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Failure of aerosolised ^{99m}Tc DTPA clearance to predict outcome in patients with adult respiratory distress syndrome

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ABSTRACT The rate of clearance of technetium-99m labelled diethylene triamine pentacetic acid (^{99m}Tc DTPA) was measured in 32 patients with adult respiratory distress syndrome to determine if a more rapid clearance rate, possibly reflecting a more severe abnormality of pulmonary function, was associated with a reduced likelihood of recovery from pulmonary failure. Although the mean rate of clearance from lung to blood (T½LB) of ^{99m}Tc DTPA was more rapid in the patients (T½LB = 29 (SEM 3·2) min than in 42 normal subjects (T½LB = 59 (1·8) min), there was no difference between the clearance rate in the 18 patients who recovered from respiratory failure (T½LB = 31 (5) min) and the 14 who died (T½LB = 27 (4) min). Additionally, not all patients studied had abnormally rapid clearance rates. In 12 of the 32 patients the T½ fell within the range for normal individuals; this was found more commonly in patients who were predisposed to develop adult respiratory distress syndrome by pancreatitis or massive blood transfusion. These data suggest that a single measurement of ^{99m}Tc DTPA clearance in patients with established respiratory failure and adult respiratory distress syndrome is of no value in assessing the likelihood of recovery from this condition.

The adult respiratory distress syndrome (ARDS) was described nearly 20 years ago.[1] Despite this the pathogenesis of the condition in man remains poorly understood and is inferred largely from studies in animals. The fundamental abnormality in the syndrome is thought to be an increase in the permeability of the alveolar-blood barrier to water and solutes, especially proteins, the increased permeability being an integral part of an acute inflammatory reaction located in the lungs. Recently methods to measure indices of lung permeability have been developed that can be used safely in man.

In a previous study using the single pass multiple indicator dilution technique[2] the product of permeability and surface area for the tracer molecule urea (PSu) was significantly greater in patients with respiratory failure and pulmonary oedema than in patients with cardiac failure alone. While these data support the hypothesis that lung permeability is increased in patients with adult respiratory distress syndrome, of possibly greater importance was the finding that the permeability-surface area product (PSu) was higher in those patients who died than those who survived.

A simpler and less invasive method of determining an index of the permeability of the alveolar-blood barrier is to measure the rate of clearance of aerosolised technetium-99m labelled diethylene triamine pentacetic acid (^{99m}Tc DTPA) from the lung into the blood. A rapid rate of clearance of ^{99m}Tc DTPA is taken to imply an increase in alveolar-blood barrier permeability. The rate of clearance of radiolabelled DTPA has been shown previously to be abnormally rapid in pulmonary oedema of non-cardiac origin in both man[3,4] and animals,[5] and normal in patients and animals with pulmonary oedema associated with increased microvascular pressure.

The primary aim of this present study was to determine whether a single measurement of the rate of clearance of ^{99m}Tc DTPA made early in the course of the lung disease could predict outcome as assessed from two end points: reversal of the pulmonary failure and mortality.

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Secondly, previous studies have reported differences in the incidence and mortality from adult respiratory distress syndrome depending on the predisposing stimulus or condition leading to development of the syndrome.[6 7] This finding may have reflected differences in the nature and degree of lung reaction in response to the type of insult. To examine this hypothesis further the rates of clearance of ^{99m}Tc DTPA were compared in the different conditions predisposing to the development of the clinical syndrome.

Methods

^{99m}Tc DTPA clearance was measured in 32 patients (24 male, eight female) who were admitted to the intensive care unit with a diagnosis of adult respiratory distress syndrome. The patients' ages ranged from 16 to 75 years. Diagnosis of the adult respiratory distress syndrome was based on the criteria of Fowler *et al.*[6] At the time of study all patients had *(a)* acute respiratory failure requiring intubation and mechanical ventilation; *(b)* an arterial to inspired oxygen partial pressure ratio of less than 0·2; *(c)* a total static pulmonary compliance (CL) of less than 30 ml/cm H_2O; *(d)* bilateral infiltrates on the chest radiograph; *(e)* mean pulmonary capillary wedge pressure (PCWP) (when measured) of less than 12 mm Hg.

Patients were excluded from the study if they were younger than 16 years of age, had known interstitial or neoplastic lung disease, or had smoked tobacco products within the past six months. Any patients who had a pathogenic organism isolated from sputum or samples of tracheal aspirate before or within 24 hours of admission to the unit were also excluded. The results from a subgroup of patients who developed the syndrome after bone marrow transplantation have been reported previously[8] and have not been included here.

Conditions predisposing to the development of the syndrome were *(a)* aspiration of gastric contents (n = 6), which was either witnessed or inferred by suction of gastric contents from the lungs; *(b)* bacteraemia (n = 6), defined as at least two blood cultures, taken either at different times or from different sites, which grew a known pathogen; *(c)* open heart surgery with cardiopulmonary bypass (n = 3); *(d)* massive blood transfusion (n = 8), defined as the transfusion of more than 20 units of unfiltered blood in 12 hours with at least 10 units not crossmatched; *(e)* acute haemorrhagic pancreatitis (n = 4), diagnosed according to the criteria of Imrie *et al.*[9] Five further patients had two predisposing conditions for the syndrome. Of three patients who underwent surgery with cardiopulmonary bypass, one had positive blood cultures, one required transfusion of 32 units of blood in the postoperative period after rupture of the thoracic aorta, and the final patient required a 27 unit blood transfusion for upper gastrointestinal tract haemorrhage after cardiopulmonary bypass. The other two patients had pancreatitis; in addition, one had positive blood cultures and one had aspirated gastric contents.

MEASUREMENT OF THE CLEARANCE OF ^{99m}Tc DTPA

Measurement of the clearance of ^{99m}Tc DTPA was made usually on the day the patient was admitted to the intensive care unit and always within 24 hours of the clinical diagnosis of adult respiratory distress syndrome. Written informed consent to the study was obtained from the patient's nearest relative. The study had the full approval of the institute's ethical committee.

The method used in patients receiving mechanical ventilation has been described previously.[10] In brief, an aerosol of ^{99m}Tc DTPA was generated by a conventional jet nebuliser fitted with a particle separator to remove particles of more than 2 μm aerodynamic diameter[11] (Optimist, Medic-Aid UK Ltd). The aerosol was inflated into the patients with a self inflating bag attached to a non-return valve. This aerosol was introduced over two to three minutes until an external scintillation detector placed over the right chest showed a count rate of over 20 000 scintillations a minute. The 5·1 × 5·1 cm sodium iodide crystal used was positioned so that its centre was 4·8 cm below the clavicle and in the mid clavicular line. The clearance of the tracer was followed for 20 minutes. The lung counts were corrected for the increase in blood and tissue activity that occurred during the study as previously described.[10] The corrected counts were then plotted on a logarithmic scale against time. From a computer fitted regression line of this time-activity curve, the half time of clearance of ^{99m}Tc DTPA from the lung into the blood (T½LB, min) was then calculated. The results for patients in this present study were compared with the ^{99m}Tc DTPA clearance rates derived from measurements made in 42 healthy non-smokers aged 18–64.[8 12–14] The corrected clearance curves were monoexponential in all patients and normal subjects studied.

TREATMENT

All patients were receiving mechanical ventilation at the time of the study. Ventilator settings were adjusted to produce normal arterial pH and partial pressure of carbon dioxide. None of the patients was ventilated with an end expiratory airway pressure raised more than 5 cm H_2O before or during the study. Some patients, however, subsequently had to

have their end expiratory pressure increased in an attempt to improve oxygenation.

Where appropriate patients received treatment to reduce the pulmonary arterial and capillary wedge pressure using diuretics and vasodilators, usually sodium nitroprusside for the patients who had undergone open heart surgery and nitrates for other patients. Dopamine, augmented with dobutamine and adrenaline if necessary, was used to maintain a mean arterial blood pressure of more than 60 mm Hg and a cardiac index of more than $1{\cdot}8\,m^{-2}\,min^{-1}$. Treatment with steroids was not given routinely.

OUTCOME DEFINITION

The criteria for reversal of pulmonary failure were based on those for assessing suitability for weaning from mechanical ventilation,[15] as follows: *(a)* an improvement in oxygen transfer such that an arterial oxygen tension (Pao_2) of 10 kPa or greater was obtained with an inspired fractional oxygen concentration (Fio_2) of 0·4 or less; *(b)* a 50% improvement of static compliance or an increase to a value of greater than 30 ml/cm H_2O; *(c)* deadspace to tidal volume ratio and carbon dioxide productions such that a normal arterial carbon dioxide tension ($Paco_2$) was maintained with a minute volume of ventilation less than twice normal. Despite meeting these criteria for recovery from pulmonary failure the patients may have remained on assisted ventilation for other reasons, such as cardiovascular instability or neurological problems, and may have died subsequently.

STATISTICAL ANALYSIS

Results for each variable are expressed individually and as means with standard errors in parentheses. An unpaired *t* test was used to compare the results for clearance of ^{99m}Tc DTPA from normal subjects with those from the patients when reversal or non-reversal of pulmonary failure or death was regarded as the end point. Analysis of variance for unbalanced design (GLIM, Royal Statistical Society) was used for the comparison between aetiological groups for clearance of ^{99m}Tc DTPA, compliance, and wedge pressure.

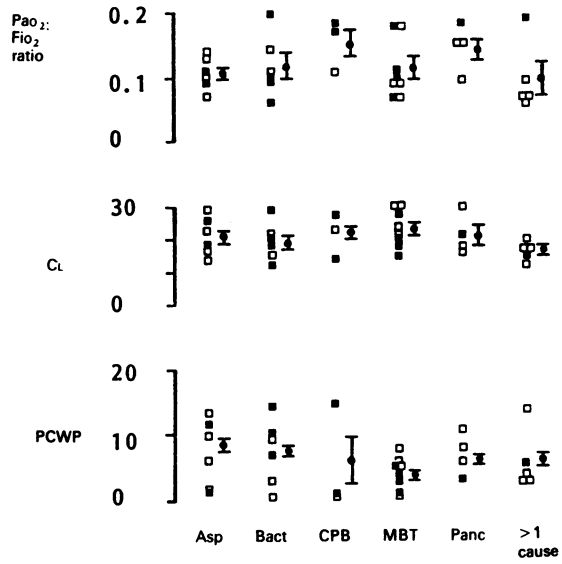

Fig 1 *Individual results with means and standard errors for ratio of arterial to inspired oxygen tension (Pao_2:Fio_2), total respiratory compliance (C_L, ml/cm H_2O), and pulmonary capillary wedge pressure (PCWP) (mm Hg). Results are divided into subgroups based on predisposing conditions. Asp—aspiration of gastric contents; Bact—bacteraemia; CPB—following open heart surgery with cardiopulmonary bypass; MBT—following a massive blood transfusion; Panc—pancreatitis; and > 1 cause—had predisposing conditions falling into two aetiological subgroups. Open symbols represent results from patients who recovered pulmonary function and closed symbols results from patients who did not.*

Results

The rate of clearance of ^{99m}Tc DTPA in the 32 patients with adult respiratory distress syndrome ($T\frac{1}{2}LB$ = 29 (SEM 3·2) min) was significantly ($p < 0{\cdot}001$) faster than in 42 healthy controls ($T\frac{1}{2}LB$ = 59 (1·8) min). There were, however, no significant differences between the clearance of ^{99m}Tc DTPA in those patients with adult respiratory distress syndrome who recovered from respiratory failure as defined above ($T\frac{1}{2}LB$ = 31 (5) min, n = 18) and those who did not ($T\frac{1}{2}$ = 27 (4) min, n = 14). Similarly, there were no significant differences between outcome groups if abnormalities of gas exchange or cardiorespiratory mechanics were compared. The length of stay in the intensive care unit of those patients recovering from respiratory failure (6·2 (3·6), range 2–18 days) was not different from that of patients who did not (5·9 (4·4), range 3–26 days). With death as the end point there were again no significant differences between the clearance rates for ^{99m}Tc DTPA in those who survived and left the intensive care unit ($T\frac{1}{2}$ = 27 (5·3) min, n = 13) and those patients who died in the unit ($T\frac{1}{2}$ = 30 (4) min, n = 19).

The individual values for Pao_2:Fio_2 ratio, C_L, and PCWP divided by the subgroups of predisposing conditions are shown in figure 1. These values were recorded on admission to the intensive care unit. There was no statistical difference between predis-

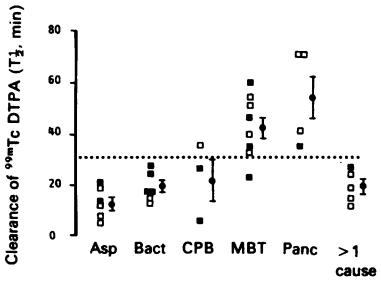

Fig 2 *Individual results with means and standard errors for clearance of technetium-99m labelled diethylene triamine pentacetic acid (^{99m}Tc DTPA) for each predisposition to the adult respiratory distress syndrome studied, as defined in the legend to figure 1. Open symbols show results from patients who had reversal of pulmonary failure and closed symbols results from patients not satisfying the criteria for reversal of pulmonary failure. The dotted horizontal line represents the value of the lower 95% confidence interval for normality of 32 minutes. This value was derived from the data for the 42 normal non-smoking control subjects, the upper 95% confidence interval being 121 minutes.*

posing conditions for any of the variables and no trend toward differences.

In contrast, there was a difference between subgroups of predisposing conditions for the clearance of ^{99m}Tc DTPA (fig 2). The mean clearance rates in the patients who had suffered from aspiration, bacteraemia, or the effects of cardiopulmonary bypass and in those patients with more than one identified predisposition were not different from each other. Clearance rates for these four subgroups, however, were all significantly ($p < 0.02$) more rapid than the values in the pancreatitis and massive blood transfusion groups. There was no difference between values for these latter two subgroups.

From the data obtained from a normal non-smoking control population the lower 95% confidence of T½LB for this laboratory was 32 minutes. This value is shown as the dotted line in figure 2. Twelve of the 32 patients with adult respiratory distress syndrome had values that were not outside this range of normality. In particular, all four patients with pancreatitis and seven of the eight who had had a massive blood transfusion had values within the normal range.

Finally, analysis of the individual data showed no evidence to suggest that a more rapid clearance could predict lack of recovery or death. For example, the patients with the most rapid clearance rates in the aspiration subgroup (5 min) survived, whereas the patient with the most rapid clearance in the cardiopulmonary bypass group (6 min) died.

Discussion

This study has confirmed previous reports that the clearance of ^{99m}Tc DTPA is abnormally rapid in most patients with adult respiratory distress syndrome.[3 4] Our data, however, showed no relationship between the result of the clearance measurement at the time of study and either reversal of pulmonary failure or survival in this study population. A second observation was that in certain patients with clinical adult respiratory distress syndrome and established respiratory failure the clearance of ^{99m}Tc DTPA was not abnormally rapid compared with that in healthy non-smokers.

Because cardiorespiratory mechanics and gas exchange provide a non-specific approach to assessing pulmonary injury,[16] it seemed more appropriate to relate the probability of recovery of pulmonary function to some index that has a putative direct relationship to the fundamental pathophysiology of adult respiratory distress syndrome. Previous studies have shown that the degree of abnormality of the rate of clearance of ^{99m}Tc DTPA is significantly related to other indices of inflammatory response, such as lung lavage fluid protein concentration[17] or the inflammatory cell population found in lavage fluid.[18] The rate of clearance of ^{99m}Tc DTPA is also related to the degree of pulmonary microvascular protein leakage in patients with adult respiratory distress syndrome.[13] These previous studies, together with studies showing that the rate of clearance appears unaffected by pulmonary oedema due to increased hydrostatic pressure,[3-5] suggest that the method provides a reasonable assessment of the degree of inflammation of the lung alveolar-blood barrier in man.

The study design, because of the nature of the disease process under investigation, was inevitably relatively unbalanced. Further analysis of the data, however, suggests that there was a 91% chance of detecting a significant ($p < 0.05$) difference between groups if recovery of pulmonary function was used as the end point (if such a difference actually existed) and an 86% chance of detecting such a difference if death was used as the end point.

On the assumption that the method provided a reasonable assessment of lung inflammation and that there were no errors of statistics, what other problems could lead to the negative conclusion? Following the rate of clearance of the tracer from the lung with a single probe detector may have led to an inaccurate assessment of solute clearance, especially if the distribution of pulmonary abnormality was patchy. The low ratio of Pao_2 to Fio_2 in the patients we studied, however, would indicate widespread pulmonary disease and thereby less likelihood that this mechanism

was a major source of error.

There are other potential sources of error in this study. Firstly, the measurement of clearance was made at a single time point. It could be argued that this approach overlooked the development of the lung pathology before admission to the intensive care unit. All patients, however, met the same clinical criteria for respiratory failure in the 24 hours before admission and measurement of clearance. Furthermore, there was no difference between variables in the comparison of those patients with a relatively prolonged phase before admission to the intensive care unit (bacteraemia and pancreatitis) and those in whom there was an acute insult where the temporal relationship of this insult to admission to the unit was known exactly (aspiration and massive transfusion).

Secondly, the death of the patient from a non-pulmonary cause could have prevented these patients meeting the criteria for recovery of pulmonary function. The lack of difference in clearance rates between survivors and non-survivors together with the similarity in the number of days spent in the intensive care unit tend to negate this.

Finally, the measurement of clearance of ^{99m}Tc DTPA is known to be affected by several relatively innocuous perturbations. It could be that the panoply of pharmacological and ventilatory interventions necessary for the patients' life support may have affected the results of the measurements. For example, recent studies have shown that clearance of ^{99m}Tc DTPA from normal lungs was increased if resting lung volume was increased.[19 20] This effect of hyperinflation, however, was not found when the lungs had been subjected to prior insult due to tobacco smoke[14] or cardiopulmonary bypass.[21] The effect of other therapeutic interventions on small solute flux from the lung remains to be investigated.

An unexpected finding of this study was that clearance rates were not abnormally rapid in studies of 12 of the 32 patients who had established respiratory failure. This finding was not highlighted in previous reports by Mason and colleagues[4] or Sibbald and colleagues.[3] This may be due in part to the inclusion of patients in these two earlier studies who were smoking up to the time of their illness. Although the abnormally rapid rate of clearance of ^{99m}Tc DTPA in otherwise healthy smokers quickly returns towards normality,[22] the rate is still not normal seven days after smoking has ceased. This effect may have contributed to previously reported results.[4]

Even more intriguing was that all four patients with pancreatitis and seven of the eight patients in the massive blood tranfusion group had clearance rates that fell within the 95% confidence limits for normal non-smoking individuals. What reasons could be put forward to explain these data?

It could be argued that the use of spontaneously breathing healthy subjects as controls for the desperately ill patients was inappropriate. To explain the results in this study it would be necessary, however, for normally ventilated subjects to have a slower clearance rate. Studies in animal models have shown the opposite effects in that exposure to increased inspired oxygen concentrations[23] (as in the patients in the present study) and positive pressure ventilation[24] increase solute and protein flux into the lung. In neither of these latter studies, however, was a molecule as small as ^{99m}Tc DTPA used.

A second explanation could be that there was a reduced pulmonary blood flow in those patients with clearance rates within the normal range. Reduction in the rate of clearance of ^{99m}Tc DTPA, however, requires a fall in blood flow well below that allowed in the patients in the present study.[19]

The clearance of ^{99m}Tc DTPA could be affected by the pattern of ventilation in that an increase in peribronchial oedema and airway narrowing would limit peripheral deposition of the tracer, thereby preventing the molecule from reaching the inflamed area. This again seemed an unlikely element as clearance rates of ^{99m}Tc DTPA are unaffected in patients with grossly disturbed ventilation secondary to obstructive airway disease.[25] In addition, the particle size distribution of the aerosol used in this study produces a lung deposition close to gas ventilation.[11]

As discussed above, the more likely reason for this result was that the measurement of clearance rate was made at a single time point. This had a fixed temporal relationship to the development of clinical signs of respiratory failure necessitating intensive care unit support. None the less, this may not have been related to the development of the pulmonary abnormality. In addition, it could have been that only pulmonary microvascular endothelial integrity was abnormal in these patients with "normal" clearance of ^{99m}Tc DTPA, which reflects an index of epithelial permeability.

Support for these latter notions comes from recently described studies in animals. The infusion of α thrombin into sheep produces an increase in lung lymph protein clearance, which is dependent on the presence of neutrophils and continues for four to six hours after the cessation of the stimulant infusion.[26] In the same model the clearance of aerosolised ^{99m}Tc DTPA is increased only during the course of the infusion of α thrombin. The increase in clearance of ^{99m}Tc DTPA is therefore independent of the presence of circulating neutrophils but dependent on an intact clotting mechanism.[27]

Possibly in some patients abnormal clearance of ^{99m}Tc DTPA is a transient phenomenon not detected on admission to the intensive care unit. If this is the case then perhaps the time window for therapeutic intervention with anti-inflammatory agents is very short. On the other hand, maybe the epithelial lining is relatively intact in certain conditions such as pan-

creatitis. If this is the case then measurement of clearance of ^{99m}Tc DTPA may not be the appropriate method to detect certain pathological lung lesions.

In conclusion, future studies where indices of permeability are measured earlier in the clinical course of lung injury may aid our understanding of the pathogenesis of the lesion in patients at risk of adult respiratory distress syndrome, and serial studies after the development of respiratory failure may be useful in evaluating patterns of progression of and recovery from acute lung injury in patients. A single measurement of the rate of clearance of ^{99m}Tc DTPA alone, however, in patients with established respiratory failure appears to be of no value in assessing the prospects of recovery.

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