Extrapulmonary Radioactivity in Lung Permeability Measurements

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The pulmonary clearance rate of aerosolized and deposited [^{99m}Tc]DTPA is used to assess pulmonary epithelial permeability to solutes. To evaluate whether it is necessary to correct these measurements for radioactivity in the chest wall and pulmonary vasculature five patients with no ventilation to one hemithorax were studied. After inhaling a submicronic aerosol of [^{99m}Tc]DTPA a gamma camera measured count rates over both hemithoraces for 20 min. The observed $T_{1/2}$ for clearance from the normal hemithorax was 56 min (range 18–115 min), and when this was corrected for chest wall contribution (derived from the abnormal hemithorax) the average $T_{1/2}$ was 52 min (range 17–107 min). To simulate infinitely permeable lungs we measured thoracic radioactivity in two adults and six children who were injected i.v. with a known amount of [^{99m}Tc]DTPA. The count rate over the thorax was only 8.1% (range 2.7%–11%) of that obtained when a similar amount of aerosolized [^{99m}Tc]DTPA was deposited in the lungs during a subsequent study. We conclude that it is not necessary to correct for nonpulmonary epithelial radioactivity during the measurement of [^{99m}Tc]DTPA clearance rate from the lungs.

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The measurement of the rate of clearance from the lungs of small radiolabeled solutes is being used to assess human pulmonary epithelial permeability to solutes (*1–8*). A frequently used method involves inhalation of an aerosol containing technetium-99m diethylenetriamine-pentaacetic acid ([^{99m}Tc]DTPA, mol wt = 492), followed by measurement of the subsequent disappearance from the lungs by an external scintillation probe or gamma camera. However, the [^{99m}Tc]DTPA that traverses the pulmonary epithelium enters the blood stream and equilibrates within the extracellular fluid compartment and is excreted by the kidneys. Therefore, any external counting device will not differentiate between radioactivity originating from the pulmonary epithelium and that originating from the chest wall tissues or pulmonary vasculature. Other investigators have detected significant increases in radioactivity originating from systemic vascular beds following inhalation of an aerosol of [^{99m}Tc]DTPA and have suggested that monitoring counts from the thigh and an i.v. injection of [^{99m}Tc]DTPA are required to accurately determine the pulmonary clearance rate for [^{99m}Tc]DTPA (*4*). Since we are interested in measuring pulmonary epithelial permeability in critically ill premature infants with hyaline membrane disease (*3*) we wished to avoid the additional radiation resulting from an intravenous injection of [^{99m}Tc]DTPA. We therefore assessed the contribution of nonpulmonary epithelial sources to the radioactivity detected by external detectors in pediatric and adult patients who had no ventilation to one hemithorax. To simulate diseased lungs with maximally increased permeability and immediate clearance of isotope from the lungs eight additional subjects received i.v. injections of known amounts of [^{99m}Tc]DTPA.

METHODS

Five patients with no ventilation to one hemithorax underwent quantitative ventilation perfusion lung scans for clinical reasons. Patient 1 was born following a full-term gestation and was noted to have a congenital tracheo-esophageal fistula. At time of corrective surgery the left main stem bronchus was inadvertently transected and re-anatomosed. Although the lung re-expanded, severe bronchial stenosis resulted. A lung scan was performed at 5 mo of age. Patient 2 was a 20-yr-old male with severe cystic fibrosis lung disease who had a collapsed left lower lobe and an expanded but essentially nonventilating left upper lobe. Patients 3, 4, and 5 were 50, 58,

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and 70 yr old, respectively, and had previously undergone pneumonectomy as part of the treatment for carcinoma of the lung.

Quantitative ventilation-perfusion lung scans were performed as previously described (*9*). The ventilation scintigram was obtained by having the patient inhale a submicronic aerosol containing [^{99m}Tc]DTPA. The [^{99m}Tc]DTPA aerosol was generated by a jet nebulizer and has a 0.6-micron aerodynamic mass median diameter and geometric s.d. of 1.97. The [^{99m}Tc]DTPA was prepared as previously described (*3*) and contained >98% [^{99m}Tc]DTPA and <2% as $^{99m}TcO_2$ or $^{99m}TcO_4^-$. Following inhalation of the aerosol the subject was placed in front of a large field-of-view gamma camera and posterior views of the ventilated lung were obtained for the pulmonary scintigram. Any radioactivity observed in the opposite hemithorax was assumed to result from the chest wall, pulmonary vasculature, or background scatter originating from the ventilated hemithorax. Count rates were then continuously recorded in 15-sec frames for 20 min from regions of interest (ROI) around each lung field to exclude radioactivity originating from the mediastinum. In the two children with no ventilation in one lung, perfusion was present but reduced. The perfusion scintigram was used to guide the placement of the ROI. In the three patients with pneumonectomy, we had to estimate the position of the "absent lung" using radioactive markers on the chest wall. In all cases, the ROI over both hemithoraces were the same size. Counts per minute (cpm) from the ventilated lung were plotted as a function of time and the single exponential line of best fit was determined by least squares on a digital computer. The pulmonary half-life ($T_{1/2}$) of [^{99m}Tc]DTPA in the ventilated lung was calculated from the slope of the line (k) using the formula $N = N_o e^{-kt}$, where N_o is the intercept and N is radioactivity at any time t. Counts per minute were corrected for radioactive decay of ^{99m}Tc. Clearance $T_{1/2}$ was calculated in two ways. First, we used the raw cpm arising from the ventilated hemithorax and, second, we subtracted the counts in the unventilated hemithorax from the counts in the ventilated hemithorax at each time point. In this way we calculated a $T_{1/2}$ corrected for the nonpulmonary epithelial radioactivity.

We wished to determine if the chest wall might contribute significantly to thoracic counts when the lungs are severely damaged and have increased permeability to solutes (*3*). Under these conditions the [^{99m}Tc]DTPA that had been deposited within the lung would be rapidly absorbed into the blood stream. To investigate this possibility ventilation lung scans were performed on two normal adult volunteers followed immediately by an i.v. injection of a known amount of ^{99m}Tc-labeled macroaggregates of albumin ([^{99m}Tc]MAA). By comparing the count rate after aerosol inhalation with the count rate after injection [^{99m}Tc]MAA we were able to quantitate the amount of aerosolized [^{99m}Tc]DTPA that had been deposited within the lungs. One week later an amount of [^{99m}Tc]DTPA equivalent to that which had previously been aerosolized and deposited within the lungs was injected intravenously while monitoring the radioactivity in both hemithoraces for 5 min. This simulated the instantaneous absorption of all the [^{99m}Tc]DTPA that had been deposited during aerosol inhalation. This is similar to the technique used by Yeats et al. (*10*) to correct for chest wall contributions. Because we have a major interest in the pediatric age group, it was important to obtain more information on the effect of extra pulmonary epithelial radioactivity on clearance measurements in children. To do this, we first measured the amount of aerosol inhaled by six children aged from 2 mo to 6 yr who were having ventilation-perfusion lung scan for clinical investigation. This was done as described above by comparing the count rate from the lungs after aerosol inhalation with the count rate after intravenous injections of a known amount of [^{99m}Tc]MAA. We considered it unethical to inject these children with [^{99m}Tc]DTPA as we had done with the adult volunteers. Instead we measured the count rate from the hemithoraces of five children aged 2 mo to 6 yr who had been injected with a known amount of [^{99m}Tc]DTPA for renal scan. From these children, we obtained the external count rate from the lungs per microcurie of injected [^{99m}Tc]DTPA 5 min after injection. We then used this count rate to estimate the nonpulmonary epithelial radioactivity in the six age matched children who had had ventilation scintigrams obtained with known amounts of inhaled [^{99m}Tc]DTPA.

RESULTS

Figure 1 is an example of time-activity curves obtained from Patient 5 with only one lung. Counts from the left lung cleared with a $T_{1/2}$ of 27 min. At zero time there were 1,800 counts/frame from the right hemithorax compared with 25,066 counts/frame in the left lung. This count rate in the right hemithorax probably arose from photons from the left lung that have under-

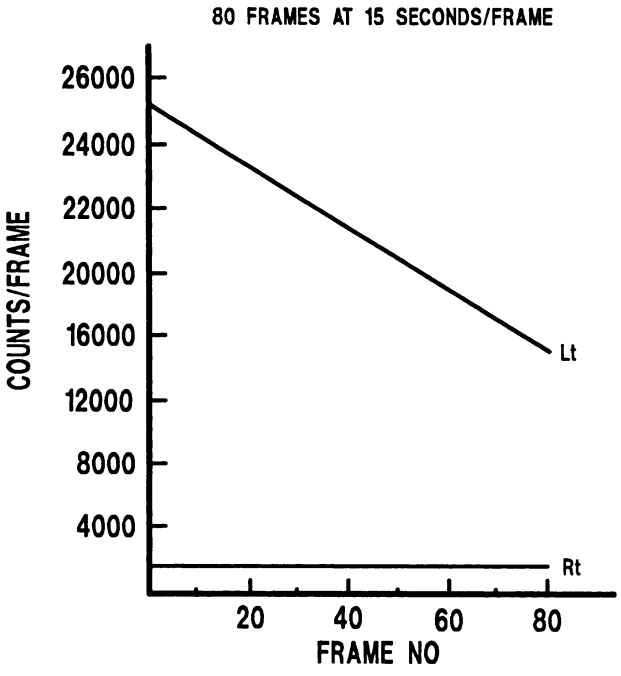

FIGURE 1
Radioactivity arising from left and right hemithorax in Patient 5 who has previously undergone a right pneumonectomy. The amount of radioactivity from the right hemithorax represents Compton scatter into the ^{99m}Tc photopeak and slight build up of [^{99m}Tc]DTPA in the chest wall and intrathoracic blood.

gone Compton scatter into the ^{99m}Tc photo peak and background from the room. Background counts were <100 per frame and were ignored. At 20 min there were 14,988 counts/frame from the left lung and the counts from the right hemithorax had risen to 1,906. The Compton scatter counts from the right hemithorax should have decreased as the isotope cleared from the left lung. In fact they increased slightly. We applied the same fractional rate of DTPA clearance $0.693/T_{1/2}$ to the 0 time counts coming from the right hemithorax. The 0 time counts of 1,800 counts/frame should have decreased to 1,098 counts/frame by 20 min. The difference between the actual counts (1,906) and the expected counts (1,098) at 20 min represents counts arising from isotope in the chest walls and intra-thoracic blood volume. In the case of Patient 5 the extrapulmonary counts accounted for 5.4% of the observed counts from the left lung at 20 min. This was the highest percent contribution in the five patients. The above corrections for Compton scatter into the nonventilated hemithorax was made for all five subjects. Table 1 contains the percent nonpulmonary epithelial contribution, the observed clearance $T_{1/2}$ and the $T_{1/2}$ corrected for the extra pulmonary contribution into the five patients studied.

In the two adult volunteers the i.v. injections of [^{99m}Tc]DTPA produced, after allowing 5 min for mixing within the vascular compartment, 11% and 8.9% of the count rate obtained from the hemithoraces after the subjects inhaled the same amount of [^{99m}Tc]DTPA. In the five children who had received i.v. [^{99m}Tc]DTPA the mean external count rate from the lungs 5 min postinjection was 14 ± 8 cpm/μCi of injected isotope. We used this calibration factor to calculate the extrapulmonary contribution to the external count rate from the lungs in the six children who had undergone ventilation-perfusion lung scintigraphy. These calculations assume infinitely increased permeability to solutes with instantaneous transport into the blood of all of the inhaled isotope. The mean nonpulmonary contribution was 4.6% with a range of 2.7%–7.8%.

DISCUSSION

The amount of isotope in the blood at any given time after inhaling aerosolized [^{99m}Tc]DTPA depends upon its rate of diffusion into the interstitial space, its rate of clearance by the kidney and its rate of transport from air space to blood. The latter is a function of the permeability of the epithelium, which is known to be much more restrictive than the endothelium to solute movement. In subjects with a rapid pulmonary clearance rate of [^{99m}Tc]DTPA one would expect a more rapid increase of isotope concentration in blood. This is exactly what has been shown by Elwood (*8*) and O'Byrne (*6*). In our limited number of patients the ones with the shortest $T_{1/2}$ (highest clearance rate) had the higher nonpulmonary contribution. However, even when we simulated instantaneous transport of all the inhaled isotope into blood the highest percent nonpulmonary contribution was only 11%. This would have negligible effect on an already very short $T_{1/2}$. For example, if the $T_{1/2}$ was 2 min, the correction for chest wall contribution would reduce the $T_{1/2}$ by only 0.3 min. In the five patients with only one ventilated lung, three had increased clearance rates. The highest nonpulmonary contribution was 5.4% and this changed the $T_{1/2}$ by only 2.5 min.

Our data from the five patients with either no ventilation to one lung or only one lung may be an underestimate of the true blood background because blood volume in the effected hemithorax may be less than that on the normal side. However, severe hypoxia causes only a 5% reduction in central blood volume in humans (*11*). Therefore in Patients 1 and 2 with no ventilation (Table 1) the pulmonary blood volume in that lung would be almost the same as the other intact side. Similarly in the two volunteers and six children who had intravenous DTPA equivalent to instantaneous absorption of all the inhaled isotope the maximum contribution was 11%. We therefore feel that our data are a close approximation to the true chest wall and pulmonary blood volume contributions to the externally detected counts. In calculating the effect of the extra counts on the calculated $T_{1/2}$ we have assumed that the extra counts continue to accumulate at the same rate as in the 20-min observation period. This is not so since intravascular [^{99m}Tc]DTPA is being lost rapidly through glomerular filtration. Thus, our correction for a $T_{1/2}$ of more than 20 min is an overestimate

TABLE 1
Effect of Extrapulmonary Epithelial Radioactivity on Measured $T_{1/2}$ for [^{99m}Tc]DTPA Clearance

Patient no.	Age (yr)	Diagnosis	Extrapulmonary epithelial radioactivity at 20 min (%)	Observed $T_{1/2}$ (min)	Corrected $T_{1/2}$ (min)
1	5/12	Bronchial stenosis	3.7	18	17.1
2	20	Cystic fibrosis	2.2	31	29.5
3	50	Pneumonectomy	0.85	115	107.3
4	58	Pneumonectomy	1.3	88	81.2
5	70	Pneumonectomy	5.4	27	24.5

of the true tissue and blood background, i.e., the corrected $T_{1/2}$ should be even closer to the observed calculated $T_{1/2}$.

There are no valid methods of correcting for the nonpulmonary epithelial contributions when measuring [^{99m}Tc]DTPA clearance rate. Jones et al. (*4,12*) simultaneously measured external counts from thigh and lung and then calibrated the two probes by injecting a small amount of [^{99m}Tc]DTPA intravenously. Elwood et al. (*8*) take blood samples from the patients and calibrate their gamma camera system so that they know the relation between count rate from blood and count rate from gamma camera.

For our purpose neither method of correction would be suitable for use in the neonate. Our data would indicate that the contribution from [^{99m}Tc]DTPA in the blood and chest wall tissue is small and that any correction for this contribution is unnecessary for most situations in which pulmonary-epithelial permeability is being measured. These conclusions agree with Rizk et al. (*13*) who stated they found it unnecessary to correct for isotope content in the blood when measuring [^{99m}Tc] DTPA clearance in dogs.

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