Imaging

Radioaerosol Delivery and Clearance in Patients with Respiratory Failure

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A technique for radioaerosol delivery to patients requiring mechanical ventilation is described. Ventilation images and pulmonary radioaerosol clearance rates were successfully obtained in 35 patients regardless of ventilator type or level of positive end-expiratory pressure (PEEP). Those patients with noncardiogenic pulmonary edema (NPE) had significantly increased clearance rates relative to those patients in whom NPE was not present.

The clearance rate of an inhaled radioaerosol from the lungs has been described as a measure of alveolar–capillary permeability (*1*). Accelerated clearance, a reflection of increased permeability, has been described in healthy cigarette smokers (*2,3*) and in patients with interstitial lung disease (*4*), scleroderma (*5*), *Pneumocystis carinii* pneumonia (*6*), and adult respiratory distress syndrome (*7*), and in premature infants with hyaline membrane disease (*8*). A recent report has noted a more rapid pulmonary clearance of radioaerosol in patients with noncardiogenic pulmonary edema (NPE) than in patients with congestive heart failure (*9*). The authors of this report, however, did not detail their technique for radioaerosol delivery to those patients who required mechanical ventilation. Vezina et al. (*10*) recently described their technique for delivering radioaerosol to ventilator-dependent patients who were receiving ventilation–perfusion scans for suspected pulmonary embolism. One problem with this technique was that they could not deliver adequate radioaerosol to those ventilated patients requiring positive end-expiratory pressure (PEEP) greater than 10 cm H_2O. Patients with NPE frequently need high levels of PEEP to maintain adequate oxygen delivery, and even its brief discontinuation can result in severe cardiopulmonary compromise (*11*). A technique to obtain ventilation images of patients while on PEEP would therefore be useful.

The purpose of our study was twofold: 1) to develop a technique for radioaerosol delivery to patients requiring mechanical ventilation; and 2) to obtain ventilation images and measure the rate of pulmonary radioaerosol clearance in a series of patients with respiratory failure. The technique we describe is simple, reliable, and can be used effectively regardless of ventilator type or level of PEEP. We evaluated the clearance values obtained and found they may be useful in distinguishing between the absence or presence of NPE in patients with respiratory failure.

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MATERIALS AND METHODS

Radioaerosol clearance studies were performed using modifications of a technique previously described for spontaneously breathing patients (*4*). Technetium-99m diethylenetriaminepentacetate (^{99m}Tc DTPA) was prepared within 4 hr of each study using a commercial kit. The resulting preparation, both before and after aerosolization, contained less than 2% free [^{99m}Tc] pertechnetate as assessed by thin-layer paper chromatography.

The aerosol-generating apparatus used a commercially available nebulizer* modified for patients on ventilators. The modifications required no additional tubing or valves. The only changes made were modifying the circuit by eliminating some of the respiratory tubing and changing the original placement of the remaining tubing as illustrated in figure 1. No additional gluing or support was needed for the joints within the system. The one-way valve placed at C_1 (Fig. 1), provided in the original kit, was important to prevent back pressure into the nebulizer and spillage of the ^{99m}Tc DTPA solution into the lead cannister when high levels of PEEP were in use. It also prevented spillage prior to disconnecting the circuit from the ventilator when the oxygen generating the aerosol was turned off. The short tubing extending from the one-way valve at C_2 (Fig. 1) allows flow into the system during negative inspiratory pressures. During positive pressure ventilation, however, the one-way valve stays closed and no airflow through C_2 occurs. The tubing extending from the nebulizer to the patient was at a length that allowed convenient placement of the lead cannister near the patient. The efficiency of radioaerosol delivery is

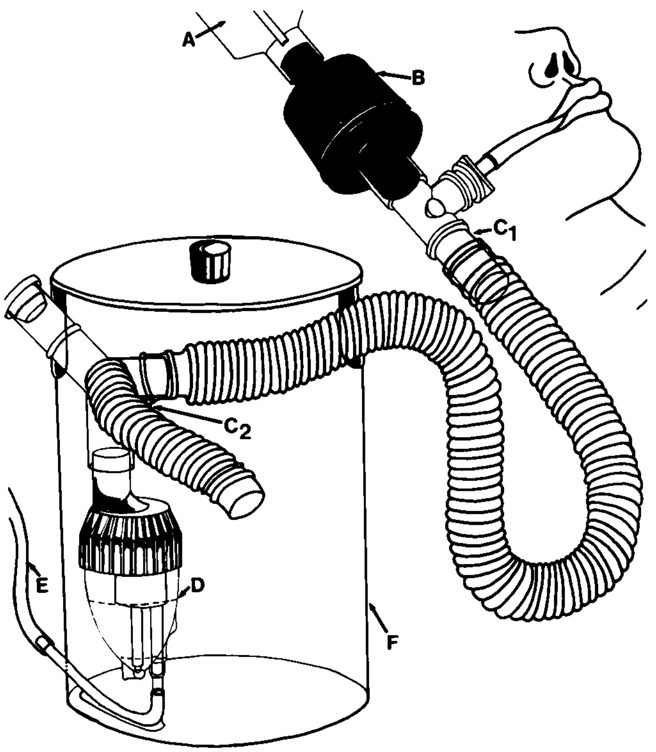

FIG. 1. Radioaerosol delivery system. A, tubing to ventilator; B, bacterial filter; C_1, one-way valve; C_2, one-way valve; D, nebulizing unit; E, O_2 tubing; F, lead cannister.

reduced by impaction of the particles on the tubing. As a tradeoff, this does lead to smaller particles reaching the patient. A bacterial filter (able to filter particles 0.20 μ in size) was placed to prevent ventilator contamination with radioaerosol.

A 3-cc saline solution containing 30–50 mCi (1110–1850 MBq) ^{99m}Tc DTPA was instilled into the nebulizer reservoir, which was then placed on-line to the patient. After connection into the ventilatory circuit, the aerosol was generated with nonhumidified oxygen from a portable tank or central oxygen supply connected to a standard wall unit and able to generate at least 100 cm H_2O pressure. The flow rate was turned to 15 L/min. After 3–6 min of radioaerosol delivery, the time needed to achieve total chest activity of 50,000–100,000 counts/min, the oxygen generating the aerosol was turned off and the unit was disconnected from the ventilatory circuit.

Information was acquired during aerosol delivery and washout by a scintillation camera positioned over the patient's anterior chest. The camera was fitted with a diverging-hole low-energy collimator and peaked for ^{99m}Tc at 140 keV with a 20% window. The camera was interfaced to a portable computer, which accumulated data in 64 × 64 matrices framed for 30-sec intervals. The computer acquired washout data for 15 min. After acquisition, areas of interest were drawn around each lung as displayed by the computer, excluding the area of the large bronchi. The acquired images were dynamically displayed with superimposed regions of interest as a check for patient movement during the study. Time–activity curves were generated for each area of interest. The best fit line was then determined for each decay-corrected washout curve through the first 7 min of washout. The line was described by: $Y = Ae^{-Bt}$, where A represented initial radioactivity, Y was radioactivity at time t, and B was the slope. The B value was converted into percentage washout per minute, which represented the clearance rate for each lung. For each subject, the clearance rates for each lung were combined to give a mean value.

The aerosol droplet size was measured using a cascade impactor (*12*). To mimic clinical conditions, the nebulizer was connected on-line with a time-cycled ventilator with the particles measured as they exited an endotracheal tube. The mass median aerodynamic diameter was 0.50μ with geometric standard deviation of 1.85. This size meets theoretical considerations for aerosol deposition in the alveoli or respiratory bronchioles (*13*). Because the general design of the cascade impactor is an open system, we could not increase pressure significantly to mimic conditions of increased PEEP when measuring particle size.

Patients were recruited for the study from the medical and surgical intensive care units. Patients eligible for the study were those who had been admitted with acute respiratory failure and subsequently required mechancial ventilation. All subjects or next of kin signed an informed consent statement approved by the human research committee. In those patients who required diagnostic or therapeutic bronchoscopy for management of their respiratory failure, bronchial fluid was collected for albumin quantitation.

One investigator (RPB), who was blinded to the pulmonary radioaerosol clearance data, retrospectively reviewed the patients' charts and determined the presence or absence of NPE in each case. The diagnosis of NPE was based on the following inclusive criteria: 1) critical hypoxemia with PaO_2/FiO_2 ratios (ratio of arterial oxygen pressure to percentage of inspired oxygen, an index of respiratory failure) less than 300; 2) new diffuse bilateral infiltrates on chest roentgenogram in the absence of underlying cardiac disease; 3) pulmonary capillary wedge pressure less than 18 mm Hg in those patients with indwelling Swan–Ganz catheters.

All clearance values are expressed as mean ± SEM. A Student's unpaired t-test was used to compare the data, with P values less than 0.05 considered significant.

RESULTS

We performed pulmonary radioaerosol clearance studies on 35 patients with acute respiratory failure who required mechanical ventilation. In each case we were able to deliver adequate radioaerosol to visualize both lung fields and calculate the clearance rates. Representative images with regions of interest and clearance curves are displayed in figure 2. There were varying degrees of central radioaerosol deposition in the patients; however, this did not interfere with the visual interpretation of the ventilation images or with the calculation of the clearance rates. The types of ventilators used were: 1) volume cycled (Bennett Respiration Unit Models MA-1 and MA-2); 2) time cycled (IMV Bird); 3) high frequency pulse generator (VDR 1–Sinusoidal Percussionator). Positive end-expiratory pressure values employed ranged from 0 to 25 cm H_2O. Underlying clinical conditions with clearance data, ventilator type, level of PEEP, and absence or presence of cigarette smoking are detailed in Tables 1 and 2.

TABLE 1. Patients without NPE*

Patient	Diagnosis	PEEP	Clearance rate (percent/min)
1	Penumonia	0	2.1
†2	Cardiogenic shock	0	1.3
3	Congestive heart failure	0	1.2
†4	Aspiration	0	2.8
5	Congestive heart failure	0	2.9
6	Pneumonia	0	3.0
†7	Pneumonia	0	1.8
8	Pneumonia	0	1.4
9	Chronic obstructive pulmonary disease	0	0.5
†10	Pneumonia	10	2.1
†11	Drug overdose	5	1.6
12	Hepatorenal syndrome	0	0.8
13	Aspiration	5	2.0

*All patients on Bennett MA1 or MA2 Ventilators.
†Smoking within 3 days of clearance study.

Twenty-one of the 35 patients were judged to have NPE. One of the remaining 14 patients without NPE was eliminated from analysis due to underlying idiopathic pulmonary fibrosis, a condition associated with accelerated radioaerosol clearance (*4*). The mean clearance rate of the patients with NPE was 6.0% ± 0.7%/min, whereas the clearance of the remaining 13 patients was significantly slower (Fig. 3) (1.8% ± 0.2%/min, $P < 0.01$).

We obtained bronchial secretions for albumin quantitation from 12 patients. There was a positive correlation between the rate of radioaerosol clearance and the albumin measured in lung fluid (Fig. 4) ($r = 0.65$, $P < 0.01$).

DISCUSSION

The ability to deliver radioaerosol to any patient requiring mechanical ventilation and thus obtain ventilation images of the lungs is a useful addition to the examinations offered by nuclear medicine. Ventilation scans when combined with perfusion scans are helpful in the diagnosis of pulmonary emboli (*14*). Increased accuracy in the diagnostic inclusion or exclusion of pulmonary emboli in these critically ill patients greatly adds to their management. Although we did not study patients with suspected pulmonary emboli, we have demonstrated the ability to obtain ventilation images of any patient who was being mechanically ventilated regardless of ventilator type or level of PEEP. Vezina et al. (*10*) needed to temporarily discontinue PEEP in those patients receiving high levels of PEEP when they delivered the radioaerosol. In our experience and others', however, even brief discontinuation of PEEP, especially in those patients requiring high levels, can result in severe cardiopulmonary compromise (*11*).

We were able to deliver the radioaerosol while maintaining PEEP levels of up to 25 cm H_2O. The pressure generated from the portable tank or central oxygen supply (minimum of 100 cm H_2O but usually much greater) was adequate to deliver the aerosol to the patients, despite the high PEEP. We did not measure the rate of aerosol deposition into the lungs but rather continued aerosolization until a preset number of counts was achieved. Longer aerosolization times to achieve the necessary counts did not seem to be needed in those patients on high PEEP. The quality of the images was independent of the level of PEEP or type of ventilator. We did observe varying degrees of radioaerosol impaction on the endotracheal tube. This finding tended to occur in patients with large amounts of bronchial secretions. We found that by suctioning the patient prior to initiating the test, the degree of endotracheal radioaerosol deposition could be reduced.

In addition to obtaining ventilation images, we determined the pulmonary radioaerosol clearance rate in each patient. We

TABLE 2. Patients with NPE*

Patient	Diagnosis	Ventilator	PEEP	Clearance rate (percent/min)
14	Penumonia	Bennett	10	6.0
15	Metastatic cancer	Bennett	0	4.2
*16	Pneumonia	Bennett	10	2.0
17	Status post-C-section	Bennett	5	6.9
18	Hepatorenal syndrome	Bennett	10	6.0
19	Aspiration	Bennett	15	6.2
20	Aspiration	Bennett	0	3.9
21	Pneumonia	Bennett	10	6.1
22	Perforated colon	Bird	16	6.7
23	Multiple Blood transfusion—surgery	Bird	20	4.3
24	Burn	Bird	5	5.5
25	Sepsis	Bird	5	6.0
26	Aspiration	Bird	21	3.3
27	Multiple blood transfusion—surgery	Bird	20	4.3
28	Drug overdose	Bird	5	11.2
29	Trauma, sepsis	VDR	25	6.7
30	Perforated colon	VDR	10	16.7
31	Burn, sepsis	VDR	15	6.7
32	Pulmonary contusion	VDR	13	6.1
33	Pneumonia	VDR	5	3.5
34	Multiple blood transfusion—surgery	VDR	5	11.2

*Smoking within 3 days of clearance study.

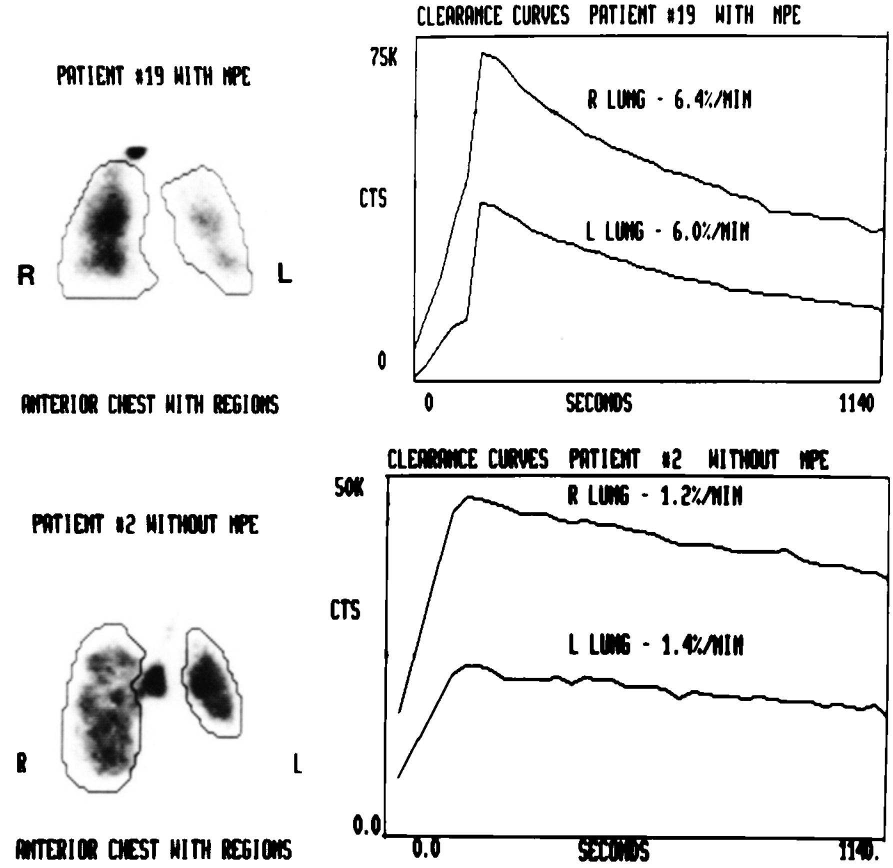

FIG. 2. Anterior ventilation images with superimposed regions of interest and clearance curves in representative patients with (top) and without (bottom) NPE.

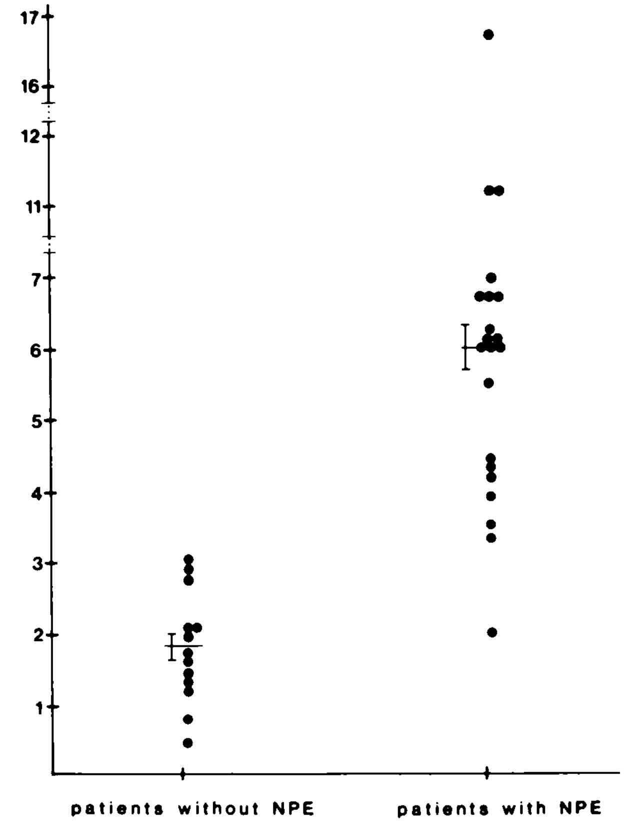

FIG. 3 Clearance rates of patients with and without NPE. Mean ± SEM indicated.

found the clearance values to be increased in patients with NPE relative to patients without NPE. The clearance rates in patients without NPE were within the range of a group of normal control subjects on whom we have previously reported (1.10% ± 0.4%/min) (*15*). The clearance curves in patients with NPE appeared to have both a rapid and a slow component. This finding has been described by others as well (*7*). Although future studies may demonstrate significance to the two components, we chose to fit the data into a monoexponential curve for reasons of improved standardization and reproducibility.

Radioisotopes have played an important role in studying the integrity of the alveolar-capillary membrane in patients with NPE. The clearance of injected iodine-131 (^{131}I) human serum albumin (HSA) from blood to lung (as measured by bronchial aspiration) has been used to detect increased alveolar-capillary membrane permeability in patients with NPE (*16*). The movement of ^{99m}Tc HSA or indium-113m (^{113m}In) transferrin from blood to lung by examining lung/heart ratios after the intravenous injection of the radionuclide has also been used to study the integrity of the alveolar membranes (*17,18*). These techniques, however, are invasive, complicated, poorly quantified, or not widely available. The pulmonary radioaerosol clearance study is noninvasive and can be done in any institution with the capability of interfacing a gamma camera to a computer.

Much work has been done in establishing the technique as a measure of alveolar-capillary membrane permeability (*1*), and it is currently regarded as a sensitive indicator of pulmonary membrane damage. This concept is supported by our

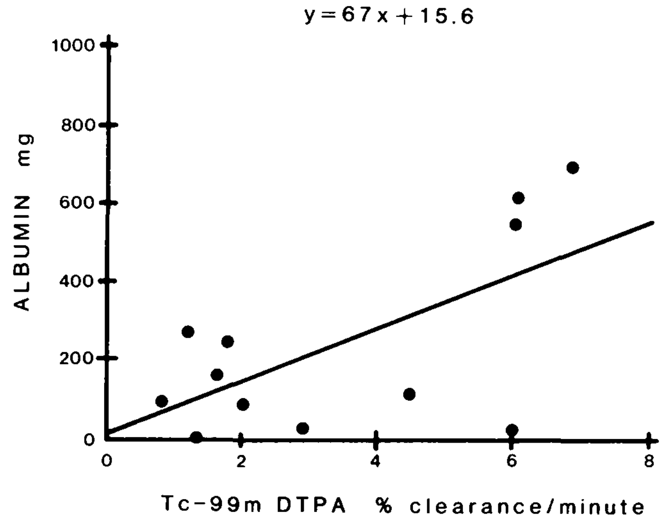

FIG. 4. A significant correlation was seen between ^{99m}Tc DTPA clearance and albumin in lung fluid (r = 0.65, P < 0.01).

finding a positive correlation between lung fluid albumin (elevated amounts reflecting increased pulmonary membrane permeability) and pulmonary radioaerosol clearance. We reported a similar, although stronger, positive correlation between those two tests in a previous study involving a different subject population in which lung fluid was obtained by bronchoalveolar lavage, and albumin was quantified using methylene blue as a control for variable fluid return (*15*). Using a different technique, others have also found that protein flux into the lung correlated well with ^{99m}Tc DTPA clearance in patients with NPE (*18*).

Our findings of accelerated pulmonary radioaerosol clearance in patients with NPE corroborates similar findings reported by others (*7,9,18*). In the correct clinical setting the clearance study thus may be useful in assessing the presence of NPE in patients with respiratory failure.

The use of PEEP in patients with respiratory failure may alter their ^{99m}Tc DTPA clearance rates since PEEP has been shown to increase the clearance rates in normal lungs (*19,20*). Its effect on clearance from diseased lungs, however, is not known. We and others have found no correlation between PEEP levels and clearance rates in a series of patients with respiratory failure (*9*, Tennenberg SD, manuscript submitted for publication). Studies in animal models too have found clearance to be unaffected by PEEP after lung injury (*21*). More work is needed to further define the relationship between PEEP and clearance, although at this point clearance in patients with respiratory failure appears to be unaffected by PEEP.

A recent history of cigarette smoking in patients with respiratory failure introduces another possible source of error when interpreting clearance data in these patients, since clearance rates are increased in cigarette smokers (*2,3,18,22*). We do not believe, however, that this factor influenced the results of our study. We identified the cigarette smokers in our study population, and although there were several in our group of patients without NPE, none had elevated clearance rates. This finding a positive correlation between lung fluid albumin (elevated amounts reflecting increased pulmonary membrane variation. Clearance rates begin to return toward normal soon after cessation of smoking (*2,3*). A smoking history is important when interpreting clearance data. A control for its effects may now exist but it will require validation (*23*).

Radioaerosol can be delivered to any patient requiring mechanical ventilation regardless of ventilator type and level of PEEP used. Ventilation scans and pulmonary clearance rates may be obtained. An elevated pulmonary radioaerosol clearance rate represents alterations in the alveolar-capillary membrane and may be useful in detecting NPE.

NOTE

*Cadema Medical Products, Middletown, NY.

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