

## Pulmonary epithelial permeability in ARDS and cardiogenic pulmonary oedema

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*Pulmonary epithelial permeability in ARDS and cardiogenic pulmonary oedema. T. Todisco, M. Dottorini, F. Rossi, A. Baldoncini, R. Palumbo.*

Clearance of inhaled  $^{99m}\text{Tc}$ -labelled diethylene triamine pentaacetate ( $^{99m}\text{Tc}$ -DTPA) from the lung, an index of pulmonary alveolar epithelial permeability (PAEP), was measured in 13 patients with cardiogenic interstitial pulmonary oedema (CIPO) and in 7 patients with adult respiratory distress syndrome (ARDS). Thirty-five normal subjects (22 nonsmokers and 13 smokers) were evaluated as controls. Half-time clearance ( $t_{0.5}$ ) values in ARDS patients (mean  $\pm$  SD:  $15 \pm 2$  min) were significantly lower than in CIPO patients ( $62 \pm 9$  min). This PAEP increase in ARDS was impressive, even in comparison to heavy smokers. Loss of the PAEP vertical gradient (apical PAEP > base PAEP) was observed in both cardiogenic and ARDS lungs and among smokers.

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The role of pulmonary endothelial and/or epithelial damage in the pathogenesis of pulmonary oedema due to permeability, adult respiratory distress syndrome (ARDS) and to high pressure (cardiogenic interstitial pulmonary oedema (CIPO) is still debated [1-3]. Pathological studies of ARDS patients show evidence of necrosis in the alveolar epithelium [4]. Even in experimental models of ARDS, in addition to cellular and intercellular lesions in the endothelium, damage at the level of the alveolar epithelium was observed [5, 6]. Among the cell systems involved in ARDS, type II alveolar cells with surfactant abnormalities [7, 8], neutrophils recruited into the alveolar space by macrophage chemoattractants [9] and consequent release of noxious oxidants and unbalanced proteases [10] have been advocated. Furthermore, it is possible that the qualitative and quantitative variations in trans-membrane electrical fields and of proteoglycans and glycoproteins at the alveolar-capillary level may alter alveolar wall permeability even before morphological damage has been established [11-13].

The  $^{99m}\text{Tc}$ -labelled diethylene triamine pentaacetate ( $^{99m}\text{Tc}$ -DTPA) (hydrophilic solute, MW 492 Daltons) inhaled aerosol allows one to measure the pulmonary alveolar epithelial permeability (PAEP) in a non-invasive way [14] when the aerosol is administered to the patient in a particle size that favours

alveolar rather than bronchial deposition [15]. How the  $^{99m}\text{Tc}$ -DTPA passes from the alveolar space to the pulmonary capillary blood has not yet been established, although it is suspected that there is a passive diffusion through the epithelial and endothelial intercellular junctions [16]. *In vitro* studies show that paracellular permeability might be increased by oxidants [17].

In man,  $^{99m}\text{Tc}$ -DTPA assessment of PAEP has been applied to the study of numerous conditions: cigarette smoking [14, 18], systemic sclerosis [19], pulmonary interstitial diseases [20], chronic bronchitis [21], hyaline-membrane disease [22], pulmonary thromboembolism [23] and ARDS [24, 25]. The same method was used to study PAEP due to lung damage from radiation in dogs [16] and from positive end-expiratory pressure (PEEP) in healthy subjects [26]. Unfortunately, smoking is a common denominator which reduces the specificity of  $^{99m}\text{Tc}$ -DTPA clearance as a test of lung injury in chronic bronchitis [21] and cardiogenic pulmonary oedema [24]. The aim of this study is to verify whether epithelial permeability to  $^{99m}\text{Tc}$ -DTPA in ARDS patients (non-cardiogenic pulmonary oedema) is significantly greater than in cardiogenic interstitial pulmonary oedema (CIPO).

### Materials and methods

The PAEP to  $^{99m}\text{Tc}$ -DTPA was evaluated in two groups of patients with CIPO and ARDS, respectively; a group of normals (nonsmokers and smokers) were evaluated as controls.

### Subject selection

Twenty hospitalized patients, divided into two groups, were studied and the following criteria were established for each group.

**Group 1.** Patients with CIPO (n=13). All patients had valvular heart disease; none of them was a smoker. The diagnosis for each patient had been clinically and echocardiographically proven. All patients had radiographic evidence of interstitial pulmonary oedema by the following criteria: hila (enlarged, increased density, blurred); Kerley lines; micronoduli; peribronchial and perivascular cuffs; widening of scissurae; subpleural and intrapleural effusion; diffuse increase of density [27].

**Group 2.** Patients with ARDS (n=7). These patients were selected upon admission to the intensive care unit of our hospital, according to the following criteria: 1) arterial oxygen tension ( $P_{aO_2}$ ) of 75 mmHg or less at an inspired oxygen fraction of at least 0.4; 2) sudden onset of bilateral infiltrates on chest X-ray; 3) a predisposing condition to ARDS development; 4) no other explanation to the above findings; 5) at the time of the study patients no. 1 and 6 had stopped smoking two weeks earlier. Patients were breathing spontaneously without being endotracheally intubated or receiving PEEP. All these features had to be present at the same time. All the selected patients were able to perform three to six slow inspiratory vital capacity manoeuvres as requested by the method. Table 1 shows the clinical features of the ARDS patients enrolled in the study.

**Group 3.** Thirty-five normal subjects, aged 18–50 yrs, 25 males and 10 females, 22 nonsmokers and 13 smokers (>1 pack per day for more than two years) were studied as the control group. Normal clinical, functional and radiological status was requested to be admitted to the study.

### Aerosol generation and delivery

**Radionuclide.**  $^{99m}\text{Tc}$ Technetium, chelated to diethylene triamine pentacetate (DTPA) was inhaled as an aerosol generated with RÖHLE apparatus [28], which allows the inhalation of a monodispersed radioaerosol (mass median diameter, 0.8  $\mu\text{m}$  and 2.4 geometric sd). A 3 ml saline solution of  $^{99m}\text{Tc}$ -DTPA with a concentra-

tion of 6  $\text{mCi}\cdot\text{ml}^{-1}$  was introduced into the nebulizer. The subject breathes through a mouthpiece, the nose being closed by a noseclip, into the three-way valve. After the first third of a slow vital capacity, every subject inhaled the aerosol for three to six breaths, depending on the ventilatory capacity of the subjects. The stability of the  $^{99m}\text{Tc}$ -DTPA complex was confirmed on aerosol samples obtained from the aerosol generating circuit and on plasma samples obtained after aerosol inhalation. After the respiratory manoeuvre the activity recovered from the nebulizer was measured and that retained in the lungs was calculated to be about 2.5–3 mCi.

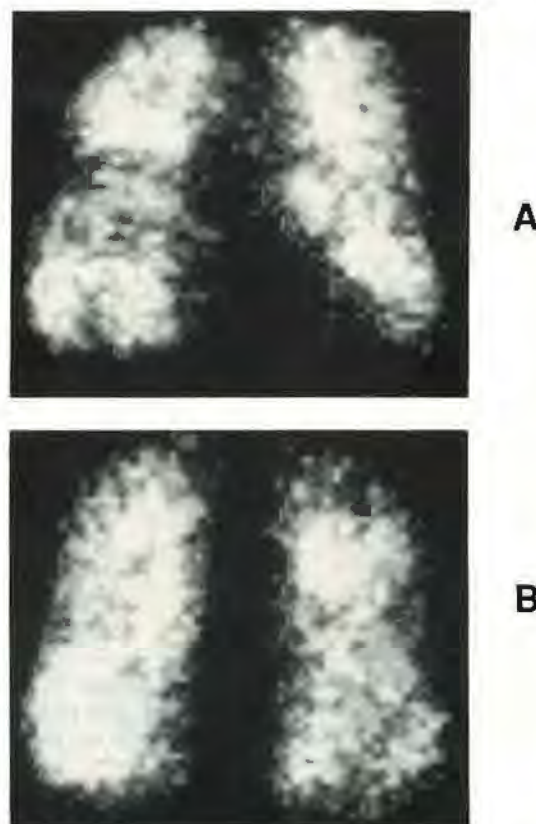


Fig. 1. –  $^{99m}\text{Tc}$ -DTPA “-ID” Deposition pattern in CIPO (A) and ARDS (B) patients. Anterior view soon after nebulization. The deposition images are very similar in both pulmonary conditions.

Table 1. – Clinical features of ARDS patients

Patient no.	Age yr	Sex	Smoking habit	Predisposing condition	Outcome*
1	54	M	Yes**	Multiple trauma	Died
2	72	M	No	Septicaemia in cancer patient	Died
3	52	F	No	Septicaemia in cancer patient	Died
4	62	M	No	Multiple trauma	Died
5	71	F	No	Septicaemia in cancer patient	Died
6	65	M	Yes**	Prolonged hypotension due to massive pulmonary thromboembolism	Alive
7	55	F	No	Multiple trauma	Died

\*: All deaths were a direct consequence of ARDS; \*\*: See methods.

Table 2. - PAEP indices ( $t_{0.5}$  min, mean $\pm$ SD) in 22 normal nonsmoking subjects and 13 normal smoking subjects (group 3)

	Right lung				Left lung			
	Whole	Upper	Middle	Lower	Whole	Upper	Middle	Lower
Nonsmokers	85 $\pm$ 34	52 $\pm$ 19	89 $\pm$ 37	85 $\pm$ 34	83 $\pm$ 26	57 $\pm$ 29	90 $\pm$ 34	94 $\pm$ 50
Smokers	43 $\pm$ 14	43 $\pm$ 15	41 $\pm$ 19	37 $\pm$ 11	49 $\pm$ 17	44 $\pm$ 20	43 $\pm$ 19	34 $\pm$ 15

PAEP: pulmonary alveolar epithelial permeability. Comparison within groups: right lung vs left lung, NS; right lung ROI vs left lung ROI, NS; nonsmokers right and left upper ROI vs right and left middle-lower ROI,  $p < 0.01$ ; smokers right and left upper ROI vs right and left middle-lower ROI, NS. ns: not significant.

Table 3. - PAEP ( $t_{0.5}$  min; mean $\pm$ SD) in CIPO and ARDS patients

Patient no.	CIPO				Patient no.	ARDS			
	Right lung					Right lung			
	Whole	U-ROI	M-ROI	L-ROI		Whole	U-ROI	M-ROI	L-ROI
1	60	80	58	68	14	17	20	23	22
2	64	70	66	65	15	14	18	16	16
3	50	51	53	46	16	18	21	20	18
4	54	57	52	51	17	15	16	17	18
5	51	53	58	56	18	11	13	11	12
6	48	48	57	63	19	18	18	21	23
7	74	63	67	70	20	15	18	19	17
8	70	64	65	70					
9	66	62	71	68					
10	61	44	53	60					
11	72	66	70	68					
12	68	42	67	70					
13	70	57	67	72					
mean $\pm$ SD	62 $\pm$ 9	58 $\pm$ 11	62 $\pm$ 7	64 $\pm$ 8		15 $\pm$ 2	18 $\pm$ 3	18 $\pm$ 4	18 $\pm$ 4

PAEP: pulmonary alveolar epithelial permeability;  $T_{0.5}$ : mean half-time clearance; M $\pm$ SD: mean  $\pm$  standard deviation; CIPE: cardiogenic pulmonary oedema; U-ROI: upper region of interest; M-ROI: middle region of interest; L-ROI: lower region of interest. For statistical analysis see the text. For  $p$  values see Results.

A scintillation count by a computerized gamma camera was then carried out for 30 min with the subject sitting with his back to the gamma camera, (fig 1) except for patients nos 1, 4, and 7 (multiple trauma, table 1), whose body position was maintained at +45°. The lung radioactivity data were framed at 30 s intervals and electronically placed regions of interest (ROI) were selected on the upper, middle and lower fields of each lung. Radioactivity was corrected for radionuclide decay and the data for each lung and each ROI were plotted on a semi-logarithmic scale against time in a linear co-ordinate. The following indices were calculated: the mean half-time clearance ( $t_{0.5}$ , min), referred to the monoexponential regression line, which follows the initial peak, and the clearance rate (K), which expressed the slope of this line as the percentage decrease per minute (% $\cdot$ min<sup>-1</sup>). Every subject was evaluated once.

### Statistical analysis

The statistical significance of differences in half-time ( $t_{0.5}$ ) and clearance rate (K) inside groups and between groups had been performed using the parametric Student's  $t$ -test applied to independent samples. The level of statistical significance was chosen at  $p < 0.05$ . All observed values were also reported as mean $\pm$ SD.

### Results

The PAEP  $t_{0.5}$  values of Group 3, mean $\pm$ SD and  $p$  values for each lung and each vertical ROI are shown in table 2; they are the reference values of our laboratory. The corresponding single values in CIPO and ARDS patients are shown in table 3. The data analysis shows that  $t_{0.5}$  value differences for corresponding ROI were highly significant ( $p < 0.001$ ) when CIPO and

ARDS patients were compared.

With respect to nonsmoking normals (table 2), both CIPO and ARDS groups recorded an increase of PAEP, this being greater in ARDS ( $p < 0.001$ ) than in CIPO patients. PAEP ( $t_{0.5}$ ) in CIPO patients increased ( $p < 0.05$ ) with respect to nonsmoking normals only in the middle-lower ROI of both lungs (whole right lung  $t_{0.5}$ , mean  $\pm$  SD, CIPO:  $62 \pm 9$ , normals:  $85 \pm 34$  ( $p < 0.05$ ); middle-lower right ROI, CIPO:  $62 \pm 7$ – $64 \pm 8$ , normals:  $89 \pm 37$ – $85 \pm 34$  ( $p < 0.05$ )). The apex-base gradient, that was demonstrated in nonsmoking subjects by us [29] and others [20, 30], was abolished in both these pathological conditions (table 3) as well as in the smokers' lungs (table 2).

### Discussion

ARDS is a life-threatening pulmonary disease with a rapidly progressive decline due mainly to multi-organ failure. Death occurs in 50–75% of ARDS cases [30] and in more than 90% when ARDS is associated with septicaemia [31]. The search for a predictive marker, useful in the early diagnosis of ARDS, is justified by its high mortality rates which are not predictable on the basis of well-known clinical roentgenographic and functional criteria [32]. The present study demonstrates that ARDS is associated with a striking increase in PAEP which is significantly higher ( $p < 0.001$ ) than in CIPO. As confirmed by previous data, PAEP may be increased after chronic exposure to cigarette smoke [14, 18, 33] but this damage is quickly reversible by interrupting the smoking habit [34]. However, to exclude the influence of smoke on PAEP, we chose nonsmoking CIPO patients. They presented  $t_{0.5}$  values between normal nonsmokers and smokers, but were closer to the nonsmokers values. A statistically significant difference between CIPO patients and smokers ( $p < 0.01$ )—whose clearance times were faster—was observed.

Among ARDS patients, patient no. 1 and patient no. 6 had stopped smoking two weeks before measurements; in any case their  $t_{0.5}$  values were close to those of other ARDS patients, so that their smoking history is likely to have no influence on measured PAEP. The mild enhancement of PAEP in CIPO patients with respect to normal subjects is limited to the middle-lower ROI (table 3). In fact the upper ROI's PAEP (normally higher than the PAEP of the remaining lung) is not further increased in CIPO patients. We believe that gravity may account for the dependent lung areas of increased permeability in CIPO patients.

Two other groups [24, 25] have recently studied  $^{99m}\text{Tc}$ -DTPA clearance in ARDS. According to MASON *et al.* [24], the striking increase in PAEP in all our ARDS patients indicates the high diagnostic sensitivity of this parameter. Our findings are also in agreement with those reported by BRAUDE *et al.* [25] who found that K values were significantly higher in ARDS patients when compared to normal controls. These investigators failed to detect a significant difference between the K values of ARDS patients (K %·min<sup>-1</sup>, mean  $\pm$  SD:  $5.2 \pm 0.9$ ) and those of normal smokers

(K  $3.6 \pm 0.8$ ) but in our opinion their smokers group was too small (7 subjects) to allow definite conclusions. The smoker's lung is undoubtedly more permeable than the nonsmoker's, but the degree of this abnormality is controversial, probably because of the large interindividual variability in susceptibility of smokers' lungs to the cigarette-induced damage. The degree of PAEP increase in the smokers group studied by us (13 subjects, age range 18–50 yrs; K  $1.9 \pm 0.7$ ) [33] completely agrees with that reported by KENNEDY *et al.* [18] (10 subjects, mean  $\pm$  SD:  $32.4 \pm 6.4$  yrs; K  $2.12 \pm 0.84$ ). From these figures it is clear that PAEP in ARDS patients (K  $4.5 \pm 1$ ) is significantly higher ( $p < 0.01$ ) without any overlap in values observed in otherwise "normal" smokers. In ARDS patients PAEP was increased 5.6-fold with respect to normal nonsmokers and was increased 2.8-fold with respect to normal smokers. The finding that the normal apex-base gradient of clearance from the lungs is lost in ARDS may be of great importance in suggesting diffuse epithelial damage, but its utility as a separate predictor of ARDS is limited at the present time by two different considerations: the occurrence of a similar event in smokers' lungs in CIPO and the lack of data on the time-course of PAEP in the early and preclinical phase of ARDS. In conclusion, if an effective therapeutic intervention is found PAEP assessment might be a life-saving tool in the first six days of this fatal disease when the mortality is at its lowest level [35, 36].

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- Perméabilité épithéliale pulmonaire dans le syndrome de détresse respiratoire aiguë et dans l'oedème pulmonaire cardiogénique.* T. Todisco, M. Dottorini, F. Rossi, A. Baldoncini, R. Palumbo.
- RÉSUMÉ: Nous avons mesuré chez 13 patients atteints d'oedème pulmonaire interstitiel cardiogénique (CIPO) et chez 7 patients atteints de syndrome de détresse respiratoire aiguë de l'adulte (ARDS), la clearance totale et régionale du pentacétate diéthylène triamine de Technécium  $^{99m}$  marqué ( $^{99m}\text{Tc}$ -DTPA). Trente-cinq sujets normaux (22 non fumeurs et 13 fumeurs) ont été évalués comme contrôles. Le temps demi moyen de clearance pour les patients atteints d'ARDS (poumon droit  $T_{0,5}$  minute,  $M\pm SD$ : 15.42 $\pm$ 2.5) s'avère significativement ( $p < 0.001$ ) plus bas que chez les patients CIPO (poumon droit  $T_{0,5}$  minute,  $M\pm SD$ : 62.15 $\pm$ 8.9). Cette augmentation de la perméabilité épithéliale des espaces aériens périphériques est impressionnante dans l'ARDS, même par comparaison avec les grands fumeurs ( $p < 0.01$ ). De plus, la perte du gradient vertical de perméabilité épithéliale des espaces périphériques (PAEP de l'apex > PAEP de la base) a été observée dans des poumons oedématisés; nous pensons qu'elle reflète une atteinte épithéliale diffuse. Toutefois, l'apparition de ce phénomène, également chez les fumeurs, et le manque de données dans l'ARDS pré-clinique, nous empêchent de la considérer comme un prédicteur séparé de l'ARDS. Nous concluons que dans l'ARDS l'augmentation importante de la PAEP reflète une atteinte plus sévère de la membrane alvéolo-capillaire que dans l'oedème pulmonaire interstitiel ou chez les fumeurs de cigarette. Si une intervention thérapeutique effective est découverte, la mesure de la PAEP pourrait être un instrument salvateur dans les six premiers jours de cette maladie fatale, c'est-à-dire au moment où sa mortalité est à son niveau le plus bas.
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