

# Correlation of Oxygenation with Vascular Permeability-Surface Area but Not with Lung Water in Humans with Acute Respiratory Failure and Pulmonary Edema

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**ABSTRACT** We used a single-pass multiple tracer technique to measure cardiac output, extravascular lung water (EVLW) and lung vascular [ $^{14}\text{C}$ ]urea permeability-surface area ( $\text{PS}_u$ ) in 14 patients with acute respiratory failure and pulmonary edema. All patients had increased EVLW, but EVLW in the 10 surviving patients ( $0.26 \pm 0.06$  SE ml/ml total lung capacity [TLC]) was not significantly different from that in the five patients who died ( $0.22 \pm 0.05$ ). EVLW did not correlate with intravascular pressures or with alveolar-arterial oxygen pressure difference ( $\text{A-aDO}_2$ ).  $\text{PS}_u$  was lower in surviving patients ( $0.50 \pm 0.16$  SE ml/s  $\times$  liter TLC) than in patients who died ( $3.44 \pm 0.36$ ;  $P < 0.05$ ) and also lower than in previously reported data in patients with normal  $\text{PS}_u$ .  $\text{PS}_u$  correlated significantly with  $\text{A-aDO}_2$ . Serial studies showed that  $\text{PS}_u$  returned from a low value toward normal in a patient who survived but remained high in a patient who died. We conclude that the amount of edema in the lungs measured by indicator methods was not the principal determinant of either the magnitude of oxygenation defect or survival in the patients studied. We interpret the low  $\text{PS}_u$  in surviving patients as decreased surface area and infer that the ability of the lung circulation to reduce perfusion of damaged and edematous areas was important in preserving oxygenation. A high  $\text{PS}_u$ , presumably reflecting perfusion of areas with increased permeability, was a sign of especially poor

prognosis. Multiple tracer techniques for measuring lung vascular  $\text{PS}_u$  may help to define the pathogenesis and to evaluate therapies of acute lung injury in humans. Such measurements may be a more useful clinical tool than measurements of lung water in patients with acute respiratory failure and pulmonary edema.

## INTRODUCTION

Pulmonary edema is commonly associated with acute respiratory failure in humans without preexisting lung disease. In the absence of heart failure, that condition is often called the adult respiratory distress syndrome (ARDS).<sup>1</sup> Although the hypoxemia in these patients is usually attributed to edema, other abnormalities in both airway and vascular function may contribute to inadequate oxygenation (1).

Lung edema in ARDS is thought to result from increased vascular permeability to water and proteins. However, the pathogenesis of the syndrome in humans has been largely inferred from animal studies, because there have been no techniques for measuring lung vascular permeability in living humans.

Apart from hydrostatic and oncotic pressures (the "Starling forces"), determinants of fluid and solute filtration from the intravascular space into the lung include both the permeability of exchanging vessels

<sup>1</sup> *Abbreviations used in this paper:* A-aDO<sub>2</sub>, alveolar-arterial oxygen gradient; ARDS, adult respiratory distress syndrome; EVLW, extravascular lung water;  $\text{PS}_u$ , urea permeability-surface area; TLC, total lung capacity.

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and their surface area (2). There is good evidence that parallel inhomogeneities in flow resistance develop in injured lungs, so that flow to hypoxic (and edematous) regions is reduced (3). This decreased perfusion of malfunctioning areas would reduce perfused vascular surface area. In patients with acute respiratory failure, both increased vascular permeability and decreased exchanging vessel surface area would be expected.

Several techniques for measuring vascular permeability have been used in experimental animals, including measurements of lung lymph flow and protein content (4-6) and external scanning of radiolabeled macromolecules (7-8). A common feature of the techniques is that the measurements do not separate permeability from exchanging vessel surface area.

Previously, we used a multiple tracer technique to measure lung water and vascular permeability-surface area in animals (9-11) and humans with chronic heart failure (12). We now have made these measurements in patients with acute respiratory failure and pulmonary edema. We found that the severity of the gas-exchange abnormality in these patients did not correlate with lung water, but did correlate with permeability-surface area for urea ( $PS_u$ ). These findings are consistent with the notion that decreased perfusion of injured (and therefore poorly ventilated) areas of the lung helps preserve oxygenation of systemic blood by improving the match of perfusion to ventilation and that failure of this regulatory mechanism results in more severe systemic hypoxemia. Low  $PS_u$  in patients surviving acute respiratory failure suggested decreased perfused surface area and high permeability-surface area in patients dying of acute respiratory failure suggested perfusion of injured areas of the lung.

We conclude that severe hypoxemia in acute respiratory failure is due, at least in part, to a failure of the lung to decrease flow to injured areas and that this abnormality, reflected by a high permeability-surface area, is a sign of particularly bad prognosis. Permeability-surface area is lower than normal in patients with milder gas exchange abnormalities, so that the measurement may permit early diagnosis. Permeability-surface area is a more useful measurement than lung water, because it relates more closely to the gas exchange function of the lung and to severity of disease reflected in survival.

## METHODS

**Patient selection.** We studied 14 patients with the clinical diagnosis of acute respiratory failure and pulmonary edema in the intensive care units at Vanderbilt University Hospital and Duke University Medical Center. The only criteria for acceptance into the study were an initial  $Pa_{O_2} < 50$  torr at  $Fi_{O_2} = 0.21$ , multilobar infiltrates on chest radiograph, and no clinical evidence of heart failure (mea-

surements of pulmonary artery and wedge pressures were made at the time of the study). Patients with prior history of chronic lung or heart disease were excluded from the study, but etiology of the constellation of physiologic abnormalities was not an exclusion criterion. Patients were studied as early as possible after admission to the hospital or onset of respiratory failure, usually within 24 h. Repeat studies were done in two patients. Patients' therapies were not altered in any way except that 10 patients were placed on  $Fi_{O_2} = 1.00$  (fractional concentration of inspired oxygen) for 15 min before the study for measurement of alveolar-arterial oxygen gradient (A-a $DO_2$ ). This was done whenever possible to standardize conditions under which oxygenation was measured. We recognize that  $Fi_{O_2}$  may affect A-a $DO_2$ , but values from patients breathing  $Fi_{O_2} < 1.00$  did not determine any of the relationships presented below.

**Indicator dilution methods.** Before the study, a sample of venous blood was obtained from each patient and the erythrocytes were labeled by incubation with  $^{51}Cr$ -sodium chromate for 1 h. The cells were washed twice with 0.89% sodium chloride solution and resuspended to the original volume. To this suspension, sterile, pyrogen-free solutions of [ $^3H$ ]water, [ $^{125}I$ ]-human serum albumin and [ $^{14}C$ ]urea were added. The volume of this mixture injected for each study was 3.0 ml, containing 15  $\mu Ci$   $^{51}Cr$ , 40  $\mu Ci$   $^3H$ , 10  $\mu Ci$   $^{125}I$ , and 45  $\mu Ci$   $^{14}C$ .

3 ml of the isotope mixture was injected as a bolus through a central venous catheter and 30 blood samples were collected at 1.5-2.0-s intervals by allowing blood to flow from a radial artery cannula into heparinized tubes mounted on a precisely timed rotating disc collector. Samples were analyzed exactly as described several times in the literature (9-13). Briefly,  $^{125}I$  and  $^{51}Cr$  activities were measured in a gamma spectrometer in each blood sample and a sample of the injected mixture. After ethanol precipitation,  $^{14}C$  and  $^3H$  activities were measured in supernatant from the same samples in a liquid scintillation counter. Corrections for isotope overlap and quenching were made.

Indicator curves were constructed for each isotope by plotting activity in each sample relative to total activity injected as a function of time after injection and the downslopes extrapolated exponentially. All curves had recoveries of injected indicator of  $100 \pm 5\%$ . We calculated cardiac output as the reciprocal of the area under the  $^{51}Cr$  curve (14).

To calculate extravascular lung water and permeability-surface area for [ $^{14}C$ ]urea, we constructed a composite intravascular indicator curve from  $^{51}Cr$  and  $^{125}I$  data, weighted for hematocrit and water content of erythrocytes and plasma as described by Goresky et al. (15). This composite curve is the appropriate intravascular reference for both [ $^3H$ ]water and [ $^{14}C$ ]urea, since both distribute in blood water and there is intravascular separation of plasma and erythrocytes in transit through the lung (16).

We calculated extravascular lung water (EVLW) as the product of intravascular water flow (cardiac output  $\times$  fractional water content of blood) and the difference between mean transit time of [ $^3H$ ]water and mean transit time of the composite intravascular curve (15). We calculated permeability-surface area ( $PS_u$ ) for [ $^{14}C$ ]urea by the formula of Crone (17):

$$PS_u = -F \times \ln(1 - E),$$

where  $F$  = intravascular water flow and

$$E = \int_{t_0}^{t_1} \frac{(C_R - C_{urea})}{C_R} dt,$$

where  $C_R$  is the relative concentration of the composite intravascular reference curve, and  $C_{urea}$  is the relative concentration of [ $^{14}$ C]urea, and  $t_a$  and  $t_p$  are the appearance time and time of the peak of the reference curve, respectively. Using the composite intravascular reference curve in the  $PS_u$  calculation assumes that erythrocyte permeability for urea is large enough that it does not limit tracer urea exchange under the conditions of our studies.

Computation of  $PS_u$  by mathematical model analysis has been shown to be a more consistent method for computing  $PS_u$  in normal patients (12) and animals (18). However, many of the studies in the series had extractions so low that model methods were invalid. Hence, all  $PS_u$  values were computed by the Crone extraction formula for consistency.

We normalized data to predicted total lung capacity (TLC) to account for differences in lung size among patients.

**Other measurements.** We measured mean pulmonary artery and pulmonary artery wedge pressures through Swan-Ganz catheters placed in the pulmonary artery through an antecubital vein. The zero reference was the midaxillary line with patients supine. We measured  $PO_2$ ,  $PCO_2$ , and pH in arterial blood samples collected anaerobically just before the indicator study and calculated alveolar  $PO_2$ , assuming a respiratory exchange ratio of 0.8. Total protein concentrations were measured in plasma samples taken at the time of the indicator studies by a modified biuret method, and protein osmotic pressures were calculated by the equation of Landis and Pappenheimer (19).

**Statistics.** Differences between groups were considered significant if  $P$  was  $<0.05$  (unpaired  $t$  test) (20). Correlation coefficients between variables were calculated for a straight line and for a parabola.

## RESULTS

Table I summarizes demographic and clinical data for the 14 patients studied. The spectrum of diagnoses is typical of acute respiratory failure. The patients with

pneumococcal pneumonia and miliary tuberculosis were included because both had extensive bilateral infiltrates on chest radiograph and acute respiratory failure. Five of the 14 patients died of respiratory failure, a mortality rate similar to that reported in the literature (21).

Fig. 1 shows a representative set of indicator curves from one of the studies. The steeper rise and higher peak of the  $^{51}\text{Cr}$ -erythrocyte curve compared with that of  $^{125}\text{I}$ -albumin is typical of animal (9–11) and human (12) studies and presumably results from separation of plasma and erythrocytes in transit through small vessels (16). The [ $^{14}$ C]urea curve falls below both intravascular curves on the upslope and the [ $^3\text{H}$ ]water curve is widely separated from the other indicators. All curves exhibited recirculation, which was eliminated by exponential downslope extrapolation.

Table II lists hemodynamic, arterial blood gas tension, and indicator data for all of the studies. There was a broad range of abnormal oxygenation and two patients had modestly elevated  $\text{Pa}_{\text{CO}_2}$  at the time they were studied. All but two patients had pulmonary artery wedge pressures  $<15$  torr. The two patients with pulmonary artery wedge pressures  $>15$  torr did not have cardiomegaly on chest radiograph and had no other evidence of heart failure. Indicator studies showed a wide range of cardiac outputs, EVLW, and  $PS_u$ .

Fig. 2 summarizes indicator measurements in this study and shows data from our previously reported studies in patients with chronic heart disease (12). Average normal data are shown for comparison. Nor-

TABLE I  
Demographic and Clinical Data for Patients with ARDS

Patient no.	Age	Sex	Weight	Height	Diagnosis	Died of respiratory failure
	<i>yr</i>		<i>kg</i>	<i>cm</i>		
1	38	F	61	158	Pneumococcal pneumonia	No
2	61	F	55	158	Interstitial pneumonitis	Yes
3	23	M	65	191	Pseudomonas pneumonia	No
4	24	M	71	171	Gram-negative sepsis	Yes
5	43	F	75	163	Viral pneumonia	No
6	44	M	66	168	Hodgkins disease	No
7	44	F	60	158	Aspiration pneumonia	No
8	49	F	52	163	Cirrhosis, seizures	No
9	43	F	76	160	Aspiration pneumonia	No
10	71	F	52	150	Miliary tuberculosis	No
11	51	M	87	173	Bronchopneumonia	Yes
12	67	M	54	165	TTP*-renal failure	No
13	59	F	133	160	Pulmonary embolism	Yes
14	30	F	50	157	Acetaminophen overdose	Yes

\* TTP, thrombotic thrombocytopenic purpura.

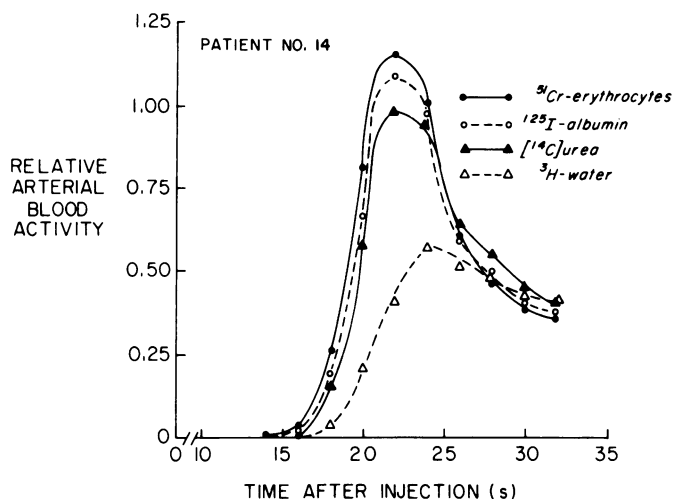


FIGURE 1 Indicator dilution curves across the lungs in a patient with acute respiratory failure and pulmonary edema.

mal values for lung water are from studies of Goresky et al. (13) in normal human volunteers. Normal values for  $^{14}\text{C-PS}_u$  are from our previously reported studies in patients with varying degrees of chronic heart failure (12). No measurements of lung  $^{14}\text{C-PS}_u$  have been made in normal humans, but we infer that values from patients with chronic heart failure are normal, because: (a) some patients in that series had normal pulmonary vascular pressures and cardiac output; (b)

there was a linear correlation of lung  $^{14}\text{C-PS}_u$  with lung volume in the entire group of patients, regardless of pulmonary vascular pressures; (c)  $^{14}\text{C-PS}_u$  did not correlate with pulmonary vascular pressures in that series of studies; and (d) animal studies showed no effect of elevated left atrial pressure on lung vascular  $^{14}\text{C-PS}_u$ .

Data from the five patients who died with respiratory failure and the nine patients who did not are shown separately in Fig. 2 and all of the data are nor-

TABLE II  
Hemodynamic, Blood Gas, and Indicator Data for Patients with ARDS

Patient no.	Study no.	PEEP*	$\text{FiO}_2$	$\text{PaO}_2$	$\text{PaCO}_2$	Mean pressure pulmonary		Plasma oncotic pressure	Cardiac output	EVLW	$^{14}\text{C-PS}_u$
						Artery	Wedge				
		cm H <sub>2</sub> O		torr		torr		torr	ml/s	ml	ml/s
1	1	15	0.50	66	34	11	7	18	155	911	0
2	1	4	0.60	43	35	22	10	17	101	711	19.0
3	1	10	0.35	87	38	24	6	18	65	558	8.3
4	1	10	1.00	161	39	24	10	15	105	1962	18.3
5	1	12	1.00	343	32	24	6	23	332	2801	2.4
6	1	10	0.35	62	31	29	12	18	76	574	6.1
7	1	15	1.00	277	36	31	9	26	325	2843	0
8	1	15	1.00	386	31	21	11	38	108	1247	0
9	1	10	1.00	360	34	27	14	29	157	748	2.4
	2	0	1.00	493	34	25	10	17	69	398	5.6
10	1	17	1.00	265	32	39	10	24	127	1669	3.8
11	1	10	1.00	324	40	25	17	17	271	2209	13.3
12	1	0	1.00	368	33	24	10	11	28	568	0
13	1	14	1.00	211	50	41	22	21	234	580	20.2
14	1	10	0.60	106	37	22	13	15	96	1010	16.5
	2	10	0.60	89	45	22	9	31	106	976	14.4

\* PEEP, positive end expiratory pressure.

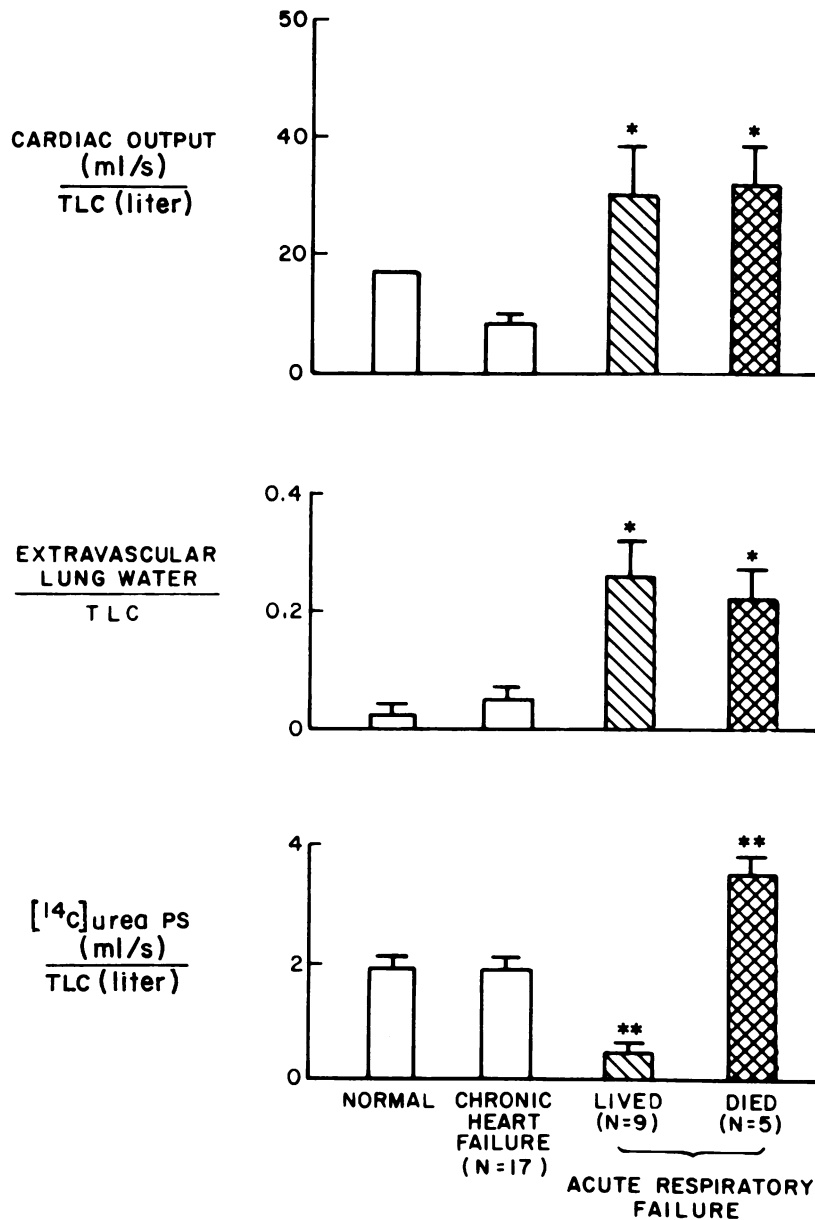


FIGURE 2 Cardiac output, EVLW, and lung vascular  $^{14}\text{C}$ -PS<sub>u</sub> in patients with chronic compensated heart failure (12) and patients with acute respiratory failure and pulmonary edema. An average normal value for cardiac output and normal values for EVLW from the literature (13) are shown for comparison. The normal value for PS<sub>u</sub> is the same as the value in patients with chronic heart failure (see text for justification). Data from patients surviving acute respiratory failure are shown separate from those who died. All data are normalized to predicted TLC. \*, significantly different from chronic heart failure ( $P < 0.05$ ); \*\*, significantly different from both of the other groups ( $P < 0.05$ ).

malized to predicted TLC to account for differences in lung size among patients. As expected, cardiac outputs were higher in patients with respiratory failure than in patients with heart disease (22), but the values in patients who died with respiratory failure were sim-

ilar to values in patients who did not. EVLW was higher in all respiratory failure patients than in patients with heart disease, but there was no significant difference between patients who died with respiratory failure and those who did not. In fact, on average,

patients not dying of respiratory failure had more edema by our measurement than those who died.  $^{14}\text{C-PS}_u$  was significantly lower in surviving respiratory failure patients than in patients with heart disease.  $^{14}\text{C-PS}_u$  was significantly higher in patients dying with respiratory failure than in either of the other groups.

In contrast to patients with chronic heart failure (12), there was no correlation between lung water and the difference between lung microvascular pressure and plasma oncotic pressure (Fig. 3). Neither was there a correlation between the amount of measured EVLW and the severity of the oxygenation defect as reflected in the A-aDO<sub>2</sub> (Fig. 4).

The relationship between  $^{14}\text{C-PS}_u$  and A-aDO<sub>2</sub> for patients with respiratory failure and pulmonary edema is shown in Fig. 5 for all of the studies. As in Fig. 2, the normal value for  $^{14}\text{C-PS}_u$  is from patients with chronic heart failure (12). Although there was a significant linear correlation between these two variables in the patients with respiratory failure, the relationship was described better by the parabola shown in the figure ( $r = 0.68$ ,  $P = 0.02$ ). The same relationship from serial studies in two patients is shown in Fig. 6. In the patient who survived,  $^{14}\text{C-PS}_u$  increased toward normal as gas exchange improved. In the patient who died,  $^{14}\text{C-PS}_u$  remained high as did A-aDO<sub>2</sub>.

As in our earlier studies (12),  $^{14}\text{C-PS}_u$  in the patients reported here did not correlate with cardiac output ( $r = 0.48$ ,  $P = \text{NS}$ ) or hematocrit ( $r = -0.37$ ,  $P = \text{NS}$ ).

## DISCUSSION

Patients with acute respiratory failure may have pulmonary edema not attributable to heart failure and

animal models of this syndrome have been studied extensively. However, it is difficult to establish a cause and effect relationship between edema and respiratory failure in patients or animal models, because changes in lung function not due to edema per se coexist with the edema (23, 24). The patients we studied had markedly increased lung water compared both with patients with chronic heart disease studied earlier (12) and with normal subjects reported in the literature (13). In our patients, the amount of lung edema measured did not relate to the severity of the oxygenation defect. This finding suggests that, although edema was present in these patients, it was not the principle cause of hypoxemia.

Some values of EVLW measured by indicator dilution are quite high. Although large values are to be expected in severely ill patients, technical factors could lead to high calculations of EVLW. If cardiac output is high, then microcirculation is rapid and it is more difficult to identify an appropriate region for the exponential extrapolation of downslope necessary in the mean transit-time method. Further, since EVLW is computed from the product of cardiac output and mean transit times, small errors in mean transit-time differences will be magnified at high cardiac output.

In addition to technical factors, another possible reason for the lack of correlation between lung water and A-aDO<sub>2</sub> could be that our method measured different fractions of actual lung water among patients. This occurs under some conditions in experimental animals (25). It is possible that inaccuracy of the method is the sole explanation of this finding. However, we saw no relationship between lung water and PS<sub>u</sub> (an index of perfusion) and in sheep given sufficient *Escherichia*

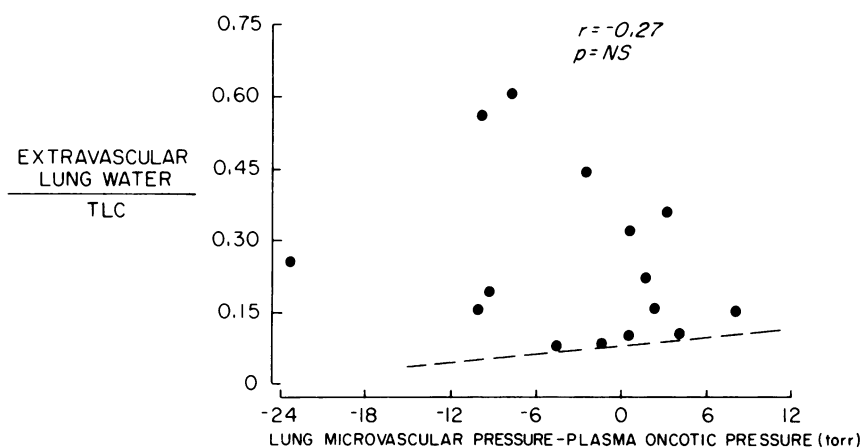


FIGURE 3 EVLW normalized to predicted TLC as a function of the difference between lung microvascular pressure [ $\text{Pla} + 0.4 (\text{Ppa} - \text{Pla})$ ] and plasma oncotic pressure in patients with acute respiratory failure and pulmonary edema. The broken line is the regression line for data in patients with chronic compensated heart failure reported previously (12).

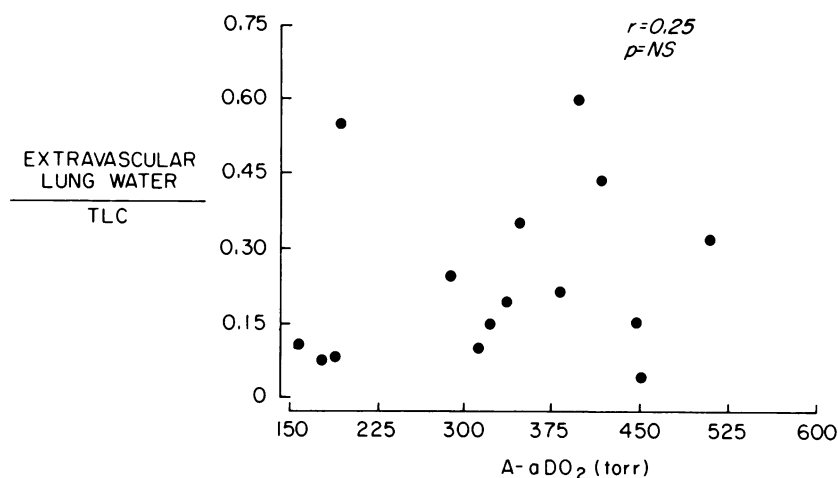


FIGURE 4 EVLW normalized to predicted TLC as a function of A-aDO<sub>2</sub> in patients with acute respiratory failure and pulmonary edema. Although 5 of the 14 patients breathed F<sub>I</sub>O<sub>2</sub> < 1.00, those values did not influence the relationship shown (see Table II).

*coli* endotoxin to produce respiratory failure and cause pulmonary edema without heart failure (an animal model that is pathophysiologically similar to the human syndrome), we saw no relationship between A-aDO<sub>2</sub> just before death and EVLW measured post-mortem by the most accurate available methods (26). Whether actual lung water content in the patients we studied correlated with oxygenation is unknown.

Since pulmonary edema occurs in patients with

acute respiratory failure in the presence of low pulmonary arterial wedge pressure, the edema is thought to result from injury to lung exchanging vessels, so that they leak excessive fluid and protein. This assumption is supported by measurements of high protein concentrations in edema fluid from humans and by extensive studies in animal models. But we found low permeability-surface area for a small hydrophilic solute in many of our patients.

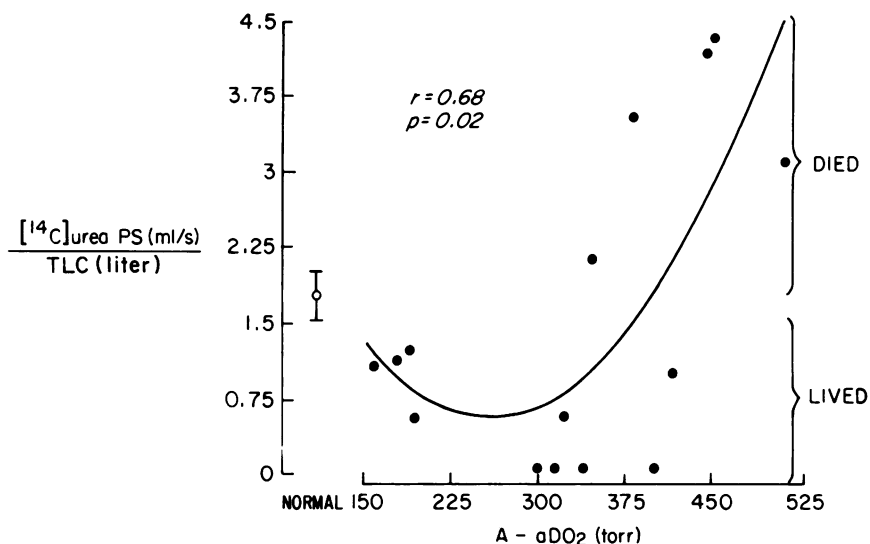


FIGURE 5 Lung vascular <sup>14</sup>C-PS<sub>0</sub> normalized to predicted TLC as a function of A-aDO<sub>2</sub> in patients with acute respiratory failure and pulmonary edema. Although five of the 15 patients breathed F<sub>I</sub>O<sub>2</sub> < 1.00, those values did not influence the relationship shown (see Table II). The normal value is from patients with chronic heart failure (12); see text for justification. The correlation does not include the normal values.

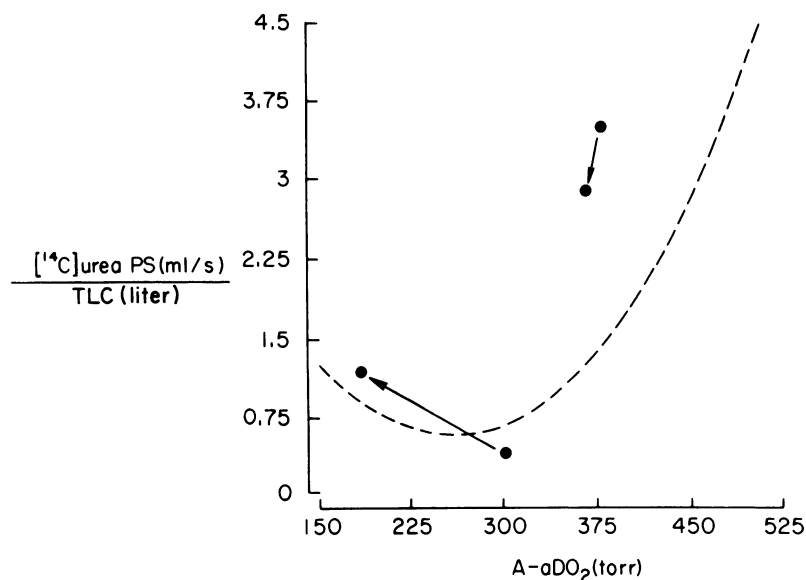


FIGURE 6 Serial measurements of lung vascular  $^{14}\text{C}$ - $\text{PS}_u$  area (PS) and A-a $\text{DO}_2$  in two patients with acute respiratory failure and pulmonary edema. The patient with lower A-a $\text{DO}_2$  and PS survived and the patient with higher A-a $\text{DO}_2$  and PS died with respiratory failure. The broken line is from the data in Fig. 5.

The most logical explanation for low  $\text{PS}_u$  values in many of our patients is decreased perfused vascular surface area. Since hypoxic vasoconstriction (3) and possibly other local forces (27) would be expected to reduce perfusion to edematous (and therefore poorly ventilated) areas of the lung, a decrease in perfused vascular surface area would be expected unless edema was completely uniform. We interpret the low  $\text{PS}_u$  values in many of our patients as a reduction of perfusion to areas of high permeability. Since labeled water is more diffusible than urea, EVLW will not be as sensitive to such changes. Thus, some edema may be measured by labeled water, even though the damaged capillaries, which generated it, are underperfused.

In some cases, there was no measurable extraction of urea and permeability-surface area was zero. This occurs in a multiple-indicator method when flow through capillaries is so high that capillary residence time is shorter than transcapillary escape time. Thus, with high flow through fewer capillaries, extraction is zero. This implies that pulmonary hemodynamics did not permit measurement of capillary permeability-surface area. This phenomenon has been demonstrated experimentally by Snapper et al. (28), who showed that urea extraction became zero as lung segments were removed, even though water extraction was high.

This interpretation is supported by the relationship between  $^{14}\text{C}$ - $\text{PS}_u$  and A-a $\text{DO}_2$ . This relationship shows a tendency toward low  $\text{PS}_u$  in patients with less severe

oxygenation defects and a very high  $\text{PS}_u$  in patients with severe deterioration of gas exchange. Serial studies in a patient during recovery indicate a return of  $\text{PS}_u$  toward normal. Further evidence that perfused vascular surface area related to oxygenation in patients with ARDS was provided by Snider et al. (29). When they infused pulmonary vasodilator drugs (presumably restoring perfusion to areas of low flow), they found that the shunt fraction increased in direct proportion to the degree of vasodilation.

It is possible that the pathogenesis of pulmonary edema in patients with a low  $\text{PS}_u$  was different than in patients with high  $\text{PS}_u$ ; i.e., vascular permeability may not be increased in the former group. Low pressure edema could occur as a result of increased epithelial permeability or possibly interstitial alterations. We think this explanation of the data less satisfactory than attributing the low  $\text{PS}_u$  values to decreased surface area, because it seems illogical to implicate decreased vascular permeability in the pathogenesis of edema and because there is nothing in the clinical data to suggest two different patient populations. However, the apparent dichotomy in  $\text{PS}_u$  values relative to survival may indicate basic and vital pathogenetic differences between patients who lived and those who died.

We interpret the relationship between  $\text{PS}_u$  and A-a $\text{DO}_2$  to mean that blood oxygenation in our patients depended on the ability of the lung to regulate distribution of blood flow. When perfusion could be re-



duced to injured (and edematous) areas of lung, oxygenation did not deteriorate severely. But, when injured areas of the lung were perfused, either because of loss of local regulatory mechanisms (for example, hypoxic vasoconstriction) or because injury was too extensive to permit reduction of perfusion of injured areas, severe respiratory failure occurred. That the severity of oxygenation defect did not correlate with the amount of edema but did correlate with  $PS_u$  suggests that loss of regulatory mechanisms may have been an important factor. This interpretation is supported by animal studies which show loss of pulmonary vasoconstriction with alveolar hypoxia following endotoxemia (30) and with pulmonary oxygen toxicity (31).<sup>2</sup>

Alternatively,  $PS_u$  could have been low in some patients as a result of such rapid flow that urea had insufficient time to cross the walls of microvessels. Since  $PS_u$  did not correlate with cardiac output, which was high in patients with high  $PS_u$  values, we think that true reduction in exchanging vessel surface area is the best explanation for the low values of  $PS_u$  in some patients.

All of our patients with high lung vascular  $PS_u$  died of respiratory failure. This could be because the patients with high  $PS_u$  simply had more severe disease (higher A-aDO<sub>2</sub>). Although that was generally true, the difference between A-aDO<sub>2</sub> in several patients who lived and the patients who died was quite small. In addition, patients who died did not have more lung water by our measurement than surviving patients. This may suggest that factors other than extent of injury and edema affect survival. The fact that  $PS_u$  was clearly different in those who died than in those who lived suggests that the ability to decrease perfusion to injured areas of the lung circulation may have been a principle determinant of survival. If these findings are confirmed by further studies, the multiple indicator technique may be useful in the early diagnosis of lung vascular injury where  $PS_u$  would be low. The  $PS_u$  measurement may also predict survival.

The lack of correlation between lung water and vascular pressures in these studies does not imply that pressures do not affect the degree of edema. If the magnitude of increased vascular permeability and perfused surface area were constant, a steep relationship between lung water and pressure would be expected (32). That we did not see such a relationship is probably because the degree of increased permeability and perfused surface area varied among our patients.

Multiple indicator dilution methods have been used

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<sup>2</sup> Newman, J. H., J. E. Loyd, and K. L. Brigham. Manuscript submitted for publication.

to measure EVLW in humans for the past 20 yr (33). Recently, these methods, using a thermal signal to measure extravascular volume, have been used more widely in intensive care units (34). Although the same techniques have been used to measure permeability-surface area for small hydrophilic molecules in several organs in experimental animals (35, 36) and the theory of such measurements has been studied extensively, measurements of lung vascular  $PS_u$  in humans with acute respiratory failure and pulmonary edema have not been reported previously.

Advantages of the multiple indicator method are that measurements of cardiac output, EVLW, and  $PS_u$  can be made in 5 min without moving the patient and in most patients in intensive care units no additional catheters are required (central venous and arterial catheters are usually placed for monitoring pressures). Disadvantages are that, at least at present, the measurement requires use of radioisotopes and processing of samples requires several hours.

One limitation of the indicator method is that it does not measure vascular permeability and surface area separately. However, no method applicable to intact organs, even in experimental animals, can separate permeability from surface area, and permeability-surface area may be more relevant clinically than either variable alone. The data in this paper would support that argument. In experimental animals, we have investigated a large number of substances as possible permeability indicators in the lung (37). Based on that experimental work and on extensive theoretical work (19), [<sup>14</sup>C]urea has emerged as the most appropriate indicator to date. The fact that in our previous studies in humans (12) and in this study, <sup>14</sup>C- $PS_u$  did not correlate with cardiac output or hematocrit further supports the conclusion that urea is a diffusion-limited indicator and that its behavior in the lungs is unaffected by erythrocyte transport. Further, extensive theoretical and experimental studies have demonstrated that erythrocyte exchange does not invalidate permeability-surface area measurements made with our techniques (38–42).

*Summary and conclusions.* We have used a multiple indicator technique to measure cardiac output, EVLW, and lung vascular <sup>14</sup>C- $PS_u$  in patients with acute respiratory failure and pulmonary edema. We found that lung water measured by the indicator methods we used did not correlate with the severity of the oxygenation defect but that <sup>14</sup>C- $PS_u$  did. Patients dying with respiratory failure had high  $PS_u$  values, whereas patients surviving did not. Many patients with modest degrees of oxygenation defect had lower than normal  $PS_u$ .

We conclude that although all of our patients had pulmonary edema, indicator dilution measurements

of lung water did not predict either the severity of hypoxemia or outcome. That patients dying with respiratory failure had high  $PS_u$  values and that the values were low in surviving patients suggest that the ability of the lung to divert blood flow away from injured and edematous areas was a major factor in preserving oxygenation. Loss of that function was a particularly bad prognostic sign. Multiple indicator measurements of lung vascular  $PS_u$  in humans may be useful clinically in diagnosis of lung vascular injury, in evaluating therapies and in predicting outcome.

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#### REFERENCES

1. Simmons, D., G. Nash, K. L. Brigham, and D. Tierney. 1979. Adult respiratory distress syndrome. *West. J. Med.* 130:218-235.
2. Staub, N. 1974. Pulmonary edema. *Physiol. Rev.* 54:678-811.
3. Goldzimer, E., R. Donopta, and K. Moser. 1974. Reversal of the perfusion defect in experimental canine lobar pneumococcal pneumonia. *J. Appl. Physiol.* 37:85-91.
4. Staub, N., R. Bland, K. L. Brigham, R. Demling, J. Erdmann, and W. Woolverton. 1975. Preparation of chronic lung lymph fistulas in sheep. *J. Surg. Res.* 19:315-320.
5. Erdmann, J., T. Vaughan, K. L. Brigham, W. Woolverton, and N. Staub. 1975. Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. *Circ. Res.* 37:271-284.
6. Brigham, K. L., R. E. Bowers, and P. J. Owen. 1976. Effects of antihistamines on the lung vascular response to histamine in unanesthetized sheep. Diphenhydramine prevention of pulmonary edema and increased permeability. *J. Clin. Invest.* 58:391-398.
7. Gorin, A., W. Weidner, R. Demling, and N. Staub. 1978. Noninvasive measurements of pulmonary transvascular protein flux in sheep. *J. Appl. Physiol.* 45:225-233.
8. Gorin, A. B., J. Kohler, and G. DeNardo. 1980. Noninvasive measurement of pulmonary transvascular protein flux in normal man. *J. Clin. Invest.* 66:869-877.
9. Brigham, K. L., T. R. Harris, and P. J. Owen. 1977.  $^{14}\text{C}$ -Urea and  $^{14}\text{C}$ -sucrose as permeability indicators in histamine pulmonary edema. *J. Appl. Physiol.* 43:99-101.
10. Harris, T. R., K. L. Brigham, and R. D. Rowlett. 1978. Pressure, serotonin, and histamine effects on lung multiple-indicator curves in sheep. *J. Appl. Physiol.* 44:245-253.
11. Brigham, K. L., H. Sundell, T. R. Harris, Z. Catterton, I. Kovar, and M. L. Stahlman. 1978. Lung water and vascular permeability in sheep: newborns compared with adults. *Circ. Res.* 42:851-855.
12. Brigham, K. L., J. Snell, S. Marshall, T. R. Harris, J. Haynes, and J. Perry. 1979. Indicator dilution lung water and vascular permeability in humans: effects of pulmonary vascular pressure. *Circ. Res.* 44:523-530.
13. Goresky, C. A., J. Warnica, J. Burgess, and B. Nadeau. 1975. Effect of exercise on dilution estimates of extravascular lung water and on the carbon monoxide diffusing capacity in normal adults. *Circ. Res.* 37:379-389.
14. Chinard, F., T. Enns, and M. Nolan. 1962. Pulmonary extravascular water volumes from transit time and slope data. *J. Appl. Physiol.* 17:179-183.
15. Goresky, C. A., R. F. P. Cronin, and B. E. Wangel. 1969. Indicator dilution measurements of extravascular water in the lungs. *J. Clin. Invest.* 48:487-501.
16. Brigham, K. L., W. Woolverton, and N. Staub. 1975. Effects of changing hemodynamics on the plasma space in the lungs of sheep. *Microvasc. Res.* 10:352-359.
17. Crone, C. 1963. Permeability of capillaries in various organs as determined by use of the "indicator diffusion" method. *Acta Physiol. Scand.* 48:292-305.
18. Rowlett, D., and T. R. Harris. 1976. A comparative study of organ models and numerical techniques for the evaluation of capillary permeability from multiple indicator data. *Math. Biosci.* 29:273-298.
19. Landis, E., and J. Pappenheimer. 1963. Exchange of substances through the capillary walls. *Handb. Physiol.* 2(Sect. 2, Circulation):961-1034.
20. Snedecor, G., and W. Cochran. 1967. *Statistical Methods*. The Iowa State University Press, Ames, IA. Sixth edition.
21. Hudson, L. 1981. Adult respiratory distress syndrome. *Semin. Respir. Med.* 2:99-174.
22. Kariman, K., S. L. Young, and S. Burns. 1981. Comparison of hemodynamic features of adult respiratory distress syndrome (ARDS) and cardiogenic pulmonary edema. *Clin. Res.* 229:447A. (Abstr.)
23. Snapper, J. R., M. L. Ogletree, A. A. Hutchison, and K. L. Brigham. 1981. Meclofenamate prevents increased resistance of the lung ( $R_L$ ) following endotoxemia in unanesthetized sheep. *Am. Rev. Respir. Dis.* 123:200a. (Abstr.)
24. Murphy, T., R. Allison, T. Weisman, D. McCaffree, and B. Gray. 1981. Role of platelet serotonin in the canine pulmonary response to endotoxin. *J. Appl. Physiol.* 50:178-184.
25. Pearce, M., J. Yamashita, and J. Beazell. 1965. Measurement of pulmonary edema. *Circ. Res.* 16:482-488.
26. Esbenshade, A. M., J. H. Newman, P. M. Lams, and K. L. Brigham. 1980. High dose endotoxin in sheep: a model of primary pulmonary edema with respiratory failure. *Am. Rev. Respir. Dis.* 121:430a. (Abstr.)
27. Bhattacharya, J., K. Nakahara, and N. Staub. 1980. Effect of edema on pulmonary blood flow in the isolated perfused dog lung lobe. *J. Appl. Physiol.* 48:444-449.
28. Snapper, J. R., T. R. Harris, and K. L. Brigham. 1982. Effect of changing lung mass on lung water and permeability surface area in sheep. *J. Appl. Physiol.* 52:1591-1597.
29. Snider, M., M. Rie, J. Lauer, and W. Zapol. 1980. Normoxic pulmonary vasoconstriction in ARDS: detection by sodium nitroprusside and isoproterenol infusions. *Am. Rev. Respir. Dis.* 121(Suppl. 4):191a. (Abstr.)
30. Weir, E., J. Mlczoch, J. Reeves, and R. Grover. 1976. Endotoxin and the prevention of hypoxic pulmonary vasoconstriction. *J. Lab. Clin. Med.* 88:975-983.
31. Newman, J., I. McMurtry, and J. Reeves. Vascular responses of lungs from rats exposed to high oxygen tensions. *Prostaglandins*. In press.
32. Brigham, K. L. 1978. Lung edema due to increased vas-

- cular permeability. *In Lung Biology in Health and Disease*. C. Lenfant, editor. Lung Water and Solute Exchange. N. Staub, editor. Marcel Dekker Co., New York. 7:235-276.
33. Ramsey, L., W. Puckett, A. Jose, and W. Lacy. 1964. Pericapillary gas and water distribution volumes of the lung calculated from multiple indicator dilution curves. *Circ. Res.* 15:275-276.
  34. Lewis, F., J. Christensen, and V. Elings. 1981. The effect of PEEP on noncardiogenic pulmonary edema. *Crit. Care Med.* 9:258a. (Abstr.)
  35. Alvarez, O., and D. Yudilevich. 1969. Heart capillary permeability to lipid insoluble molecules. *J. Physiol.* 202:45-58.
  36. Goresky, C., G. Bach, and B. Nadeau. 1975. Red cell carriage of label: its limiting effect on exchange of material in the liver. *Circ. Res.* 36:328-351.
  37. Harris, T. R., and K. L. Brigham. 1982. The exchange of small molecules as a measure of normal and abnormal lung microvascular function. *Ann. N.Y. Acad. Sci.* 384:417-434.
  38. Brigham, K. L., T. R. Harris, R. D. Rowlett, and P. J. Owen. 1977. Comparisons of  $^{14}\text{C}$ -urea and  $^3\text{H}$ -mannitol as lung vascular permeability indicators in awake sheep: evidence against red cell urea trapping. *Microvasc. Res.* 13:97-105.
  39. Roselli, R. J., and T. R. Harris. 1979. A four-phase model of capillary tracer exchange. *Ann. Biomed. Eng.* 7:203-238.
  40. Roselli, R. J., and T. R. Harris. 1979. The effects of red cell and tissue exchange on the evaluation of capillary permeability from multiple indicator data. *Ann. Biomed. Eng.* 7:239-282.
  41. Roselli, R. J., T. R. Harris, and K. L. Brigham. 1982. Effect of red cell exchange on calculated sheep lung  $^{14}\text{C}$ -urea and  $^{14}\text{C}$ -thiourea vascular permeability. *Respir. Physiol.* 49:11-21.
  42. Parker, R. E., R. J. Roselli, R. J. Haselton, K. L. Brigham, and T. R. Harris. 1982. Effects of altering injectate and perfusate hematocrits on  $^{14}\text{C}$ -urea extraction PS in the isolated dog lung. *Physiologist.* 25:205a. (Abstr.)