Serial assessment of pulmonary microvascular permeability in a patient developing the adult respiratory distress syndrome

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ABSTRACT: Serial measurements of lung extravascular accumulation of $^{113m}$Indium-transferrin were made in a patient with acute respiratory failure during the development of the adult respiratory distress syndrome (ARDS). Abnormality of this index of pulmonary microvascular permeability antedated radiological change and appeared to predict the onset of frank ARDS.

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Keywords: Adult respiratory distress syndrome; lung permeability.

Received: August 6, 1991; accepted after revision December 10, 1991.

This work was supported by Dunhill Medical Trust.

The existence of a spectrum of lung injury in patients predisposed to developing adult respiratory distress (ARDS) [1] underlines the need for sensitive and specific methods of assessing alveolar-capillary integrity. Increased lung extravascular accumulation of $^{113m}$Indium-transferrin, as an index of microvascular permeability, appears specific to lung injury [2]. However, little information exists as to its sensitivity in early injury, particularly before radiological changes are prominent.

We report serial measurements of pulmonary microvascular permeability in a patient with acute respiratory failure, where the radiological appearances progressed over a week to fulfil ARDS criteria [3]. This is the first description of serial pulmonary microvascular permeability measurements during the evolution of ARDS.

Case report

A 50 yr old, nonsmoking male was admitted for open lung biopsy. From the respiratory viewpoint he had been well until 6 yrs previously, when he presented with breathlessness, a year after successful two vessel coronary vein grafting. A diagnosis of cryptogenic fibrosing alveolitis (CFA) was made on clinical, radiological and physiological criteria, although tissue was not obtained. The patient was treated with oral prednisolone with objective and symptomatic improvement and maintained thereafter on low-dose alternate day therapy.

Eighteen months prior to admission, a small opacity became apparent in the right mid-zone which subsequently enlarged. The appearances on computed tomographic scanning were felt to be atypical for CFA and accordingly he proceeded to open lung biopsy. Preoperative assessment showed an arterial oxygen tension ($\text{Pao}_2$) of 11.2 kPa breathing room air and a forced expiratory volume/forced vital capacity ($\text{FEV}_1/\text{FVC}$) of 2.7/3.4 l. Histology confirmed moderately active cellular CFA.

The perioperative period was uneventful but 36 h after the procedure he became febrile and breathless and was noted to be markedly hypoxaemic ($\text{Fio}_2=0.45; \text{Pao}_2$ 4.1 kPa, arterial carbon dioxide tension ($\text{Paco}_2$) 5.2 kPa). After initiation of mechanical ventilation, some improvement in gas exchange was noted ($\text{Fio}_2=0.5; \text{Pao}_2$ 9.4, $\text{Paco}_2$ 4.5 kPa). The $\text{Pao}_2/\text{Fio}_2$ ratio was 19 (normal range >50). The chest radiograph showed basal subsegmental atelectasis but no evidence of pulmonary oedema (fig. 1a). The pulmonary artery pressure was 47/21 mmHg and the pulmonary capillary wedge pressure (PCWP) was 12 mmHg. The total thoracic compliance (expired tidal volume/plateau inspiratory pressure - positive end expiratory pressure; normal range >80) was 52 ml/cmH$_2$O$^{-1}$. Although the patient was pyrexial during the first four days of mechanical ventilation (37–38°C), there were no clinical or laboratory data to suggest sepsis. He was haemodynamically stable, the surgical wounds were satisfactory and fluid balance over this period was marginally negative. All of the microbiological investigations, including blood cultures and tracheal aspirates were negative.

Measurements of the lung extravascular accumulation of $^{113m}$In-transferrin [4] were made on days 1, 2, 4, 7 and 12 after initiation of mechanical ventilation. Briefly, scintillation detectors were placed over right and left lung upper zones anteriorly and over the heart to monitor the intravascular pool.
Fig. 1. – Chest Radiograph from a) day 1 showing only basal atelectasis and b) on day 5 showing diffuse bilateral airspace consolidation typical of ARDS.

<table>
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<tr>
<th>Days</th>
<th>$\text{Pao}_2/\text{FiO}_2$</th>
<th>Compliance $\text{ml} \cdot \text{cmH}_2\text{O}^{-1}$</th>
<th>Mean $\text{PAI \times 10}^3$</th>
<th>PCWP $\text{mmHg}$</th>
<th>Chest X-ray score*</th>
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<tr>
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<td>27</td>
<td>4.2</td>
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*: chest X-ray pulmonary oedema score - lung divided into 3 horizontal zones bilaterally; 1 point if zone more than 75% opacified; $\text{Pao}_2$: arterial oxygen pressure; $\text{FiO}_2$: fraction of inspired oxygen; $\text{PAI}$: protein accumulation index; PCWP: pulmonary capillary wedge pressure.

The lung:heart count ratio for radiolabelled protein, and a similar ratio for radiolabelled red blood cells (as a 'non-diffusible' marker) were monitored. A regression equation was computed for lung:heart protein/lung:heart red blood cell counts versus time, and an arbitrary protein accumulation index ($\text{PAI}$) derived from the slope of the regression line. Mean $\text{PAI (SEM)}$ in normal subjects was $0.18 \pm 0.08$, while in ARDS it was $2.88 \pm 0.63$ [4]. Table 1 summarizes gas exchange, lung compliance, mean $\text{PAI (\times 10}^3\text{)}$, PCWP and chest radiographic appearance over the first 12 days of mechanical ventilation. The chest radiograph was scored for pulmonary oedema as described previously [5]. Development of frank pulmonary oedema on Day 5 (Fig. 1b) was unaccompanied by changes in the central venous pressure, electrocardiography (ECG) or serum creatine phosphokinase, although a pulmonary artery flotation catheter was not reinserted until Day 6, when the PCWP was 14 mmHg. The patient's further clinical course was complicated by increasingly refractory hypoxaemia and he died eventually on Day 39. Post-mortem histology confirmed diffuse alveolar damage with organization and fibrosis.

Discussion

Mortality associated with ARDS of up to 70% in selected patient groups has changed little over the last 20 yrs, notwithstanding advances in understanding and intensive care management of the syndrome [6]. Therefore, increasing attention has focused on identifying patients at risk for ARDS, or with early lung injury. The measurement of extravascular lung water (EVLW) is less sensitive than pulmonary microvascular protein permeability in mild experimental lung injury [7], but little information exists on their comparison in the clinical situation. This patient only fulfilled ARDS radiographic criteria on the fifth day of mechanical ventilation. This unusually slow evolution provided an important opportunity for assessing the usefulness of the $\text{PAI}$ measurement in early lung injury.
and comparing it with the chest radiograph, as an index of EVLW.

The mean value of PAI increased in the first 2 days (table 1), but was already clearly abnormal [4]. Of particular note was the very marked increase noted on Day 4, when the upper zones (where the scintillation counters were placed) were still clear radiologically. Although an elevated PAI has been described without significant radiographic change after pancreatitis [8], this is the first serial assessment of an index of lung permeability during the evolution of frank ARDS. The following day, dramatic deterioration in the chest radiographic appearances were noted with diffuse bilateral airspace consolidation (fig. 1b). The early abnormality in PAI could be construed as representing inflammatory activity due to CFA, although this association has not previously been formally examined. The doubling of mean PAI on Day 4 however, just preceding radiological deterioration, strongly suggests that the technique was an accurate index of worsening lung injury. Thus, in this patient, the PAI measurement did appear to predict frank alveolar flooding and fulfilment of ARDS criteria.

Along with increasing PAI, the first 5 days were characterized by gradually reducing lung compliance, although oxygenation was little changed. This pattern of abnormality is in keeping with present concepts of ARDS pathophysiology: no association appears to exist between oxygenation and EVLW, the former being related only to the extent of derecruitment of injured areas [9]. Decreasing lung compliance does imply an increase in EVLW; the chest radiograph is experimentally insensitive in this regard, requiring at least a 20% gravimetric EVLW increase before any changes are apparent [10]. Furthermore, as mentioned above, the PAI is experimentally a more sensitive index of mild to moderate lung injury than gravimetric EVLW. Presumably, EVLW did increase from Days 1 to 4, but on Day 5 it finally overcame lymphatic clearance producing frank alveolar flooding. Thus, although there was a temporal disparity in the abnormalities of protein (PAI) and water (chest radiograph) accumulation, this probably relates to the differing sensitivity of the two techniques in lung injury. Little attention has previously been focused on the sensitivity of PAI as an early diagnostic indicator of ARDS. Rocker et al. [1] found no difference between the PAI of patients with respiratory failure who subsequently progressed to ARDS and those who did not. No individual serial data were, however, presented and therefore the usefulness of the trend in individual patients could not be assessed.

These data suggest that lung extravascular accumulation of $^{113m}$In-transferrin may predict progression to ARDS and warrants further prospective study in at-risk patients.

References


