Clinical Studies of Measuring Extravascular Lung Water by the Thermal Dye Technique in Critically Ill Patients*

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We measured extravascular lung water (EVLW) by the thermal-dye technique in a broad group of critically ill patients who had either acute cardiac or noncardiac illnesses. A portable AP supine chest roentgenogram, reviewed blindly, was used to classify patients as to the presence or absence of pulmonary edema; by clinical history we categorized patients into either a cardiac or noncardiac (ie, ARDS) group. With a normal chest roentgenogram, the mean EVLW was 5.6±1.8 ml/kg, and the pulmonary capillary wedge pressure (PCWP) was 11.3±5.3 mm Hg (mean ± SD). In contrast, patients with pulmonary edema on a cardiac basis had a mean EVLW of 10.2±3.1 ml/kg (mean PCWP, 20.5±8.2 mm Hg), while patients with clinically defined noncardiac pulmonary edema and a normal PCWP (11.6±5.7 mm Hg) had a mean EVLW of 15.8±4.6 ml/kg, significantly higher than in the cardiac group (p <0.001). On a severity system of 04, the EVLW increased in parallel to the severity of the chest radiologic appearance of edema in both the cardiac (r² = .44; p <0.001) and noncardiac (r² = .59; p <0.001) patients. This study defined a normal range of thermal-dye EVLW in critically ill patients without radiologic evidence of pulmonary edema. We further demonstrated the increased pulmonary microvascular permeability of noncardiac pulmonary edema compared with cardiac edema by the greater EVLW at normal microvascular hydrostatic pressures in the former group.

Pulmonary edema, an increase in extravascular lung water (EVLW), is a common finding in critically ill patients. It is most frequently recognized by characteristic associated clinical signs and is accompanied by arterial hypoxemia, reduced pulmonary compliance, and typical chest radiologic changes. In critically ill patients, however, arterial hypoxemia and reduced pulmonary compliance are not unique to a diagnosis of pulmonary edema. Similarly, the chest roentgenogram is considered by some to be a relatively insensitive measure of EVLW accumulation because of a characteristic "lag" period between alterations in the forces favoring edema formation and the typical radiologic changes.1 Alterations in lung volumes, as occur with the application of positive end-expiratory pressure (PEEP), will also affect radiologic determinations of the severity of pulmonary edema.4,5 Clearly, a simple and reliable method to assess the EVLW might provide important ancillary clinical information for confirming the applicability of both diagnostic and therapeutic strategies in critically ill patients.

Lewis and colleagues4,5 have recently described a method for EVLW measurement which is clinically attractive because it can be performed easily at the bedside. It is based on a double-indicator dilution technique using indocyanine green as a nondiffusible indicator, and heat as the diffusible indicator.4,5 The measurement provided with this technique is referred to by some as the pulmonary extravascular thermal mass to reflect concerns that the measured thermal space might not totally represent the extravascular water space; however, EVLW reported by this technique has been demonstrated to correlate well with gravimetric determinations of EVLW in both cardiac and noncardiac disease states in both animal4,6 and human studies.8 In initial clinical studies this technique has also been used to define changes of EVLW in acutely ill patients without preexisting acute cardiac illnesses.7

It was therefore the purpose of this study to assess the clinical applicability of measuring EVLW by the thermal-dye technique in a broad range of critically ill patients with both acute cardiac and noncardiac illnesses. We sought to characterize a "normal" range of EVLW, as defined in patients without radiologically demonstrable pulmonary edema, and to then assess the ability of this technique to detect differences of the EVLW in patients with radiologically defined pulmonary edema on either a cardiac or noncardiac basis. Because of the good correlations between measured EVLW by gravimetric techniques and the extravascular thermal space, we report values obtained by the thermal-dye technique as the extravascular lung water. We also compared this measure of EVLW with other monitored indices traditionally used to assess pulmonary dysfunction in critically ill patients with and

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without pulmonary edema.

**METHODS**

**Patient Population**

During a 16-month period, thermal-dye EVLW was measured in 79 acutely ill patients in the Critical Care/Trauma Unit at Victoria Hospital. The patients were subdivided by the underlying illness, primarily cardiac or noncardiac in origin, and then further subdivided based on the presence or absence of pulmonary edema as defined by a chest roentgenogram performed simultaneously with measurement of the EVLW. Therefore, we identified four groups of patients for comparison.

Group 1 consisted of 16 patients who had sustained either an acute cardiac or noncardiac event and had no pulmonary edema on the chest roentgenogram at the time of study. All of these patients required invasive central arterial blood pressure monitoring during the initial course of the illness, which permitted the use of an Edwards thermal-dye lung water catheter (model 96-02-5F, Edwards Laboratories) as an arterial line. Eight patients had sustained an acute traumatic event, two had a pericardial effusion requiring surgical intervention, three had fulminant hepatic failure on an alcoholic basis, and there was one patient each with acute on chronic respiratory failure, a ventricular aneurysm with low cardiac output syndrome, and an overdose complicated by hypotension.

Group 2 consisted of 14 patients with an acute septic or inflammatory illness, but again no pulmonary edema evident on the chest roentgenogram. Five patients had peritonitis, five had a primary bronchopulmonary source of infection (pneumonia or lung abscess), two had a bacteremia without a clinically defined source, and two had suppurative pancreatitis.

Group 3 consisted of 20 patients with radiologically defined pulmonary edema and a recognizable cardiac cause. Fifteen patients had pulmonary edema complicating an acute myocardial infarction, of which two were traumatic; five had decompensated left ventricular failure, with subsequent respiratory failure, secondary to underlying coronary artery disease, or long-standing hypertensive heart disease without documentation of a recent myocardial infarction.

Group 4 consisted of 29 patients with radiologically defined pulmonary edema and no recognizable antecedent acute cardiac event, or adult respiratory distress syndrome (ARDS). Eight patients had bacterial peritonitis, nine had a primary pulmonary focus of infection (abscess; aspiration), six had positive blood cultures without the primary site even being identified, three had sepsis secondary to full thickness burns, two had biopsy-proved pulmonary arteritis, and one had pulmonary edema complicating an ASA overdose.

Other pertinent data for the patients studied in all groups are listed in Table 1.

**Treatment Modalities**

Indications for intubation of any patient included a depressed level of consciousness sufficient to interfere with airway protection, the need to provide bronchopulmonary toilet or the need to provide assisted ventilation. The FIO₂ selected was determined to maintain the PaO₂ over 70 mm Hg. When mechanical ventilation was provided, a volume-cycled ventilator was used with a tidal volume of 10 to 15 ml/kg. The respiratory rate was then secondarily adjusted to maintain the PaCO₂ between 37 and 42 mm Hg. PEEP was used in some patients (Table 1) and was not believed to be important to the analysis of data in this study, since PEEP has negligible effects on EVLW accumulation. The PCWP was assumed to reflect the Pmv, although this ignores the possibility of downstream resistance affecting the PCWP, which may be a negligible consideration, particularly in patients with pulmonary edema. Levels of PEEP ≤12 cm H₂O do not interfere with an accurate reflection of the left atrial pressure by the PCWP. In a few patients, the level of PEEP employed exceeded 12 cm H₂O. In these instances the transmural PCWP was calculated by measuring the intraesophageal pressure with a fluid-filled catheter system as previously described.

All patients were studied as soon as possible after admission, but of necessity therapy for the underlying disease had been instituted prior to measurement of the EVLW, particularly in group 3 and group 4 patients.

**Protocol for Measurement of EVLW**

All patients had had a flow-directed thermodilution Swan-Ganz catheter (Edwards Laboratories) inserted percutaneously, prior to study, for clinical assessment and monitoring of the effects of subsequent alterations in therapy, both pharmacologic and nonpharmacologic. Patients with congestive heart failure also received a combination of diuretics to reduce left ventricular preload and vasodilators to reduce left ventricular afterload, as necessary. No patient was in clinical shock at the time of study, since inotropes had been used to treat a shock state if present on admission.

A No. 5 French catheter (Edwards Laboratories) was percutaneously inserted into a femoral artery by the Seldinger technique to provide continuous arterial pressure monitoring and withdrawal of blood for EVLW measurement and arterial blood gas determinations. EVLW was measured by injecting 10 ml of iced saline solution containing 5 mg of indocyanine green dye into the central circulation as a bolus using the CVP port of the Swan-Ganz catheter. Green dye concentration was measured by withdrawing blood sterilely from the femoral artery catheter at 30 ml/min through a cuvette (Waters Instrumentation, model 401). All withdrawn blood was reinfused with completion of each measurement. The thermal and green dye signals were digitized by a small bedside microprocessor (model 9310, Lung Water Computer, Edwards Laboratories), and EVLW was then computed as the product of the thermodilution flow (Qt) times the difference in mean transit times of the thermal and green dye curves. Three sequential EVLW measurements were made, and their mean recorded as the EVLW, expressed as ml/kg of body weight at admission.

**Other Measurements**

At the same time of measurement of EVLW, the mean pulmonary artery pressure (PAP), the balloon occluded pulmonary capillary wedge (PCWP), the central venous pressure (CVP), and the cardiac output (CO) were also measured. Cardiac output reported was

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Age, yr</th>
<th>No. of Patients Ventilated (%)</th>
<th>No. of Patients on PEEP (%)</th>
<th>PEEP (cm H₂O)</th>
<th>Respiratory Rate (min)</th>
<th>FIO₂</th>
<th>PaO₂/FIO₂ Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>53.3 ± 18</td>
<td>16 (100)</td>
<td>9 (56)</td>
<td>3.0 ± 3.0</td>
<td>13.6 ± 6.3</td>
<td>.43 ± .24</td>
<td>258.6 ± 103</td>
</tr>
<tr>
<td>Group 2</td>
<td>57.3 ± 15</td>
<td>10 (71)</td>
<td>7 (70)</td>
<td>3.5 ± 4.6</td>
<td>15.6 ± 4.2</td>
<td>.39 ± .11</td>
<td>193.9 ± 82</td>
</tr>
<tr>
<td>Group 3</td>
<td>65.4 ± 10</td>
<td>13 (65)</td>
<td>8 (62)</td>
<td>4.5 ± 5.0</td>
<td>15.5 ± 5.9</td>
<td>.44 ± .22</td>
<td>216.3 ± 99</td>
</tr>
<tr>
<td>Group 4</td>
<td>53.2 ± 15</td>
<td>28 (97)</td>
<td>28 (100)</td>
<td>11.9 ± 6.0</td>
<td>16.1 ± 6.9</td>
<td>.70 ± .27</td>
<td>148.7 ± 73</td>
</tr>
</tbody>
</table>
Figure 1. Significantly greater EVLW content in patients with ARDS (group 4) than in patients with cardiac edema (group 3) despite significantly lower PCWP in the group 4 patients than group 3. In both group 3 and 4 patients, the EVLW is significantly greater than in either group 1 or 2 patients, both of whom had had no radiologic evidence of pulmonary edema. * significantly different from group 3; +, significantly different from groups 1, 2, and 4.

measured from the thermal curve obtained from the Swan-Ganz catheter and expressed per meter squared (m²) of body surface area (cardiac index). Zero reference level for all pressures was taken at midaxillary line with the patient supine. All pressures were measured by a Hewlett-Packard 78205B arterial/venous pressure transducer and digital display system (Hewlett-Packard 78205B arterial/venous pressure modules and 7782A thermal recorder).

Arterial and mixed venous (pulmonary arterial) blood samples were drawn anaerobically into heparinized glass syringes at the same time as the pressure recordings, and the PaO₂, PaCO₂ (AME-1 Blood Gas Analyzer), and saturation (Hemoximeter, Radiometer) were then measured for calculation of the intrapulmonary shunt fraction (Qs/Qt) according to Berggren on an inspired oxygen concentration (FiO₂) required to maintain the PaO₂ greater than 70 mm Hg.

Total serum proteins were measured by the Biuret method, and the serum osmotic pressure (πmv) was then calculated by the equation described by Landis and Pappenheimer. In critically ill as well as in normal patients, the calculated colloid osmotic pressure (COP) correlates well with that measured using oncometers. Normal COP is approximately 25 mm Hg. Total thoracic compliance was measured as described by Fleming et al and expressed as effective compliance (Ceff, ml/cm H₂O). All patients also had a portable standard supine AP chest roentgenogram within one hour of measurement of EVLW as previously described. Interpretation and classification of the chest x-ray film was performed by a radiologist without knowledge of the patient’s clinical course, on a scale of 0 to 4, where 0 is no edema, + is possible mild interstitial edema, ++ is definite interstitial edema, +++ is interstitial plus patchy alveolar edema, and ++++ is diffuse, bilateral alveolar edema.

Analysis of Data

All data are expressed as the mean ± SD. In comparing groups 1 → 4, we utilized group 1 as a "normal" or control group and compared groups 2 → 4 to this group by Student's t test (unpaired). Statistical comparisons were also performed between other groups (ie, group 3 vs group 4). Therefore, to maintain an overall significance level of 0.05, each of the five t tests was made using a single level of 0.01. This per experiment rate of 0.01 is a conservative approach to maintain an experimental wide error of less than 0.05. P values are reported for all comparisons, and according to the above then, a value of 0.01 is considered to identify statistically significant differences.

To examine the significance of the means of a dependent criterion across levels of factors, analysis of variance (ANOVA) was employed. This technique accounts for the variability of the dependent variable by partitioning this variability according to the factors, and in this way assesses the importance of the factors on the dependent criterion.

In defining the correlation between the EVLW and the Qs/Qt, a linear regression model was used, treating the EVLW as the dependent variable and the Qs/Qt as the independent variables using the statistical package for the Social Sciences (SPSS) regression package program.

CONCLUSIONS

Extravascular Lung Water (EVLW) (Figure 1)

In patients without radiologic evidence of pulmonary edema and no evidence of systemic infection (group 1), the mean EVLW was 5.6 ± 1.8 ml/kg, and the mean PCWP was 11.3 ± 5.3 mm Hg (Table 2). These data did not differ from group 2 patients, similarly without radiologic evidence of edema. However, group 3 patients had a higher mean EVLW (p<0.001) and

Table 2—Data Pertinent to all Study Groups (Mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>EVLW (ml/kg)</th>
<th>PCWP (mm Hg)</th>
<th>COP (mm Hg)</th>
<th>PCWP-COP (mm Hg)</th>
<th>CXR Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>5.6 ± 1.8</td>
<td>11.3 ± 5.3</td>
<td>17.5 ± 3.4</td>
<td>−6.4 ± 7.0</td>
<td>(0)</td>
</tr>
<tr>
<td>(n = 16)</td>
<td>(3.0-8.8)</td>
<td>(02-19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>5.5 ± 1.1</td>
<td>12.5 ± 6.3</td>
<td>16.9 ± 2.6</td>
<td>−3.6 ± 7.9</td>
<td>(0)</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(3.05-7.11)</td>
<td>(03-24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>10.2 ± 3.1*</td>
<td>20.5 ± 8.2*</td>
<td>19.7 ± 3.4*</td>
<td>−4.5 ± 8.8*</td>
<td>2.0 ± .9*</td>
</tr>
<tr>
<td>(n = 20)</td>
<td>(5.65-15.94)</td>
<td>(10-31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;.001</td>
<td>p&lt;.001</td>
<td>↑</td>
<td>p&lt;.01</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Group 4</td>
<td>15.8 ± 4.6*</td>
<td>11.6 ± 5.7</td>
<td>16.7 ± 2.1</td>
<td>−5.6 ± 6.0</td>
<td>2.9 ± .9*</td>
</tr>
<tr>
<td>(n = 29)</td>
<td>(6.79-26.50)</td>
<td>(01-28)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Significant difference between groups 1 and 3.
*Significant difference between groups 2 and 4.
PCWP (p<0.001) than the group 1 patients. Despite a significantly lower PCWP (p<0.001) and more negative PCWP-COP gradient (p<0.001), group 4 patients had a significantly higher EVLW than group 3 patients (p<0.001). This latter finding is suggestive of increased permeability of the pulmonary microvascular membrane in group 4 patients when compared with group 3 patients.

Group 4 patients also differed from group 3 patients by the presence of a significantly higher mean Qs/Qt (p<0.001), the mean FIO2 required to maintain the PaO2<70 mm Hg (p<0.01), the mean level of PEEP employed (p<0.001), and a lower mean Ceff (p<0.05). The mean CI in group 4 patients was significantly greater than in group 3 patients (p<.005), as was the mean chest roentgenogram score (p<.001) (Tables 1 and 2).

**Group 1 vs Group 3 Patients**

Group 1 patients had no radiologic evidence of edema and no evidence of bacterial infection. The higher mean EVLW in group 3 than group 1 patients (p<0.001) was associated with a higher mean PCWP (p<0.001) and a less negative PCWP-COP gradient (p<0.01). The PAP was nonsignificantly higher in the cardiac patients with edema (p<0.02) than in group 1 patients. There was no significant difference between the two groups in the mean Qs/Qt, Ceff, FIO2, CI, or level of PEEP employed (Table 1).

**Group 2 vs Group 4 Patients**

In both groups, underlying diseases potentially associated with ARDS were present. But the higher mean EVLW in group 4 patients (p<0.001) was not associated with any significant difference in the mean PCWP, COP, PCWP-COP gradient between the two groups. In group 4 patients, the mean FIO2, level of PEEP employed, and PAP were significantly higher than in group 2 patients (Table 1).

**EVLW and the Qs/Qt**

There was no relationship between the calculated Qs/Qt and the EVLW in either group 3 patients (r² = .02; p = NS) or group 4 patients (r² = .04; p = NS).

**EVLW and the Chest Roentgenogram**

We found a direct and positive correlation between the chest roentgenogram score and the EVLW in group 1 and 3 patients (Y = 6.5 + 1.8X; r² = .44; p<0.001), to represent patients with potentially only hydrostatic forces influencing transmicrovascular fluid flux. Similarly, when combining group 2 and 4 to represent patients with a potential permeability change of the pulmonary microvasculature primarily affecting transmicrovascular fluid flux, we also found a direct relationship between the chest

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**Figure 2.** Correlation between EVLW content and the chest roentgenogram score on a scale of 0 (no edema) to 4 (diffuse, bilateral alveolar edema) in both cardiac and noncardiac patients. Because of small numbers in the cardiac group for a score of 4, the chest roentgenograms were arbitrarily grouped into 0, 1+2, and 3+4 for statistical comparison. In both groups EVLW content increases with a worsening chest roentgenogram score, although, noncardiac edema is characterized by a greater EVLW content at any given score than in cardiac edema.

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EVLW and the Chest Roentgenogram score and the EVLW (Y = 6.5 + 2.9X; r² = .59; p<0.001).

We then compared the relationship between the chest roentgenogram and the EVLW in defining severity of edema within and between the hydrostatic (1 and 3) and noncardiac groups (2 and 4) combined. Because of small numbers of cardiac patients defined as having a chest score of grade 4 severity, we combined chest scores of 1+2+ and 3+ and 4+ for this comparison. Analysis of variance (ANOVA) showed that in both patient groups, the chest score increased as the EVLW content increased (p<0.05). But cardiac patients had a significantly lower EVLW, with a chest roentgenogram score of 1 to 2+, similarly maintained through to the 3 to 4+ grade (p<0.001), than the noncardiac patients (Table 3; Fig 2).

**Discussion**

In this study we measured the extravascular lung water content (EVLW) by a commercially available thermal-dye technique in a representative group of patients with acute illnesses, some of whom had chest radiologic evidence of concomitant pulmonary edema. In reviewing the clinical applicability of this technique in critically ill patients, it proved easy to perform with no recognizable adverse sequelae. We defined a range of thermal-dye EVLW associated with a normal chest roentgenogram and found that the EVLW measurements had no significant relationship to direct measures of the oxygenating defect found in an acute illness. Further, data presented imply that the thermal-dye technique of EVLW measurement might be of
clinical assistance in differentiating patients with cardiac from those with noncardiac edema.

Lewis and colleagues\textsuperscript{4,5} have demonstrated the accuracy and reliability of pulmonary EVLW measurements by a double indicator technique in which indocyanine green is utilized as the nondiffusible and heat as the diffusible indicator. The technique is based on standard theory for measurement of EVLW by a double-indicator method,\textsuperscript{34} is clinically easier to perform than are the radiosotopic techniques,\textsuperscript{3} and can be sequentially and rapidly repeated. However, Oppenheimer et al\textsuperscript{8} suggested that the thermal-dye method might overestimate total EVLW due to distribution of the diffusible heat indicator in dry as well as wet tissues of the lung, although this problem decreased as pulmonary edema developed, and lung dry-to-wet weight ratio decreased. Hill et al\textsuperscript{16} found a minor but significant inverse correlation between cardiac output and EVLW content, suggested as secondary to detection of nonpulmonary water within vascular and myocardial walls. Similarly, Rice and Miller described minimal dependency of extravascular thermal volume on cardiac output.\textsuperscript{35} Despite these and other\textsuperscript{1} theoretical concerns about the use of this double-indicator technique, recent studies have demonstrated a close correlation between the thermal-dye EVLW and EVLW measured by gravimetric techniques in both hydrostatic (cardiac)\textsuperscript{9} and permeability (nonhydrostatic) pulmonary edema,\textsuperscript{4} in both human\textsuperscript{8} and animal\textsuperscript{5,7,10} studies.

For the purposes of this study, in assessing the magnitude of thermal-dye EVLW in states of pulmonary edema, we assumed that a chest roentgenogram without evidence of edema reflected a state of normal EVLW in critically ill patients. However, studies by Pistolesi and Guintrini\textsuperscript{16} and by Snashall et al\textsuperscript{15} demonstrated that chest roentgenograms could become recognizable, albeit minimally, abnormal before lung water was appreciably increased. Thereafter, the chest roentgenogram grade and lung water content were positively correlated.\textsuperscript{28} Conversely, others\textsuperscript{1} have referred to a "diagnostic lag" period in which a chest roentgenogram may be particularly influenced by preexisting pulmonary parenchymal disease\textsuperscript{30} and/or the state of lung volume.\textsuperscript{3} Yet the chest roentgenogram, admittedly not free of interpretative difficulties in critically ill patients, remains the standard against which most other techniques designed to clinically assess pulmonary edema are compared. In patients in this study defined as "normal" for comparison, not only were the chest roentgenograms free of changes typically described with pulmonary edema, but there was also a simultaneous lack of clinical signs of pulmonary edema.

Assuming that a chest roentgenogram without evidence of edema would not likely represent any more than a 35 percent increase in EVLW,\textsuperscript{25} we have therefore defined a normal mean EVLW in a broad group of critically ill patients as 5.6±1.8 ml/kg (range 3.0 to 8.8 ml/kg) (group 1). This value is slightly greater than a value of 3.9±1.49 ml/kg found by Pietzman et al\textsuperscript{17} and similar to the results of Funderbunk and Baundendistal\textsuperscript{34} of 4 to 6 ml/kg. The difficulty in defining a normal range for EVLW in this study probably results from the need to compare normalcy with a chest roentgenogram, which, as previously discussed, has its own potentially inherent problems in interpretation. Furthermore, the degree of recruitment of the pulmonary microvasculature in the normal situation could conceivably alter EVLW measured by the thermal-dye technique.\textsuperscript{36}

Despite some minimal overlap (Table 2), likely due to the phenomenon of posttherapeutic\textsuperscript{14} or diagnostic lag,\textsuperscript{34} in patients with radiologically determined pulmonary edema on a cardiac basis, the mean EVLW was approximately twice that of our control group, as was the pulmonary microvascular hydrostatic pressure (Pmv), defined by the PCWP. Pulmonary edema occurring on a cardiac basis (ie, left ventricular failure) is due to an increase in the Pmv. In animal studies Guyton and Lindsay\textsuperscript{22} showed that as the Pmv increased, a "critical" level was reached when pulmonary defense against EVLW accumulation was overcome, and pulmonary edema (EVLW) rapidly accumulated. Similar to other studies,\textsuperscript{13,24} their data also defined the importance of the microvascular colloid osmotic pressure (πm) in minimizing the pulmonary transmicrovascular flux of fluid. Clinical studies have assessed the severity of cardiac pulmonary edema by chest radiology and reported a positive correlation between radiologic severity and the PCWP or the PCWP-COP gradient.\textsuperscript{24} In patients with cardiac pul-

Table 3—Analysis of Variance Relating to Comparison Between a Dependent Criterion (EVLW) Across Levels of Factors*  

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Degrees of Freedom</th>
<th>Mean Square</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1</td>
<td>144.09</td>
<td>13.83 (p&lt;.001)</td>
</tr>
<tr>
<td>CXR level (0, 1, 2, 3, 4)</td>
<td>2</td>
<td>456.39</td>
<td>41.90 (p&lt;.001)</td>
</tr>
<tr>
<td>Group by CXR</td>
<td>2</td>
<td>50.92</td>
<td>4.67 (p&lt;.05)</td>
</tr>
<tr>
<td>Residual</td>
<td>75</td>
<td>10.89</td>
<td></td>
</tr>
</tbody>
</table>

*Because of small numbers in the cardiac group for a chest roentgenogram score of 4, the groups have been combined (ie, 0, 1 and 2, 3 and 4) for statistical analysis.
monary edema, we previously demonstrated a direct correlation between the clearance from blood to pulmonary edema fluid of a small hydrophilic radiotracer, 111 Indium-DTPA, and both the PCWP and the PCWP-COP gradient. 123 Brigham et al 122 also found a good correlation between the calculated Pmv-COP gradient and extravascular water content in patients with pulmonary dysfunction on a cardiac basis, using a multiple indicator radioisotopic dilution technique. Therefore, our data are in accordance with what would be physiologically predicted in cardiac pulmonary edema; that is, as the Pmv increases, or the Pmv-rmv gradient becomes less negative, an increase in the EVLW occurs when compared with normal (ie, group 1).

This technique of measuring EVLW has also been implied as clinically useful for documenting the presence of permeability (noncardiac) pulmonary edema in critically ill patients. 8 In noncardiac edema, a primary increase in conductance of the pulmonary microvascular membrane allows for an increased flux of water and proteins from the intravascular to the interstitial and alveolar spaces, even at normal microvascular hydrostatic and colloid osmotic pressures. 36,37 For any given microvascular hydrostatic pressure, the EVLW is higher in noncardiac than in cardiac edema, as a result of the change in permeability of the pulmonary exchanging membrane in ARDS. 36 The higher mean EVLW in group 4 patients than in group 3 patients, despite a significantly lower mean PCWP and PCWP-COP gradient (ie, less negative) in the former group, confirms the existence of increased permeability of the pulmonary microvascular membrane in noncardiac pulmonary edema. 8,9 As is clinically apparent, however, not all patients with systemic sepsis have a pulmonary microvascular defect leading to ARDS, because the mean EVLW in septic patients without radiologically defined edema was similar to that in group 1, the control patients. Since the mean PCWP and cardiac index were similar in the “septic” groups 2 and 4, it is believed that differences in measured EVLW are not due to differences in heat loss in nonpulmonary tissue 36 or to differences in the pulmonary permeability surface area for heat exchange to occur. No study to our knowledge has ever prospectively defined the frequency of noncardiac pulmonary edema developing in a hospitalized patient population with systemic sepsis, and no attempt is made to define the reason for the occurrence of noncardiac pulmonary edema in some, but not all, patients with sepsis who were otherwise reasonably alike (Tables 1 and 2).

The mean chest roentgenogram score also defined greater pulmonary edema in noncardiac group 4 patients than in the cardiac group 3 patients. Snashall et al 120 demonstrated a direct relationship between EVLW measured by the wet-to-dry weight ratio and a similar method of objective radiologic grading. Although abnormalities may be seen in a technically well-performed chest roentgenogram, even if the EVLW is measurably normal, when the EVLW was increased by 35 percent, Snashall et al 121 found an approximate linear relationship between lung water content and the radiologic grade. In our study, for similar degrees of radiologic scoring, measured EVLW was greater in the noncardiac group than in the cardiac group, with the differentiation occurring at even the lowest grades of scoring; and EVLW increased in both groups in parallel to increasing degrees of severity by radiographic scoring. Therefore, despite similarity of chest radiologic appearances in pulmonary edema, EVLW is greater in noncardiac than in cardiac edema; yet within groups, a given severity of the chest roentgenogram seems to parallel EVLW accumulation.

We do not believe that the differences in EVLW content between the cardiac and noncardiac groups (groups 3 and 4, respectively) is explained by differences in the permeability surface area of the pulmonary microvasculature, since the PAPs were similar in both groups, and the PCWP was higher in group 3 patients where the EVLW was the smallest of the two. And even were the cardiac output to affect measurable thermal-dye EVLW content, such an effect would only serve to further magnify the differences reported between these two groups. 25

Many clinical studies continue to utilize measured changes in the intrapulmonary shunt fraction to imply parallel changes in EVLW content. 26,40 particularly following interventional therapy. We were unable to confirm any direct relationship between these two variables in either cardiac or noncardiac edema in accordance with data from other studies. 41,42 It is therefore apparent that caution must be exercised in interpretation of clinical data evaluating the effect of disease states or of therapeutic interventions on EVLW, when an assumption is made that changes in the Qs/Qt represent parallel changes in EVLW or the state of fluid flux across the pulmonary microvascular exchanging membrane.

In summary, we measured EVLW by the thermal-dye technique in a large number of critically ill patients to define the range associated with a normal chest roentgenogram. We also provided comparison of EVLW between patients with pulmonary edema on both a cardiac and noncardiac basis. Since thermal-dye EVLW was measurably higher in patients with noncardiac pulmonary edema than in patients with cardiac edema, despite a higher PCWP in the latter group, this method seems potentially capable of providing important ancillary data to differentiate these two disease states. We also found that the calculated Qs/Qt is an unreliable indicator of the amount of EVLW. Further studies should confirm the normal range of EVLW and evaluate the reliability of this technique in assessing.

Measuring Extravascular Lung Water in Critically Ill Patients (Sibbald et al)
changes in EVLW with therapeutic intervention.

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