Small Solute Clearance from the Lungs of Patients with Cardiogenic and Noncardiogenic Pulmonary Edema*

Gregory R. Mason, M.D., F.C.C.P.; Richard M. Effros, M.D.; J. M. Uszler, M.D.; and Ismael Mena, M.D.

The regional clearance of \(^{99m}\)Tc-diethylenetriamine penta-acetate (\(^{99m}\)Tc-DTPA) from the lungs was measured in 14 patients with noncardiogenic pulmonary edema, six patients with acute pulmonary edema secondary to heart failure, and 29 normal subjects. The radionuclide was delivered in an aerosol which was inhaled for 120 seconds, and the subsequent decline of radioactivity from the lungs was monitored for seven minutes over each of six peripheral regions of interest with a computerized scintillation camera. The average \(^{99m}\)Tc-DTPA clearance of these regions was accelerated above the 95 percent confidence limits in all but three of the patients with noncardiogenic edema. The mean clearance value in this group of patients was significantly greater than those in normal subjects or patients with cardiogenic pulmonary edema. Clearances returned toward normal in each of seven subjects who improved clinically. Only one of the patients with cardiogenic pulmonary edema had an elevated average clearance rate, and the mean clearance for this population was not statistically greater than normal. This procedure appears to detect increased epithelial permeability caused by lung injury and may help distinguish between cardiogenic and noncardiogenic pulmonary edema.

Our current understanding of the frequency of noncardiogenic pulmonary edema can be attributed in large part to the introduction of the Swan-Ganz catheter into clinical medicine.\(^1\) Measurements of left atrial pressure can be readily estimated from pulmonary artery wedge pressures determined with the catheter. When the pressures are low in patients with clinical and roentgenographic evidence of pulmonary edema, it is generally assumed that the lungs have been damaged in a manner which permits fluids to leak into the pulmonary interstitium and airspaces. Rather than high intravascular pressures, this condition may be associated with a variety of other pathologic processes ranging from direct exposure to toxic agents to less clearly understood events such as septicemia, fat embolism, and pancreatitis. These conditions have been collectively designated as the “adult respiratory distress syndrome” (ARDS) or noncardiogenic pulmonary edema.\(^2\)

Although measurements of pulmonary artery occlusion pressures have clarified our understanding of the incidence, course, and treatment of noncardiogenic pulmonary edema, they can only provide indirect evidence for increases in the permeability of the membranes which normally restrain movement of fluid into the lungs. There are two circumstances in which wedge measurements may be misleading: (1) when pulmonary edema is due to elevations in left atrial pressures which return to normal before the edema fluid has been reabsorbed; and (2) when both an increase in left atrial pressure and lung damage are present. In the former situation, a diagnosis of lung damage may be made in error, whereas in the latter situation, the presence of such an injury may be overlooked. It is clear that a direct method for detecting and quantitating the permeability of the lungs in a clinical setting would be useful.

Two continuous cellular barriers separate the vascular and gaseous compartments of the lung: the endothelium and epithelium. Alterations of both these membranes are commonly seen in morphologic studies of tissues derived from patients with ARDS.\(^3\) We have recently developed a procedure for measuring the regional clearance of aerosolized solutes from the lung which appears to detect increases in the permeability of the pulmonary epithelium in patients with chronic interstitial lung disease.\(^4\) Similar increases in solute clearance have been documented in progressive sys-
temic sclerosis⁶ and among smokers,⁷,⁸,⁹ More recently Jeffries et al have used a similar procedure to show that pulmonary epithelial permeability is increased among newborns with the neonatal respiratory distress syn-
drome.¹⁰

Our objective in this study was to determine whether the radioserosal procedure can detect acute injury to the pulmonary epithelium in adults with

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Smoking History</th>
<th>Interval between Smiling and Scan</th>
<th>Days Hospitalized Days on Ventilator</th>
<th>Mean Clearance Rate (%/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (yr)</td>
<td>Sex</td>
<td>Precipitating Illness</td>
<td>Time from Presentation to Scan</td>
<td>Patient Position Mode of Ventilation During Study</td>
</tr>
<tr>
<td>Adult Respiratory Distress Syndrome</td>
<td>1</td>
<td>25 F</td>
<td>Complications of molar pregnancy</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>36 M</td>
<td>Sepsis</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>54 F</td>
<td>Sepsis, bacterial and fungal</td>
<td>5 weeks</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>31 M</td>
<td>Aspiration, pneumonia</td>
<td>4 days</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>28 F</td>
<td>Sepsis</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>70 F</td>
<td>Peritonitis</td>
<td>8 days</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>52 F</td>
<td>Sepsis</td>
<td>4 days</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>49 F</td>
<td>Salicylate overdose and sepsis</td>
<td>16 days</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>49 M</td>
<td>Sepsis &amp; aspiration pneumonia</td>
<td>20 days</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>62 M</td>
<td>Postoperative pneumonia</td>
<td>11 days</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>26 M</td>
<td>Aspiration pneumonia</td>
<td>11 days</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>47 M</td>
<td>Massive transfusion</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>76 M</td>
<td>Sepsis</td>
<td>23 days</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>45 F</td>
<td>Acute interstitial pneumonitis</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

(continued on next page)
documented ARDS. In addition, we measured radioaerosol solute clearance in patients with cardiogenic pulmonary edema who presumably had sustained less injury to the pulmonary membranes.

**METHODS**

**Radioaerosol Procedure and Data Acquisition**

The radioaerosol procedure used in this study has been described in detail previously. Each of the subjects inhaled 2 ml of an aerosol containing 99mTc-DTPA dissolved in an isotonic saline solution, and the subsequent regional decline of radioactivity was monitored with a scintillation camera. The aerosol was generated into a 30-L balloon with an acorn nebulizer. This permitted settling of larger droplets. The median aerodynamic diameter of aerosol droplets averaged 1.8 μm with a geometric standard deviation of 1.7 and a count median diameter of 0.84 μm.

Each of the subjects who was not receiving mechanical ventilation inhaled the aerosol for two minutes through a mouthpiece with a noseclip in place. A one-way valve was used to discharge the exhaled gas and droplets into a shielded trap. In those individuals receiving mechanical ventilation, the aerosol was administered for two minutes through the intake valve of a volume respirator at the same rate, tidal volume, and end-expiratory pressures as those received immediately prior to the test. Small sealed 52Co point sources were placed on the shoulders and right flank of most of these patients to detect patient movement.

**Clinical Studies**

Each of the 13 normal, nonsmoking subjects (age range 20 to 66, average 39), three of the patients with noncardiogenic pulmonary edema, and one patient with cardiogenic pulmonary edema were studied in a fully upright, seated position with their backs against the scintillation camera. Eleven of the normal subjects, five of the CHF patients, and the remainder of the noncardiogenic pulmonary edema patients were studied in an anterior supine position, between 0° and 30° above horizontal with the scintillation camera placed over the anterior chest. Positive end-expiratory pressure (PEEP) was administered in the supine position with a volume-cycled ventilator to trained subjects who learned to relax with a mouthpiece and noseclip while being ventilated. A change in FRC was documented with an integrated pneumotachographic record as PEEP was removed. As indicated below, these positional differences and the presence of PEEP had a minor effect upon average clearance rates.

Continuous data were directly acquired by a minicomputer system and partitioned into 30-second sequential frames. A typical study consisted of four frames (two minutes) of increasing counts during the "loading" period and 14 frames (seven minutes) of declining counts as the inhaled solute moves into the bloodstream and out of the camera view. The sequential frames of data were corrected for radioactive decay. Regional data were analyzed by electronically defining regions of interest (ROIs) over the peripheral regions of the upper, middle, and lower portions of each lung. Each ROI represented approximately 20 percent of the posterior or anterior aspect of each lung. The rate of clearance was calculated from the negative slope of the best fit line on semilogarithmic coordinates over the seven-minute washout interval and was expressed as percent decline per minute (k). In several instances in which overall clearance rates were very slow, values of regional activity actually increased slightly (by less than 1 percent/minute). Clearance rates over these regions were assumed to be zero. In one patient with ARDS (No. 2), the data from three regions of interest in one lung were lost by the computer.

**Diagnostic Criteria**

The diagnosis of pulmonary edema was based on the rapid onset of a diffuse alveolar or interstitial infiltrate on the chest x-ray film. These x-ray films were evaluated independently by a radiologist and one of the investigators before the aerosol clearance studies were conducted.

The edema was attributed to CHF if (1) a predisposing cardiac disease was documented, (2) pulmonary artery occlusion pressures were above 20 cm H₂O, and (3) rales were present at the time of the study. The diagnostic criteria for noncardiogenic pulmonary edema were as follows: (1) presence of an illness associated with noncar-
Cardiogenic and Noncardiogenic Pulmonary Edema (Mason et al)

RESULTS

The chest x-ray film of patient 10 who had ARDS following a prolonged surgical procedure is shown in Figure 1 with a subsequent film obtained a week later after he had recovered. The scintillation camera studies obtained at the time of these x-ray films are shown in Figure 2. The images represent the scintiscans obtained at the end of the loading period and seven minutes thereafter. The decline in radioactivity observed over six regions of interest for these two studies are shown in Figure 3. Note that the activity decreases more rapidly during the acute phase of the illness than during the recovery period.

The average values for the mean clearance rates of $^{99m}$Tc-DTPA over six regions of interest were greatest among the patients with ARDS (Fig 4 and Table 2). Both the patients with ARDS and the normal subjects on PEEP were placed in separate groups from those not receiving PEEP because of several reports which suggest that PEEP can increase $^{99m}$Tc-DTPA clearance. However, the use of PEEP did not have a statistically significant effect upon clearances in either group. The failure to find an influence of PEEP in the normal population may have been due to the effect of the wide distribution of the ARDS data upon the analysis of variance.

Position of the patient and camera had no significant influence upon mean clearance rates. The average clearance values of the ARDS populations exceeded that of the patients with cardiogenic pulmonary edema

<table>
<thead>
<tr>
<th>ARDS not on PEEP</th>
<th>9</th>
<th>5.1 ± 0.7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS on PEEP</td>
<td>5</td>
<td>6.8 ± 1.0*</td>
</tr>
<tr>
<td>CHF</td>
<td>6</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>Normal Posterior-upright</td>
<td>13</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Anterior-supine, PEEP</td>
<td>5</td>
<td>2.4 ± 0.1</td>
</tr>
</tbody>
</table>

*Significantly different from normals on or off PEEP (p<0.01) and patients with CHF (p<0.05) (completely randomized analysis of variance).
(CHF) (Table 2). Although the average clearance rate of the CHF patients was greater than normal, this difference was not significant.

Mean clearance rates obtained in individual patients were compared to comparable normal populations to determine whether they were elevated. The clearance values which were greater than normal are indicated by the closed symbols in Figure 4. It will be noted that clearances were abnormally elevated in 11 of 14 patients with ARDS but only one of six patients with CHF (No. 18) who had chronic mitral valve disease and very elevated left atrial pressures.

The use of a scintillation camera made it possible to compare regional clearance rates in our patients with regional measurements in our normal subjects. Increased rates of clearance were observed in 48 percent (38 of 81) of the regions of interest in patients with noncardiogenic pulmonary edema and 19 percent (seven of 36) regions of interest in patients with CHF. Only one patient with CHF had more than one abnormal region of interest while ten of 14 of the patients with ARDS had more than one abnormal region of interest. All areas of the lungs appeared to be susceptible to injury.
Serial studies were performed in seven of the patients with noncardiogenic pulmonary edema who improved clinically thereafter as indicated by the clearing of chest x-ray films and reduction in requirement for supplemental oxygen. As shown in Figure 5, solute clearance decreased in each of these patients. However, the decrease in clearance was minimal in patient 13. This individual had been removed from PEEP and extubated at the time of the second study. Respiratory insufficiency recurred, and he subsequently died despite resumption of ventilatory support.

As reported previously,5,7 upper lung clearances were significantly greater than lower lung clearances in normal subjects seated with their backs against the scintillation camera (1.06 ± 0.20 percent/min SEM and 0.58 ± 0.09 respectively, p<0.05). This difference in regional clearance was not found in the 11 normal subjects who were restudied in a supine position with the camera positioned anteriorly or in any of the patient groups. Overall clearance in the normal subjects was not significantly greater in the supine than

\[ \text{Figure 3. Decline in radioactivity observed over regions of interest from the studies shown in Figure 2. Best exponential fit is determined by the least squares methods for the seven-minute interval following loading.} \]

\[ \text{Figure 4. Clearance values in normal subjects, congestive heart failure patients (CHF), and adult respiratory distress syndrome (ARDS) patients. Clearances were greatest among patients with ARDS (Table 2). Closed symbols indicate studies in which the clearances were elevated compared to normal values (p<0.02) whereas the open symbols represent studies within the 98 percent confidence limits of normal. The circles represent studies in patients in the seated position with their backs against the camera. Upright triangles indicate studies in the supine position with an anteriorly placed camera. Inserted triangles represent studies of individuals on PEEP and were performed in the supine position with the camera over the anterior chest.} \]

\[ \text{Figure 5. Decline in average clearance rates in seven patients with noncardiogenic pulmonary edema who improved clinically. Time interval from initial scan is indicated. (In order from highest to lowest initial clearance rates: patients 10, 8, 13, 5, 11, 12, and 13.)} \]
upright position, but values for studies performed with each approach are indicted separately in Figure 4.

DISCUSSION

The data obtained in this study suggest that the radioaerosol procedure can be used in a clinical setting to detect lung injury in patients who have pulmonary edema. The highest rates of $^{99m}$Tc-DTPA clearance were observed in patients who had noncardiogenic pulmonary edema (ARDS). Among these individuals, clearances tended to be elevated regardless of their position or the use of PEEP. Of nine patients with ARDS who were not on PEEP, seven had clearance values which exceeded the upper limit of normal subjects in the same position (see closed symbols in Fig 4). Although PEEP may increase clearances in normal subjects, the values obtained in patients with ARDS on PEEP were significantly greater than those obtained in normal subjects on PEEP. The mean value of the normal subjects on PEEP in the present study exceeded that of normal subjects, who were not on PEEP, but this difference was not significant by an analysis of variance. This failure to observe a difference between the normal subjects on PEEP and those not receiving PEEP may have been related to the wide range of clearances in the patient population.

It is difficult to know whether the magnitude of the increase in clearance among the ARDS patients was determined by the severity of the injury. However, slowing of indicator clearance was observed in each of seven patients who improved clinically as judged by clearing of chest x-ray films and improvement of gas exchange. In the patient who had the least normalization of clearance, the clinical response proved to be transient, and he subsequently died of his illness.

Clearance rates were significantly lower in patients who had pulmonary edema secondary to CHF than in those who had ARDS. The average clearance rate in this population was not significantly greater than normal but one patient with chronic mitral valve disease had a mean clearance rate which was distinctly abnormal. Furthermore, abnormally high clearance rates were observed in individual regions of interest in some of these patients.

Elevation of $^{99m}$Tc-DTPA clearance in patients with ARDS is consistent with an increase in epithelial permeability related to lung injury. Alternative factors such as mucociliary transport, local blood and lymph flow, site of aerosol deposition, and epithelial surface area appear to have relatively little influence upon clearance rates in comparison to the effect of epithelial permeability. Evidence that the clearance of this indicator from the lungs is accelerated by lung injury has now been reported among patients with chronic interstitial lung disease, progressive systemic sclerosis, and neonatal respiratory distress syndrome, as well as in normal smokers. It is possible that there may have been a modest injury to the pulmonary epithelium in some of our patients with CHF.

The delivery of the aerosol droplets is presumably limited to ventilated portions of the lung rather than those which are filled with fluid. The increase in clearance observed in patients with ARDS must consequently reflect the permeability of regions of the lung which have not yet been flooded with edema fluid.

Because of the noninvasive manner in which the radioaerosol procedure is performed, it is readily applicable to patients in an intensive care environment. Although a prior history of smoking might complicate interpretation, elevated clearances in smokers rapidly return towards normal when smoking is discontinued and would not be expected to result in a persistently rapid rate of clearance. Clearances in the three patients who had smoked within one week of the study were no greater than the other patients with ARDS.

A portable scintillation camera was used to detect regional abnormalities over the peripheral portions of the lungs in our patient population. Single crystal probes have been used by both Jones et al and Minty et al and Jeffries et al to detect lung injury in a variety of conditions. Since all regions of the lung seemed to be equally susceptible to injury, such an approach would be expected to detect abnormally rapid $^{99m}$Tc-DTPA clearance in the majority of patients with ARDS. However, regional differences are found in some patients. The value of employing a scintillation camera is indicated by the fact that clearance rates were not necessarily uniform in the lungs of patients with ARDS. For example, six of these individuals had one or more regions of interest which were normal and in two patients, normal clearances were identified in two or more regions of interest. In this respect, the use of a scintillation camera which monitors all lung regions may prove to be a more reliable approach than studies based on single crystal probes.

Radioaerosol diffusion studies may prove useful in a number of ways in patients with pulmonary edema. Although the distinction between CHF and ARDS can often be made on clinical grounds, this new approach may permit detection of lung injury when CHF is also present. Furthermore it is possible that the clearance of $^{99m}$Tc-DTPA increases before significant edema formation has occurred. In addition, serial studies may help in evaluating therapeutic measures and predicting clinical outcome.

REFERENCES
2 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute
7 Mason G, Effros RM, Uszler JM, Reid E. Rapidly reversible alterations of pulmonary epithelial permeability induced by smoking. Chest 1983; 83:6-11