

Effect of Cardiac Output on Extravascular Lung Water Estimates Made with the Edwards® Lung Water Computer

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The Edwards® lung water computer system uses the thermal-dye indicator technique to estimate the lung extravascular fluid volume (EVLW). The authors tested the effect of changes in cardiac output (CO) on EVLW estimates made with the lung water computer in six dogs anesthetized with halothane. Baseline CO was 2.5 ± 1.3 l/min (mean \pm SD); CO subsequently was increased either by 220% or decreased by 70% by either giving 0.5 mg/kg of isoproterenol or increasing the inspired halothane (1-4%), respectively. There was a significant correlation between the estimated EVLW and CO in each animal ($P < 0.05$) such that a 50% decrease in CO from baseline caused an approximately 40% increase in estimated EVLW. Postmortem examination showed that the lungs were not edematous, even though the lung water computer data indicated that severe pulmonary edema had developed at reduced COs. At increased COs, estimated EVLW decreased. The authors conclude that the Edwards® lung water computer overestimates lung water, possibly because the thermal indicator diffuses into nonpulmonary as well as pulmonary tissue. The overestimate is greatest at low cardiac outputs. (Key words: Lung; extravascular fluid; pulmonary edema. Measurement techniques: indicator dilution; thermal dye.)

THE ACCURATE ESTIMATION of lung extravascular water volume (EVLW) has important research and clinical applications. Recently, investigators have attempted to measure EVLW with a thermal-indocyanine green dye technique (double indicator dilution).¹⁻³ A bolus of cold, dye-containing solution is injected into the vena cava, and the change in temperature and the dye concentration in aortic blood is detected. Theoretically, the thermal indicator will diffuse throughout the lung tissue, while the dye remains in the intravascular space. By this technique, EVLW should equal the cardiac output times the difference in the mean transient times of the thermal and dye indicators. This technique has been used in human and animal studies, and there now is a commercially available thermal-dye computer for

patient use (Edwards® lung water computer§). Some investigators have suggested that the EVLW, estimated with the thermal-dye technique, may vary with the cardiac output.^{1,4} In this study, we tested the effect of changes in CO upon EVLW estimated with the Edwards® lung water computer. We estimated EVLW at baseline and after increasing or decreasing CO to various levels in anesthetized dogs. We found that the EVLW estimate was dependent upon CO.

Materials and Methods

Six dogs initially were anesthetized with sodium pentothal. They were intubated and ventilated using a mechanical respirator (Harvard®) at a tidal volume of 15 ml/kg and 12 breaths/min. The inspired gas mixture was approximately 50% O₂ and 50% room air and contained 1% halothane. We placed catheters into the aorta and central vena cava via the left femoral artery and vein. The venous catheter volume was less than 0.5 ml as required for use with the Edwards lung water computer. We placed a 5 F thermistor catheter (Edwards Laboratories femoral artery lung water catheter) into the right femoral artery. A 5 F thermistor-catheter was placed into the pulmonary artery via an external jugular vein. We used this catheter to confirm that there were no substantial changes in pulmonary artery or pulmonary artery wedge pressures during the experiments. Once the catheters were placed and each dog was given 200-300 ml of isotonic saline, normal acid base status of arterial blood samples was confirmed with an Instrumentation Laboratory® model 813 pH-Blood Gas analyzer.

ESTIMATION OF THERMAL-DYE EXTRAVASCULAR LUNG WATER (EVLW)

We used an American Edwards Laboratories Model 9310® lung water computer to estimate EVLW. Ten milliliters of ice-cold isotonic saline solution containing 0.25 g/ml of indocyanine-green dye were injected into

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§ The lung water computer kindly was provided by American Edwards Laboratories, Irvine, California. We demonstrated the EVLW versus CO relationship to representatives of Edwards Laboratories. They were unable to explain our findings, based on malfunction or misuse of the instrument.

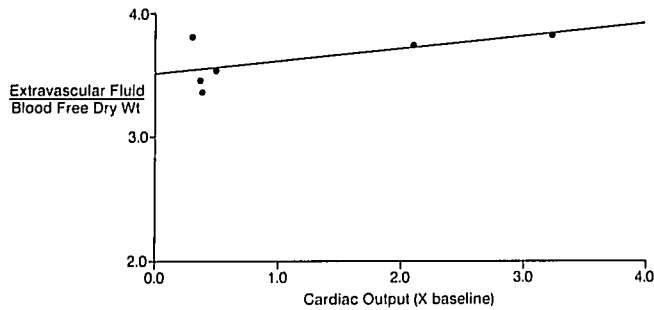


FIG. 1. The postmortem extravascular fluid–blood free dry weight ratio *versus* the final cardiac output for each experiment. The regression was not significant ($r = 0.647$).

the central venous catheter. Femoral arterial blood was withdrawn through the 5 F thermistor-catheter at 30 ml/min. The blood was directed through a densitometer cuvette for the estimation of indocyanine-green dye concentration with a Waters D402A® densitometer. The output from the densitometer and the thermistor port of the catheter were connected to the lung water computer, as has been described elsewhere.³ The computer used the thermal and dye concentration curves to estimate the thermal and dye mean transient times. The computer also used the thermal curve to estimate CO and determined EVLW as CO times the thermal minus the dye mean transient times.

EXPERIMENTS

We estimated EVLW at baseline CO in each dog. Then we decreased the CO by increasing the halothane concentration in the inspired gas up to 4% or increased CO by infusing 0.5 mg/kg of isoproterenol into the femoral venous catheter. We measured the CO with an Instrumentation Laboratory® (Model 601) thermal dilution CO computer to verify that the drugs had changed CO. EVLW then was estimated, and the CO was further increased or decreased. We estimated EVLW six to 10 times in each dog. CO was both increased and decreased in two dogs, decreased only in two dogs, and increased only in two dogs.

After the last EVLW estimate in each dog, we took a 50-ml sample of arterial blood and killed the dogs with iv KCl. The lungs rapidly were removed, and the extravascular fluid volume and blood-free dry weight was estimated with a modification of the method of Pearce.^{5,6}

STATISTICS

All summary data are reported as mean \pm 1 SD. The method of least squares was used to estimate the relationship between variables. Student's *t* test for paired

data was used to determine the significance of differences in EVLW and postmortem lung water data. $P < 0.05$ was considered significant.

Results

The baseline CO and estimated EVLW were 2.5 ± 1.3 l/min and 161 ± 34 ml, respectively. The postmortem extravascular fluid–blood free dry weight ratio for all lungs (3.6 ± 0.2) was consistent with the ratios of 3.5 to 3.8 found by other investigators for nonedematous lungs.^{6,7} We varied CO from 30% to 320% of baseline, but we did not find a significant correlation between the extravascular fluid volume–blood free dry weight ratio and CO (fig. 1).

In each experiment there was, however, a significant inverse relationship between estimated EVLW and CO. Figures 2 and 3 show the EVLW data for two experiments. At baseline, estimated EVLW was significantly greater than the postmortem lung water (table 1). Increases in CO caused large decreases in EVLW (fig. 2). At high COs, estimated EVLW tended to approach the postmortem water, however, decreases in CO resulted in a larger overestimation of postmortem water (fig. 3).

Because the error in estimated EVLW appeared to be proportional to the reciprocal of CO, we used linear regression to estimate the relationship between estimated EVLW and $1/\text{CO}$ for each experiment:

$$\text{EVLW} = A/\text{CO} + B \quad (1)$$

The correlation coefficients for the six experiments ranged from 0.86 (fig. 2) to 0.94 (fig. 3), and each correlation was significant. Table 1 gives the regression coefficients for the relationship in each experiment.

We used equation (1) to plot the regression curves in figures 2 and 3. This equation is linear for EVLW *versus* $1/\text{CO}$, however, it is nonlinear for EVLW *versus* CO. Because we plotted EVLW *versus* CO in these figures, the regression curves are nonlinear.

Discussion

We did not produce pulmonary edema in this study. The postmortem extravascular fluid to blood free dry weight ratios were all well within the normal range for dog lungs.^{6,7} The lungs appeared normal on cut section, and there was no evidence of fluid in the perivascular spaces or edema foam in the airways. On the other hand, the lung water computer indicated that severe edema occurred at low cardiac outputs. In the four experiments with reduced cardiac outputs, the computer-estimated EVLW divided by the postmortem blood-free dry weight was 8.0 ± 1.8 , a level of edema that Guyton and Lindsey⁸ found to cause respiratory death in dogs. Yet the postmortem lung extravascular fluid–dry weight

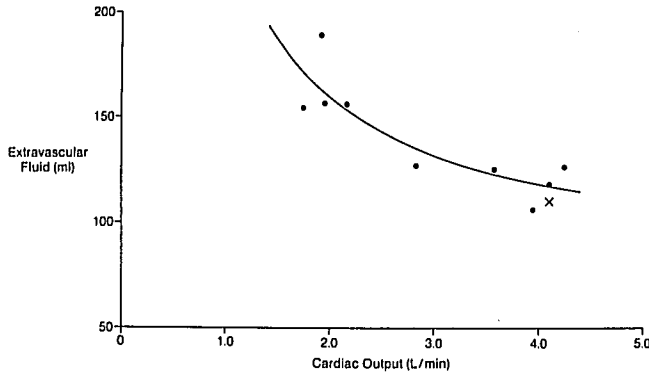


FIG. 2. Thermal-dye estimate of lung extravascular fluid volume (●) versus cardiac output for an experiment in which CO was increased only (exp. no. 6). X = postmortem extravascular fluid volume plotted at the final cardiac output.

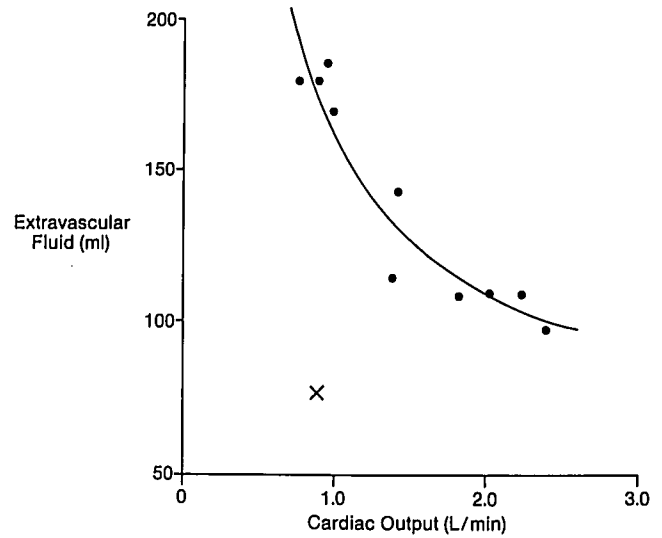


FIG. 3. Thermal-dye estimates of lung extravascular fluid volume (●) versus cardiac output for an experiment in which CO was both increased and decreased (exp. no. 1). X = postmortem extravascular fluid volume plotted at the final cardiac output.

ratio in these dogs was only 3.6 ± 0.2 and was significantly less than the 8.0 ± 1.8 value we calculated from the lung water computer data ($P < 0.01$).

The lung water computer data indicated a strong relationship between EVLW and cardiac output in every experiment (figs. 2 and 3). Because there was no change in the true lung water, these changes in estimated EVLW must have been erroneous. We believe that this error was due to the detection of nonpulmonary water by the lung water computer. As the thermal indicator passes through the vasculature, it should diffuse into the walls of the blood vessels and heart as well as the lung tissue.⁹ In addition, the thermal indicator may diffuse from the lungs into the diaphragm and chest wall. This diffusion of thermal indicator into nonpulmonary tissues would yield erroneously high estimates of EVLW. The error should be exacerbated with low cardiac outputs, because the thermal indicator should have a longer time to diffuse further into the nonpulmonary tissue.

There are other possible explanations for the effect of CO on EVLW estimated with the lung water computer. First, some of the thermal indicator may have been lost from the circulation. Previous studies have indicated that this effect is small.⁹ Second, at high COs the thermal indicator may not have time to diffuse into all of the lung extravascular volume. This would cause an underestimate of EVLW. At lower COs, the thermal indicator would have more time to diffuse throughout the lung and could detect more of the lung water. The data of Allison *et al.*¹⁰ indicate that this effect may occur in embolized lungs. This possibility also is supported by the findings that the thermal-dye technique underestimated lung water in patients with high COs and pulmonary edema.¹ We do not believe that the thermal

TABLE 1. The Lung Water Data

Exp. No.	Exp. Type*	Dog wt. (kg)	CO† (l/min)	EVLW‡ (ml)	A§ (ml·l ⁻¹ ·min ⁻¹)	B§ (ml)	Postmortem H ₂ O (ml)
1	B	11.6	1.82	108	102	58	67
2	B	15.9	2.00	166	106	96	133
3	D	24.0	4.98	212	148	163	117
4	I	18.5	1.33	175	151	91	101
5	D	18.2	3.17	148	108	120	88
6	I	19.4	1.95	157	165	77	111
Mean		17.9	2.54	161	130	100	103
±SD		4.1	1.34	34	28	36	23

* Exp. type: I = increased cardiac output; D = decreased CO; B = both increased and decreased CO.

† CO = the baseline cardiac output.

‡ EVLW = the baseline extravascular lung water volume.

§ A, B = the regression coefficients for the EVLW versus 1/CO relationships of equation (1).

¶ Postmortem H₂O is the volume of extravascular fluid estimated with the modified method of Pearce at the end of the experiments.

indicator failed to detect the total lung extravascular volume in our study, because estimated EVLW was equal to or higher than the postmortem extravascular volume (Figs. 2 and 3).

Most studies of the validity of the lung water computer have involved estimating EVLW before and after edema formation.^{3,11} These studies generally have shown good agreement between estimated EVLW and postmortem extravascular water volume, and this has led many investigators to believe that the lung water computer is very reliable. However, there have been few studies designed to test the effect of CO without edema formation.

Hill *et al.*⁴ did attempt to study the effect of CO without edema formation in dogs. They reduced CO by 47% by renal pedicle ligation and found $11 \pm 18\%$ increase in estimated EVLW. Hill *et al.*⁴ concluded that this increase was relatively minor and should not substantially impair the accuracy of the thermal-dye method in animal research or clinical studies. Our data differ from that of Hill *et al.*, because they estimated EVLW at only two different COs for each animal. There was substantial variation in the response between animals, thus it was not possible to determine an accurate EVLW *versus* CO relationship from their data. We determined EVLW at six to 10 different COs in each experiment, which allowed us to estimate the EVLW *versus* CO relationship for each animal. By eliminating the "between-animal" variation, we were able to show that there was a very large variation in estimated EVLW, with changes in cardiac output in every experiment.

Our data indicate that the Edwards® lung water computer overestimates lung extravascular water volume, and the amount of overestimate is greatest at low cardiac

outputs. This dependence on cardiac output could cause serious errors in estimated changes in EVLW in patients or experimental animals.

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