recorded by the computer which calculated the femoral thermodilution cardiac output (CO) and extravascular thermal volume (EVTV). EVTV was calculated by: $EVTV (ml) = CO \times (MTT_T - MTT_D) \times 16.7$. In less than 30 s, the computer provided a digital display of EVTV and CO (see Appendix A).³ (2) Arterial and mixed venous blood samples were analyzed for pH, P_{CO₂}, P_{O₂}, using a Corning 185® blood-gas instrument, and hemoglobin (Hb) was measured using standard colorimetric techniques. (3) Colloid oncotic pressure (COP) was measured with an Instrument Laboratory Oncometer (IL-186). (4) Mean arterial pressure, pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), LAP, CVP, pulmonary blood temperature, and heart rate were recorded.

From the measured variables the following was calculated: (1) The alveolar-arterial oxygen tension gradient (A-aD_{O₂}) from the equation $A-aD_{O_2} = (P_b - 47) F_{I_{O_2}} - (P_{aCO_2}/0.8) - P_{aO_2}$; (2) the PAOP-COP gradient; (3) Arterial and mixed venous oxygen contents (Ca_{O₂}, C \bar{v} _{O₂}) were calculated using the Severinghaus blood-gas calculator⁵; and (4) Intrapulmonary right-to-left shunt (\dot{Q}_{san}/\dot{Q}_t) from the equation $\dot{Q}_{san}/\dot{Q}_t = (C_{CO_2} - Ca_{O_2}) / (C_{CO_2} - C\bar{v}_{O_2})$, where C_{CO₂} = pulmonary capillary oxygen content.

During the experiment, the left ventricular filling pressures (PAOP or LAP \approx LVFP) were kept between 1–12 mmHg by minimizing fluid intake.

PULMONARY EDEMA ANIMALS (n = 11)

After placement of the monitoring catheters, an initial set of measured and calculated variables was obtained as in the control group. Following these measurements the left atrial balloon was inflated with 8–15 ml physiologic saline and intravenous physiologic saline was in-

fused rapidly to increase the LAP to 25–30 mmHg. The animals required fluid at rates of 2–5 l/h. After one hour of high LAP and volume infusion, the second set of measured and calculated variables were obtained. These measurements were repeated hourly during the next 2- to 4-h experimental period.

Approximately 10 min before termination, all animals were heparinized (100 IU/kg). Immediately following the last period of data collection all the animals were killed with pentobarbital (80 mg/kg). The chest was opened immediately and the lung hila clamped. The lungs, undrained of blood, were removed, weighed, and analyzed gravimetrically (Appendix B).^{3,6} After weighing, both lungs were homogenized in a Waring® commercial blender (model 32BL39) with 700 ml distilled water. An aliquot was centrifuged (10,000 g \times 30 min). Aliquots of blood (obtained at termination), lung homogenate, and lung supernatant were then weighed and dried at 80° C to a constant weight over three days. Hemoglobin concentrations (Hb) of the blood and supernatant were determined using standard colorimetric techniques within four hours of homogenization. Refer to Appendix B for calculations used to derive extravascular lung water (EVLW), extravascular dry weight (EVDW), and pulmonary extravascular tissue weight (PEW).

Statistical analysis utilized Student's *t* test for comparison of paired and nonpaired data, and linear and nonlinear regression by least-squares method, with level of significance of $P \leq 0.05$. Nonlinear analysis utilized exponential, logarithmic, and power equations.

Results

Pretermination measurements of EVTV, heart rate (HR), intravascular pressures, and gravimetric analysis of lung water were significantly different between the control and pulmonary edema groups (table 1). There were no significant differences between the two groups for cardiac output, and mean arterial pressure (MAP). Pretermination data derived from blood-gas measurements available in four control animals and nine edema animals demonstrated no significant differences between groups for arterial pH, oxygen, and carbon dioxide tension, alveolar-arterial oxygen tension gradient, and intrapulmonary shunt (table 2). The edema animals had significantly lower pretermination temperature, hemoglobin concentration, and arterial and mixed venous oxygen contents when compared to control animals. Five of the 11 edema animals developed airway flooding severe enough to result in edema fluid in the major airways and trachea.

Correlation of the pretermination EVTV with gravimetric PEW generated a close linear relationship (fig.

TABLE 1. Lung Water and Pretermination Hemodynamic Data

	Control		P	Edema	
	Mean ± SE	n		Mean ± SE	n
PEW (g/kg)	6.0 ± .6	(11)	<0.001	18.4 ± 2.7	(10)
EVTV (ml/kg)	8.4 ± .4	(11)	<0.001	23.9 ± 3.0	(10)
CVP (mmHg)	5 ± .9	(11)	<0.001	19 ± 2.0	(8)
PA (mmHg)	17 ± 1	(11)	<0.001	36 ± 2.0	(11)
LVFP (mmHg)	7 ± 1	(11)	<0.001	31 ± 2.0	(11)
COP (mmHg)	11 ± 1	(3)	<0.001	4 ± 1.0	(10)
PAOP-COP (mmHg)	-6 ± 1	(3)	<0.001	28 ± 2.0	(10)
HR (beats/min)	131 ± 13	(9)	<0.05	99 ± 6.0	(10)
MAP (mmHg)	120 ± 7	(11)	ns	100 ± 9.0	(11)
CO (l/min)	2.7 ± .6	(11)	ns	3.1 ± 0.3	(11)

PEW = pulmonary extravascular tissue weight; EVTV = extravascular thermal volume; CVP = central venous pressure; PA = Pulmonary artery pressure; LVFP = Left ventricular filling pressure;

COP = Colloid oncotic pressure; PAOP-COP = Pulmonary artery occlusion pressure-colloid oncotic pressure gradient; HR = Heart rate; MAP = Mean arterial pressure; CO = Cardiac output.

1). EVTV correlated well with any of the commonly used methods of expressing gravimetric data (table 3) but consistently overestimated extravascular lung water (EVLW). When the five animals with alveolar flooding were analyzed separately the regression equation generated ($EVTV = .69 PEW + 14.4 \text{ ml/kg}$; $r = 0.81$, $n = 5$) was not significantly different ($P > 0.50$) from the regression analysis of the remaining animals ($EVTV = 1.14 PEW + 1.87 \text{ ml/kg}$; $r = 0.94$, $n = 16$). Two of 23 animals studied were excluded from these comparisons because of technical problems with the gravimetric analysis. These two animals were included in the analysis of physiologic events which occurred during the experimental period.

A total of 324 EVTV measurements were performed in this study. Of the 85 series of EVTV measurements (3–5 measurements per series) the mean coefficient of variation was 8.2 per cent.

The relationship between EVTV obtained throughout the experiment and several physiologic measurements

commonly used for the assessment of lung water accumulation was analyzed in all animals ($n = 23$). First, EVTV was correlated with measurements of arterial oxygenation obtained during the experiment; Pa_{O_2} , $A-aD_{O_2}$, and \dot{Q}_{san}/\dot{Q}_t (fig. 2). There was a poor linear correlation between EVTV (ml/kg) and Pa_{O_2} and $A-aD_{O_2}$ ($r = 0.47, 0.45$, respectively). The Pa_{O_2} data fit best to a nonlinear regression equation. The intrapulmonary shunt fraction, using linear correlation, was the best predictor of extravascular fluid accumulation ($r = 0.72$). Second, EVTV was compared with intravascular pressure measurements; left ventricular filling pressure (LVFP), colloid oncotic pressure (COP), and PAOP-COP gradient (fig. 3). Each correlation of these three intravascular pressures with EVTV achieved the best fit to a nonlinear equation. There was no significant correlation between EVTV and cardiac output observed in this experiment.

Discussion

We evaluated a modification of the double-indicator dilution method of lung water measurement. The technique used a combination of indocyanine green and negative heat as the two indicators. (Refer to Appendix A for an explanation of indicator dilution theory and computation.) This method was recently investigated in dogs, baboons, and a few critically ill patients.^{2,3,7-10} A study of 27 dogs produced excellent results in normal and moderately edematous lungs ($EVTV = 6-17 \text{ ml/kg}$).² No animals developed airway flooding. The following regression equation was generated; $EVTV = .87 EVLW + 42 \text{ ml}$, $r = 0.96$. Despite these findings, at a recent conference on methods of lung water measurement,¹¹ it was concluded that further investigation of this technique was necessary over a wide range of conditions that were not examined by Lewis and Elings. The present study was done to evaluate the validity of the thermal dye

TABLE 2. Pretermination Blood-gas Data

	Control (n = 4) (mean ± SE)	P	Edema (n = 9) (mean ± SE)
Pa_{O_2} (mmHg)	338 ± 99	ns	226 ± 75
Pa_{CO_2} (mmHg)	41 ± 8	ns	41 ± 6
pH_a	7.29 ± .09	ns	7.10 ± .07
$A-aD_{O_2}$ (mmHg)	334 ± 99	ns	226 ± 99
\dot{Q}_{san}/\dot{Q}_t (per cent)	20 ± 7	ns	36 ± 5
Temperature (°C)	35.5 ± .6	<0.001	31.5 ± .2
Hb (g/dl)	11.2 ± .7	<0.005	7.2 ± .6
Ca_{O_2} (ml/dl)	17.2 ± 1.8	<0.001	9.2 ± .9
$C\bar{v}_{O_2}$ (ml/dl)	12.5 ± 1.9	<0.001	7.1 ± .9

Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; pH_a = arterial pH; $A-aD_{O_2}$ = alveolar arterial oxygen tension difference; \dot{Q}_{san}/\dot{Q}_t = intrapulmonary right-to-left shunt; Hb = hemoglobin concentration; Ca_{O_2} = arterial oxygen content; and $C\bar{v}_{O_2}$ = mixed venous oxygen content.

technique to quantitate lung water in a model of hydrostatic pulmonary edema. We produced a greater degree of lung injury than had been investigated previously (EVTV = 5–40 ml/kg) to determine if the measurement became unreliable when alveolar flooding occurred. A secondary aim was to examine the relationship between lung water and commonly used clinical indices of pulmonary edema.

Our results demonstrate good correlation between the double-indicator dilution measurement and gravimetrically obtained estimates of extravascular tissue weight. Our study, as well as previous work, demonstrates that this double-indicator dilution technique consistently overestimates lung water (EVLW) determined gravimetrically. There are several factors that explain the difference between “thermal” lung water and the *in vitro* (gravimetric) measurement. First, there is loss of heat to nonaqueous structures. Heat may equilibrate with nonaqueous structures (lung parenchyma, gas in the lung, mediastinum, chest wall, heart, vessel wall) depending on the specific heat of components of these structures (protein, fat, carbohydrate, elastic connective tissue, cartilage). This factor explains why EVTV correlated slightly better with PEW and EVLW (table 3). Noble *et al.* using the thermal/conductivity technique, have suggested that as much as 14 per cent of heat loss may occur in the left heart¹² and as high as 20 per cent in the right heart.¹³ This factor can artificially increase EVTV, but may be counteracted by regional lung hypoperfusion. In these areas, extravascular water volume is missed by the thermal indicator and lung water volume is underestimated. This error is much less severe with heat than with tritiated water because of the greater diffusability of thermal energy than of a molecular indicator.¹⁴ Second, the difference between EVTV and EVLW also may be related to underestimation of lung water by the standard *in vitro* method. Oppenheimer *et al.*³ have suggested that in the Pearce *et al.*⁶ gravimetric method, an error results from the assumption that all the red blood cells are intravascular. If some red cells are interstitial, which can occur in edematous states then blood H₂O is artifactually increased and the derived EVLW (and PEW) is decreased (EVLW = total lung H₂O – blood H₂O). Evidence on oleic acid-induced edema suggests this error is approximately 10 per cent.³ Despite the overestimation of lung water by EVTV, our data suggest that accurate reflections of changes in lung water are possible with this method.

The slope of the regression line generated by our data is higher than that reported by previous authors. This difference may be due to the fact that our study included animals with airway flooding not evaluated by previous authors. With airway flooding, the indicator must traverse a greater distance so there is greater potential for

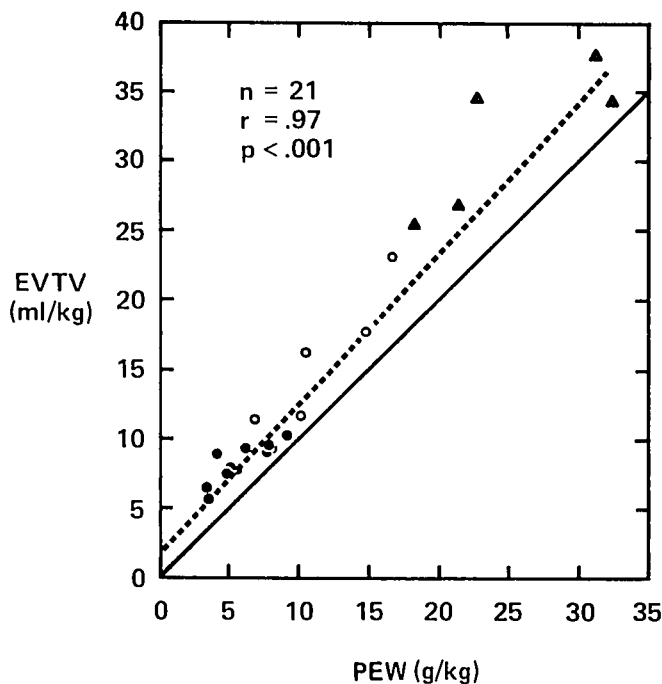


FIG. 1. Pretermination measurement of extravascular thermal volume (EVTV) is plotted against pulmonary extravascular tissue weight (PEW) obtained by gravimetric analysis. Animals with pulmonary edema but without airway flooding are represented by open circles. Animals with airway flooding are represented by triangles. Control animals are represented as closed circles. The derived regression equation (dashed line) and identity line (solid line) are shown. The EVTV measurement reflects extravascular tissue weight even in the presence of airway flooding.

error. In fact, when the five animals with alveolar flooding were analyzed separately, another regression equation was generated, but it was not statistically different from the equation produced from the remaining animals. No difference may have been seen because of the small number of animals with airway flooding. The wider scatter of the data for those animals would also suggest that

TABLE 3. Linear Correlation of Pretermination EVTV with Gravimetric Lung Water Data

Units	b	m	r
EVLW			
ml	64	1.26	0.97
ml/kg body weight	2.9	1.30	0.96
ml/g EVDW	2.9	1.19	0.94
PEW			
g/kg body weight	2.1	1.15	0.97

The correlation data shown are derived from pretermination EVTV and postmortem gravimetric lung water analysis. The data are expressed according to the linear regression; $y = mx + b$; where $y = \text{EVTV}$, $x = \text{EVLW}$ (extravascular lung water) or PEW (pulmonary extravascular tissue weight), and $r = \text{correlation coefficient}$ ($n = 21$). For all correlations $P < 0.001$.

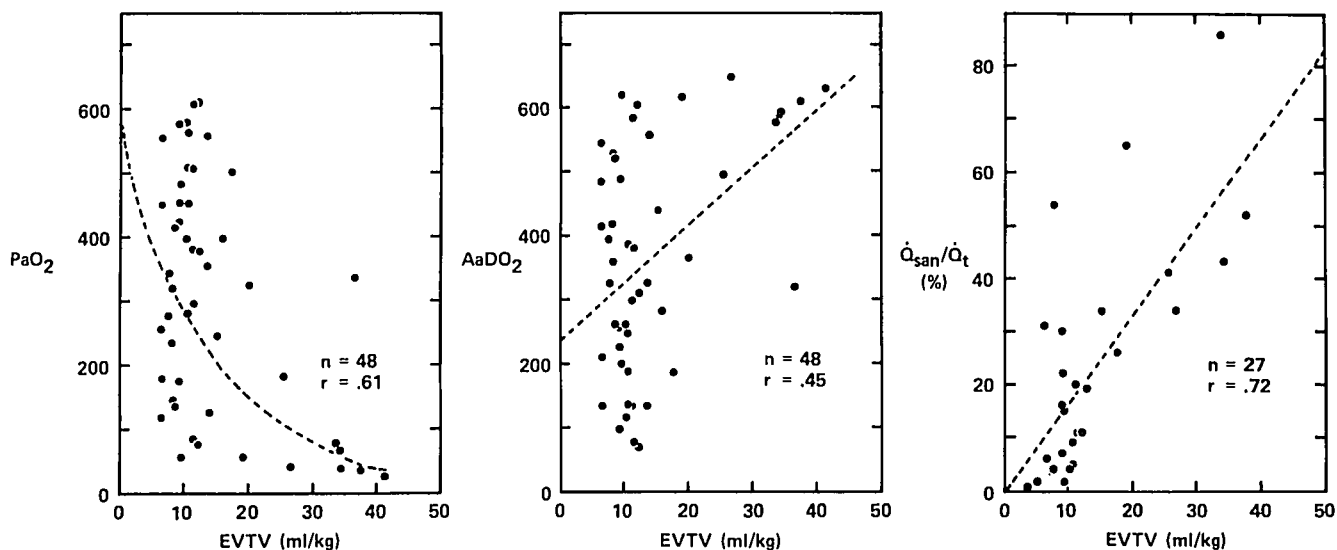


FIG. 2. Measurements of arterial oxygenation ($F_{I_{O_2}} = 1.0$) obtained throughout the course of the experiment are plotted against simultaneous measurements of EVTV. Arterial oxygen tension (P_{aO_2}), alveolar-arterial oxygen tension gradient ($A-aDO_2$) and intrapulmonary shunt (\dot{Q}_{san}/\dot{Q}_t) data are plotted on the three y-axes, with EVTV on the x-axis. Regression lines are drawn demonstrating the best fit of the $A-aDO_2$ and \dot{Q}_{san}/\dot{Q}_t data to a linear regression equation. The P_{aO_2} data were best fit to a nonlinear regression which is shown. For all correlations $P = <0.01$. The most significant correlation was found between EVTV and \dot{Q}_{san}/\dot{Q}_t where: $\dot{Q}_{san}/\dot{Q}_t = 1.68 \text{ EVTV} + 0.02$, $r = 0.72$, $P < 0.01$.

this is one source of possible error in the technique (fig. 1). Further studies of this potential problem are needed.

Our study also demonstrated the relative insensitivity of the usual indirect indicators of lung water accumulation (P_{aO_2} , $A-aDO_2$, \dot{Q}_{san}/\dot{Q}_t , LVFP, COP, and PAOP-COP gradient) during the production of hydrostatic pulmonary edema. Oxygenation variables correlated poorly with EVTV. As expected, the intrapulmonary shunt was more sensitive than simply the P_{aO_2}

or $A-aDO_2$. Since our experimental model was high pressure edema, intravascular pressures generally correlated better with EVTV than oxygenation variables. Finding the best fit to a nonlinear relationship is consistent with a similar study by Guyton and Lindsey¹⁵ which demonstrated that a critical pressure had to be reached before pulmonary edema accumulated. In our experiments the critical pressure occurred at an LVFP of 10–12 mmHg, with severe edema accumulation at 22–27 mmHg. This

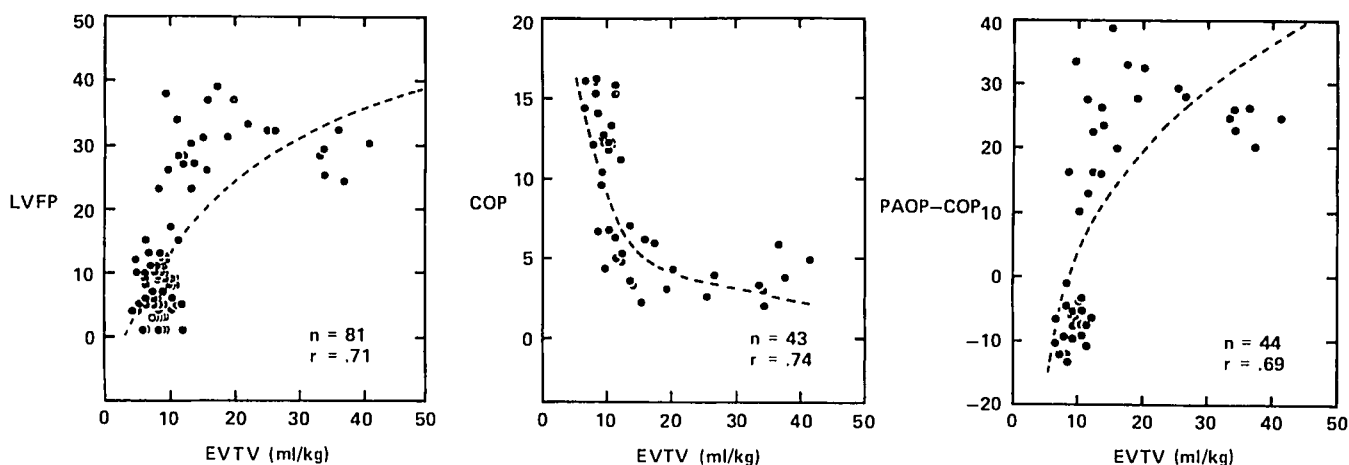


FIG. 3. Intravascular pressure measurements obtained throughout the course of the experiment are plotted against simultaneous measurements of EVTV. Left ventricular filling pressure (LVFP), colloid oncotic pressure (COP), and the pulmonary artery occlusion pressure-colloid oncotic pressure gradient (PAOP-COP) are plotted on the three y-axes with EVTV on the x-axis. All three pressure variables correlated best with EVTV in a nonlinear relationship. The regression lines are shown, demonstrating a slightly better fitting of COP than LVFP or PAOP-COP data. A logarithmic function ($y = m \ln x + b$) best fit the LVFP and PAOP-COP data and a power function ($y = mx^b$) best fit the COP data. For all correlations $P = <0.01$. Lung water begins to increase when LVFP = 10–12 mmHg and increases significantly at 22–27 mmHg.

is consistent with the Guyton and Lindsey¹⁵ findings in protein depleted animals (serum proteins decreased 47 per cent).

In our experimental model, there were several noticeable differences between control and edema group pre-termination data. There were predicted differences in PEW, EVTV, and intravascular pressures. The lower temperature of the edema group reflects the large amount of room temperature saline used to create severe pulmonary edema (8–10 l/experiment). This large saline infusion also explains the large fall in oncotic pressure and hemoglobin concentrations. With decreased hemoglobin levels, both arterial and mixed venous oxygen contents were also decreased. The control animals were fasted overnight and fluid restricted throughout the experiment. This may explain the higher heart rate observed in this group.

There was a notable lack of statistically significant differences in the pre-termination values for P_{aO_2} , pH_a , $A-aD_{O_2}$, and \dot{Q}_{san}/\dot{Q}_t between the control and edema groups (table 2). There may be several reasons for this finding. Complete blood-gas data were available from only four control animals ventilated with 100 per cent oxygen for comparison with the edema animals. Three out of these four underwent thoracotomy for placement of the left atrial catheter. Despite attempts at reexpansion, these control animals had gross evidence of atelectasis at the time of lung removal and this may explain the poor oxygenation in that group. Additionally, only five pulmonary edema animals had severe pulmonary edema with airway flooding. These factors probably explain the lack of statistical difference in oxygenation at the termination of the experiment.

Several potential sources of error in the technique were not evaluated in the present study, but may be important in its clinical application. Any impairment of regional pulmonary blood flow (emboli, decreased cardiac output, increased viscosity, vasoconstriction) may effect the adequate distribution of the thermal indicator. Oppenheimer *et al.*³ have demonstrated that with glass bead (50 μ M diameter) embolization in the presence of pulmonary edema, some lung water is not measured. In the adult respiratory distress syndrome microemboli are commonly found in the pulmonary circulation and may impair the even distribution of pulmonary blood flow. Our model did not examine this problem, since hydrostatic pulmonary edema may increase flow to the capillary bed and improve perfusion.

Reduced cardiac output may also reduce pulmonary perfusion and may potentially interfere with the technique. Reduced cardiac output has been shown to decrease the reliability of double-indicator dilution methods which use tritiated water as the extravascular indicator.^{16,17} This is due to increases in physiologic deadspace

which occur during periods of low cardiac output. Heat is 100 times more diffusible than tritiated water so it should be less dependent upon cardiac output. In the range of cardiac outputs we studied (mean \pm SD = 3.1 ± 1.5 l/min; range 1.2–6.6 l/min), the technique was reliable. However, we did not systematically examine the role of low cardiac output in impairing the precision of the technique. Finally, increased viscosity of blood may interfere with even blood flow distribution. This was also not evaluated in our study. The pulmonary edema group sustained volume expansion which would decrease viscosity, while the lower blood temperatures in this group would tend to increase viscosity.

We conclude that this double-indicator dilution technique of quantitating lung water closely approximates extravascular tissue weight in this model of hydrostatic pulmonary edema. The thermal dye measurement was a more sensitive guide to increases in lung water than were the commonly used physiologic indices of pulmonary edema. Limitations of the technique need further evaluation.

The authors recognize the assistance of Dr. Diana Guthaner, Mr. Charles Osgood, Ms. Norma Garcia, Ms. Betty Hampton, and Mr. Charles Sheldon in performing this study and in preparing the manuscript.

References

1. Fishman AP: Pulmonary edema, Pulmonary Diseases and Disorders. San Francisco, McGraw-Hill, 1980, p 733
2. Lewis FR, Elings VI: Microprocessor determination of lung water using thermal-green dye double indicator dilution. *Surg Forum* 29:182–184, 1978
3. Oppenheimer L, Elings VI, Lewis FR: Thermal-dye lung water measurements: Effects of edema and embolization. *J Surg Res* 26:504–512, 1979
4. Levine OR, Mellins RB, Fishman AP: Quantitative assessment of pulmonary edema. *Circ Res* 17:414–426, 1965
5. Severinghaus JW: Blood gas calculator. *J Appl Physiol* 21:1108–1110, 1966
6. Pearce ML, Yamashita J, Beazell J: Measurement of pulmonary edema. *Circ Res* 16:482–488, 1965
7. Holcroft JW, Trunkey DD: Pulmonary extravasation of albumin during and after hemorrhagic shock in baboons. *J Surg Res* 18:91–97, 1975
8. Holcroft JW, Trunkey DD, Carpenter MA: Excessive fluid administration in resuscitating baboons from hemorrhagic shock and an assessment of the thermodye technique for measuring extravascular lung water. *Am J Surg* 135:412–416, 1978
9. Holcroft JW, Trunkey DD: Extravascular lung water following hemorrhagic shock in the baboon. *Ann Surg* 180:408–415, 1974
10. Lewis FR, Elings VI, Sturm JA: Bedside measurement of lung water. *J Surg Res* 27:250–261, 1979
11. Staub NC, Hogg JC: Conference report of a workshop on the measurement of lung water. *Crit Care Med* 8:752–759, 1980
12. Noble WH, Obdrzalek J, Kay JC: A new technique for measuring pulmonary edema. *J Appl Physiol* 34:508–512, 1973
13. Noble WH, Severinghaus JW: Thermal and conductivity dilution curves for rapid quantitation of pulmonary edema. *J Appl Physiol* 32:770–775, 1972
14. Kreith F: Principles of Heat Transfer. Scranton, International Textbook Company, 1958, pp 495, 537

15. Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ Res* 7:649-657, 1959
16. Goresky CA, Cronin RFP, Wangel BE: Indicator dilution measurements of extravascular water in the lungs. *J Clin Invest* 48:487-501, 1969
17. Gump FE, Mashimu Y, Jorgensen S, Kinney JM: Simultaneous use of three indicators to evaluate pulmonary capillary damage in man. *Surgery* 70:262-270, 1971
18. Grodin FS: Volumes by indicator dilution methods. *Circ Res* 10:429-446, 1962

APPENDIX A

Theory and Computation

Applied double indicator dilution theory¹⁸ allows the measurement of flow (F) and volumes (V_0 and V_1) shown in figure 4. The single chamber V_0 , is surrounded by another chamber V_1 , containing nonmoving fluid. This system is analogous to the lung, where V_0 is the volume of blood and V_1 is the volume of water outside the blood vessels. An intravascular indicator like green dye injected at point A and detected at point B will allow calculation of V_0 . An extravascular indicator like heat diffuses readily into the interstitial water space (V_1) which means that the volume calculated by measuring this indicator equals $V_0 + V_1$. Therefore, the volume V_1 is calculated by: $V_1 = F \times (MTT_{cv} - MTT_{iv})$ where MTT_{cv} = mean transit time of the extravascular indicator (*i.e.*, thermal) and MTT_{iv} = mean transit time of the intravascular indicator (*i.e.*, green dye). The error introduced by the non-instantaneous indicator injection affects both indicators equally and therefore does not affect the measurement of V_1 or extravascular lung water.

The lung water computer (Edwards model 9310) consists of a microcomputer system operating under the control of a stored program which receives and analyzes the thermal signal from the catheter thermistor and the change in color signal detected

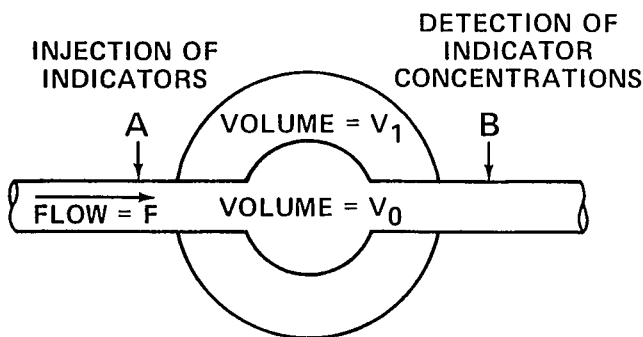


FIG. 4. Illustration of a system containing moving fluid with a volume V_0 and flow F, surrounded by a system of volume V_1 which contains nonmoving fluid.

by the Waters Instrument Model TD-1 densitometer. The signals are amplified, processed by an analog to digital converter, and then digitized at a rate of 7/s. Stored data (approximately 300 for each curve) are then analyzed. A precise beginning of each curve is derived by defining the 50 per cent and 25 per cent points from the peak of the upslope and back extrapolating a straight line to the baseline. The 75 per cent and 30 per cent points of the downslope of each curve are defined, through which an exponential curve is fitted and then extrapolated to infinity. The area under each curve from start to 30 per cent of the downslope is integrated and then added to the area under the extrapolated exponential decay. From these data, femoral thermodilution cardiac output and the mean transit times of the two indicators are derived. The extravascular thermal volume (EVTV) is then calculated from this information:

$$EVTV \text{ (ml)} = CO \times (MTT_T - MTT_D) \times 16.7.$$

In this equation, CO = femoral thermodilution cardiac output (l/min); MTT_D = mean transit time of the thermodilution curve (seconds); and MTT_T = mean transit time of the dye dilution curve (seconds). The numerical factor 16.7 converts the cardiac output from l/min into ml/s ($1000/60 = 16.7$). The computer program makes corrections for the response times of the thermal and dye indicators and the thermal injectate temperature. Deconvolution of the data is not required because recirculation of the indicators does not occur until the signal curves are less than 30 per cent of the peak.

APPENDIX B

Gravimetric Lung Water Calculations⁹

- (1) $Hb_{hom} = Hb_{sup} \times (\text{Per cent } H_2O_{hom} / \text{Per cent } H_2O_{sup})$
- (2) $W_{t_{bld}} = (Hb_{hom} / Hb_{bld}) \times W_{t_{hom}} = (Hb_{sup} / Hb_{bld}) \times (\text{Per cent } H_2O_{hom} / \text{Per cent } H_2O_{sup}) \times W_{t_{hom}}$
- (3) $H_2O_{bld} = (\text{Per cent } H_2O_{bld} \times W_{t_{bld}}) / 100 \text{ Per cent}$
- (4) $TLW = (\text{Per cent } H_2O_{hom} \times W_{t_{hom}}) / 100 \text{ Per cent} - H_2O_{added}$
- (5) $EVLW = TLW - H_2O_{bld}$
- (6) $EVDW = W_{t_{lung}} - W_{t_{bld}} - EVLW$
- (7) $PEW = EVLW + EVDW$

where: sup = lung homogenate supernatant; hom = lung homogenate; Hb = hemoglobin; $W_{t_{bld}}$ = weight of blood in lung (g); H_2O_{bld} = water contained within blood in lungs (ml); TLW = total lung water (ml); H_2O_{added} = distilled water added to lungs (ml); EVLW = extravascular lung water (ml); EVDW = extravascular dry weight (g); and PEW = pulmonary extravascular tissue weight (g).