

Role of bronchoalveolar lavage in the diagnosis of fat embolism syndrome

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Role of bronchoalveolar lavage in the diagnosis of fat embolism syndrome. N. Roger, A. Xaubet, A. Agustí, E. Zabala, E. Ballester, A. Torres, C. Picado, R. Rodríguez-Roisin. ERS Journals Ltd 1995.

ABSTRACT: Fat embolism syndrome (FES) is a serious clinical disorder occurring in trauma patients. The diagnosis of fat embolism syndrome may be difficult to establish clinically. We therefore wanted to investigate the usefulness of bronchoalveolar lavage (BAL) in the diagnostic evaluation of fat embolism syndrome.

We analysed the presence of fat droplets in BAL cells in 32 trauma patients (7 with full diagnostic criteria of fat embolism syndrome, 17 with incomplete diagnostic criteria, and 8 with no diagnostic criteria at the time of bronchoscopy), 9 nontrauma patients with acute respiratory failure and radiographic pulmonary infiltrates, and a control group composed of 10 individuals.

An increased percentage of oil red O positive alveolar macrophages (cut-off point >3%) in BAL was found in 6 out of 7 patients with definite clinical criteria of fat embolism syndrome, and in 6 out of 20 trauma patients without the clinical diagnosis of fat embolism syndrome. In two patients with fat embolism syndrome, sequential BAL showed that the percentage of positive macrophages decreased when the clinical manifestations disappeared. An increased number of BAL macrophages with fat droplets was also observed in two trauma patients without evidence of fat embolism syndrome after long-bone surgical intervention. By contrast, all nontrauma patients had a percentage of positive cells lower than 3%.

Our findings suggest that BAL oil red O positive macrophages are frequently observed in trauma patients irrespective of the presence of fat embolism syndrome. Conceivably, a high number of oil red O positive macrophages could reflect clinically silent fat embolization.

Eur Respir J., 1995, 8, 1275–1280.

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Keywords: Acute respiratory failure
bronchoalveolar lavage
mechanical ventilation
oil red O stain
trauma

Received: November 15 1994
Accepted after revision April 13 1995

Supported by a grant from SEPAR-Medical Europa 1992.

Fat embolism syndrome (FES) is a serious clinical disorder occurring in trauma patients, mainly in those with long-bone fractures. The diagnosis of FES is clinically established on the basis of the presence of acute respiratory failure with radiographic pulmonary infiltrates, neurological dysfunction and petechial rash occurring soon after long-bone fractures [1]. However, in some cases, the diagnosis of FES remains uncertain due to the absence of one or more of these criteria. In trauma patients, radiographic pulmonary infiltrates and respiratory failure can have different aetiologies, such as pulmonary infection, pulmonary contusion and aspiration pneumonia. In addition, neurological symptoms are often difficult to evaluate in sedated patients, and may be secondary to concomitant cerebral contusion. Furthermore, the characteristic petechial rash may be absent or its appearance delayed [1]. Several laboratory tests, such as the detection of fat globules in urine and in blood, or the measurement of serum lipase activity, have poor sensitivity and specificity [2–4]. Preliminary results concerning the diagnostic value of the presence of fat droplets

in pulmonary capillary blood obtained from a wedged pulmonary catheter have been reported [5, 6]; however, the specificity and the sensitivity of this invasive technique, which is not always available, has not been established. Therefore, the development of a test which enables the accurate diagnosis of this syndrome could be of clinical interest.

CHASTRE *et al.* [7] suggested that the identification of fat droplets in cells recovered by bronchoalveolar lavage (BAL) may be both a sensitive and specific tool to establish the diagnosis of FES in trauma patients. However, their findings were not confirmed by VEDRINNE *et al.* [8], who reported that, apart from FES, other clinical conditions, such as multiple organ failure, sepsis or hypertriglyceridaemia, can be associated with the presence of fat droplets in BAL cells. Thus, based on these findings, the usefulness of BAL in the diagnosis of FES has not been clearly determined.

The present study was thus undertaken to assess the role of BAL in the diagnostic evaluation of FES in trauma patients with and without clinical criteria of the syndrome.

Materials and methods

Study population

The 51 patients studied were divided into 5 groups, characteristics are shown in table 1.

Trauma group. Composed of 32 patients with long-bone and/or pelvis fractures. The trauma group was further classified into three subgroups.

Group 1A - definite FES. This subgroup was composed of seven patients with definite fat embolism syndrome. Patients were included in this group when radiological pulmonary infiltrates and/or acute respiratory failure (defined by an arterial oxygen tension (P_{a,O_2})/fractional inspiratory oxygen (F_{I,O_2}) ratio <36.7 kPa (<275 mmHg)) and at least one of the other two major diagnostic criteria described by GURD [9] were observed: 1) appearance of a petechial rash; and 2) neurological symptoms unrelated to head injury or other conditions. In patients with either thoracic or head trauma, the presence of petechial rash was required to establish the diagnosis of FES. According to the score (range 1–13) proposed by SCHONFELD *et al.* [4], the fracture index for these patients was 5.9 ± 2 (range 3–8) and all patients required mechanical ventilation. Five patients had respiratory failure. There were pulmonary infiltrates in all the patients (bilateral in four and unilateral in three), five had neurological symptoms, and six petechial rash. Five patients had associated head or thoracic injuries but all of them developed petechial rash. None of the patients had any evidence of other pulmonary disorders.

Group 1B - incomplete diagnostic criteria for FES. This subgroup was composed of 17 patients with incomplete criteria of FES. These patients fulfilled one of the three major criteria of GURD [9], and FES was suspected, but not confirmed or excluded, when BAL was performed. All but one patient required mechanical ventilation. Four patients with head injury had a petechial rash in the absence of pulmonary manifestations. Thirteen patients had pulmonary infiltrates (10 bilateral) and 10 had acute respiratory failure.

Group 1C - no evidence of FES. This subgroup was composed of eight trauma patients without any criteria of FES. All of them needed mechanical ventilation due to severe head injury. The diagnosis of FES was excluded according to the fat embolism score described by SCHONFELD *et al.* [4]. If the score remains below 5 in the first 3 days of hospitalization, the diagnosis of FES can probably be excluded. In all patients from this group the fat embolism score was lower than 5.

Nontrauma patients with lung infiltrates. Nine patients with lung infiltrates were included in this group. All of them required mechanical ventilation when BAL was performed. The aetiology of acute respiratory failure was pneumonia [5], adult respiratory distress syndrome [3] and neurogenic pulmonary oedema [1]. In all the groups, patients with clinical evidence of pulmonary aspiration were excluded from the study.

Control group. This group was composed of 10 subjects with no evidence of diffuse respiratory disease. Fibreoptic bronchoscopy was performed in view of a single episode of haemoptysis with normal chest radiograph, isolated pulmonary node, suspicion of upper airway disease or extrathoracic metastatic lesions, with no additional clinical or radiographic evidence of lung disease. In all patients, bronchoscopy was macroscopically normal.

All patients or their next-of-kin were informed of the characteristics and nature of the study and all gave written informed consent. The study was approved by the Ethics Committee of the Hospital Clinic.

Methods

Bronchoalveolar lavage was performed with 150 mL of sterile saline solution as described previously [10, 11]. The lavage was performed in the middle lobe or in the lingula in patients with diffuse radiological infiltrates or with a normal chest radiograph, or in the appropriate lobe when the radiographic abnormality was localized. Total cell counts were obtained using a Neubauer's

Table 1. – Clinical details of the 5 groups

	Group 1A (n=7)	1B (n=17)	1C (n=8)	Non-Trauma (n=9)	Control (n=10)
M/F	7/0	15/2	7/1	5/4	9/1
Age yr	30 ± 15	37 ± 16	31 ± 12	53 ± 14	63 ± 15
$P_{a,O_2}/F_{I,O_2}$ kPa	37 ± 11.7 (21.3–57.3)	39.3 ± 22.9 (17.3–64)	50.7 ± 13.7 (36.7–74.7)	30.7 ± 16.4 (12.8–63.3)	-
Fracture Index	5.9 ± 2 (3–8)	4 ± 2 (2–19)	4.7 ± 1.5 (2–7)	-	-
FE appearance h	75 ± 75 (11–192)	62 ± 63 (6–240)	-	-	-
BAL elapse time h	32 ± 18 (6–60)	40 ± 25 (12–96)	81 ± 21 (24–144)	-	-

Results are mean \pm SD, ranges in brackets. FE: fat embolism, time elapsed from trauma to clinical/radiological appearance. BAL: bronchoalveolar lavage, time elapsed from onset of FE symptoms. M: male; F: female.

camera, and the cell viability was assessed by trypan blue dye exclusion. Differential cell counts were determined in cytocentrifuge smears stained with May-Grünwald Giemsa (Cytospin 2, Shandon). To determine the presence of fat droplets in alveolar macrophages, BAL cytocentrifuge preparations were stained with oil red O. Four hundred macrophages were examined in a light microscope at a magnification of $\times 1,000$, and the percentage of cells with intracellular red-stained droplets was calculated.

Statistical analysis

Results are expressed as mean \pm SD. Bronchoalveolar lavage characteristics among the five groups were analysed by analysis of variance. Sheffe's contrast test was used to examine pairs of means when the analysis of variance was significant. Significance in all data analysis was considered to be a p-value of less than 0.05.

Results

BAL cell analysis

There were no differences in BAL fluid recovery among the different groups (table 2). Total cell counts showed

a trend to be higher in patients with definite FES compared to the other groups. However, whilst there was a greater percentage of neutrophils in all but the control group ($p < 0.01$), no differences were shown between trauma and nontrauma patients.

Identification of fat droplets in BAL cells

Group 1A - trauma patients with definite FES. Patients with definite FES (table 3) had a higher mean percentage of oil red O positive macrophages ($40 \pm 24\%$) (fig. 1) compared to the other groups ($p < 0.001$). Based on the data obtained in the control group, a cut-off point equal to or below 3% of alveolar macrophages containing fat droplets was used to define a negative BAL for FES. Six out of the seven patients with definite FES had an increased percentage of positive oil red O macrophages ($> 3\%$) ($47 \pm 18\%$, range 25–75%) (patients Nos. 1–6). In the remaining case (patient No. 7), the diagnosis of FES was established according to the presence of neurological dysfunction along with petechial rash and pulmonary infiltrates. Five patients showed a favourable outcome, but two died due to head injury and acute respiratory failure (patients Nos. 4 and 6, respectively).

Group 1B - trauma patients with incomplete diagnostic criteria of FES. The final clinical diagnoses in this

Table 2. – Bronchoalveolar lavage characteristics of the study population

Group	Volume recovered mL	Total cells $\times 10^4 \cdot \text{mL}^{-1}$	Cell Viability %	Macrophages %	Lymphocytes %	Neutrophils %	Eosinophils %
FES (1A)	61 \pm 14 (42–74)	232 \pm 133 (57–393)	83 \pm 11 (65–93)	66 \pm 24 (33–93)	10 \pm 11 (2–34)	23 \pm 25 (5–61)	0.6 \pm 0.8 (0–2)
Incomplete criteria of FES (1B)	40 \pm 12 (22–56)	187 \pm 250 (12–1000)	87 \pm 8 (70–98)	62 \pm 27 (8–100)	3 \pm 3 (0–10)	34 \pm 28 (0–92)	0.5 \pm 1 (0–6)
No criteria of FES (1C)	38 \pm 14 (14–51)	39 \pm 37 (0–11)	77 \pm 31 (0–98)	57 \pm 33 (3–98)	4 \pm 3 (0–10)	37 \pm 34 (1–97)	0.3 \pm 0.7 (0–2)
Non trauma (lung filtrates)	49 \pm 27 (29–108)	88 \pm 120 (6–385)	76 \pm 9 (61–93)	47 \pm 37 (9–92)	7 \pm 7 (0–24)	45 \pm 35 (0–85)	0.5 \pm 0.8 (0–2)
Control	55 \pm 9 (44–68)	96 \pm 142 (3–450)	87 \pm 15 (50–99)	94 \pm 3* (86–98)	4 \pm 4 (1–13)	0.5 \pm 0.9* (0–3)	0.2 \pm 0.4 (0–1)

Values are presented as mean \pm SD, and range in parenthesis. FES: fat embolism syndrome. *: $p < 0.01$ with respect to other groups.

Table 3. – Characteristics and outcome of trauma patients with definite FES (1A)

Case No.	Injuries	Neurological symptoms	Petechiae	Chest radiograph	$P_{a,O_2}/F_{I,O_2}$ kPa mmHg	Oil red O %	Outcome
1	H,T,A	Coma	Yes	BAI	33.6 252	75	S
2	A	Coma	Not	RAI	21.3 160	54	S
3	H,T	Not	Yes	BAI	30.3 227	52	S
4	H,T	Coma	Yes	BAI	35.6 267	46	D
5	H,T,A	Not	Yes	BAI	34.4 258	29	S
6	H,T,A	Coma	Yes	RAI	57.3 430	25	D
7	Not	Convulsion	Yes	RAI	47.3 355	0	S

FES: fat embolism syndrome; P_{a,O_2} : arterial oxygen tension; F_{I,O_2} : fractional inspiratory oxygen; H: head; T: thoracic; A: abdominal; BAI: bilateral lung alveolar infiltrates; RAI: right lung alveolar infiltrates; S: survived; D: died.

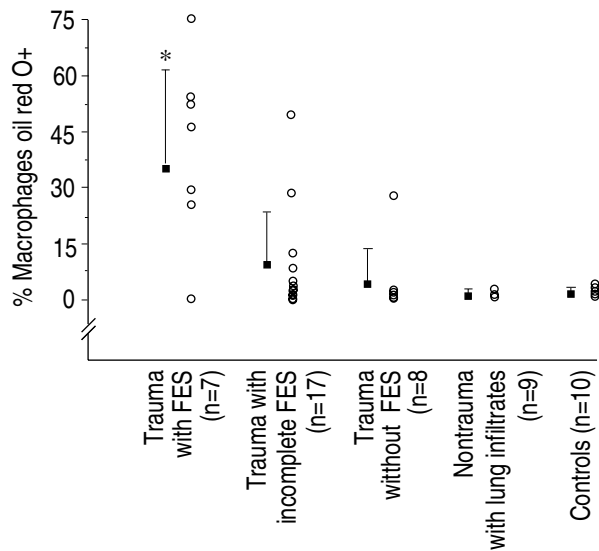


Fig. 1. — Individual (O) and mean \pm SD (■) of macrophages oil red O positive in bronchoalveolar lavage of the different groups. FES: fat embolism syndrome. *: $p < 0.001$, with respect to the other groups.

subgroup (table 4) were as follows: pneumonia (4) (clinical and radiographic criteria as well as a positive bacterial culture from a telescoping plugged catheter); pulmonary contusion (3); adult respiratory distress syndrome (ARDS) (3) (massive blood transfusion (2) and abdominal injury (1)); and heart failure (2) (confirmed by right-sided heart catheterization). The presence of FES was suspected by the appearance of a petechial rash in four patients (patients Nos. 9, 10, 12 and 17). However, it was not possible to establish a full diagnosis of FES, since the patients did not have radiological pulmonary infiltrates or acute respiratory failure. In one patient, the aetiology of pulmonary infiltrates could not be established (patient No. 1). In this subgroup, the main percentage of oil red O positive macrophages was $7 \pm 13\%$

(fig. 1). Five of the 12 (41%) patients of this subgroup without the clinical diagnosis of FES had more than 3% of BAL positive cells (patients Nos. 2–6).

Group 1-C - Trauma patients without evidence of FES. In this subgroup, composed of eight trauma patients, the percentage of macrophages containing fat droplets was $3 \pm 9\%$ (range 0–27%) (fig. 1). Only one subject had more than 3% of positive macrophages in BAL (27%), having a favourable outcome with no manifestations of FES.

Thus, BAL showed an increased number of oil red O positive macrophages in 6 out of 20 (30%) trauma patients without the clinical diagnosis of FES (five from Group 1-B, and one from Group 1-C).

Non-trauma patients and control group. No differences in the mean percentage of oil red O positive macrophages were shown between nontrauma patients with acute respiratory failure and the control group ($0.5 \pm 0.9\%$ and $0.8 \pm 1\%$, respectively) (fig. 1).

Sequential BAL

Sequential BAL was carried out in two trauma patients with full diagnosis of FES (patients Nos. 3 and 5, table 3) who had an increased number of oil red O positive alveolar macrophages in BAL. Lavage was repeated at 9 and 14 days, when the clinical findings and radiographic infiltrates had considerably improved. The percentage of oil red O positive macrophages decreased from 52 and 29%, to 24 and 0%, respectively. Furthermore, in two other subjects (patients Nos. 1 and 14, table 5) a second BAL performed 48 h after femur surgery showing a marked increase in the percentage of oil red O positive macrophages (3 to 40% and 0 to 10%, respectively) but without clinical or radiographic data suggestive of FES.

Table 4. — Characteristics and outcome of trauma patients with incomplete FES

Case No.	Injuries	Neurological Symptoms	Petechiae	Chest radiograph	$P_{a,O_2}/F_{I,O_2}$ kPa mmHg	Oil red O %	Clinical diagnosis	Outcome
1	H,T	Coma	Not	BAI	61.7 463	49	Unknown	S
2	H,T	Coma	Not	BAI	35.1 263	28	Pneumonia	S
3	H,T,A	Coma	Not	BAI	17.3 130	12	Pneumonia	S
4	H,T,A	Not	Not	BAI	31.3 235	12	Lung contusion	S
5	H,T,A	Not	Not	BAI	32.4 243	8	Cardiac failure	D
6	T,A	Not	Not	BAI	32.3 242	4	ARDS	S
7	H,T,A	Coma	Not	BAI	40.9 307	3	ARDS	S
8	T	Confusion	Not	BAI	39.3 295	2	Cardiac failure	D
9	H	Confusion	Yes	Normal	64.0 480	1	Unknown	D
10	H	Coma	Yes	Normal	46.8 351	1	Unknown	S
11	T,A	Not	Not	RAI	28.8 216	1	Lung contusion	S
12	H	Confusion	Yes	Normal	45.3 340	0	Unknown	S
13	H,T,A	Coma	Not	BAI	32.4 243	0	ARDS	S
14	T	Not	Not	LAI	20.7 155	0	Lung contusion	D
15	H,T,A	Not	Not	LAI	17.3 130	0	Pneumonia	S
16	H,T,A	Coma	Not	BAI	17.6 132	0	Pneumonia	S
17	A	Confusion	Yes	Normal	60.3 452	0	Unknown	S

LAI: left alveolar infiltrates; ARDS: adult respiratory distress syndrome. For further abbreviations see legend to table 3.

Discussion

Our study shows that in patients with full clinical diagnosis of FES, the percentage of oil red O positive macrophages was increased in six cases, whereas BAL was negative in one. In contrast, BAL showed an increased number of macrophages containing fat droplets in 6 out of 20 trauma patients without the clinical diagnosis of FES (five from Group 1-B, and one from group 1-C). It is widely accepted that some degree of pulmonary fat embolization occurs in almost all patients with long-bone fractures, but only 6–10% clinically develop the full syndrome [12, 13]. Although in a recent study, PELL *et al.* [14] indicated that the amount of fat in the lung may determine the degree of pulmonary manifestations, the correlation between the presence of pulmonary intravascular fat and pulmonary manifestations in postmortem lung studies is poor [15]. It has been suggested that FES would occur only when the fat present in the lungs directly affects the pneumocytes, hence producing pulmonary manifestations [16]. It has been shown that pulmonary fat embolism is unrecognized in many cases because symptoms are mild or absent and chest roentgenogram can be normal [12]. Thus, the presence of oil red O positive macrophages by itself in BAL of trauma patients can be due to clinically silent fat embolism. However, in the five patients of group 1-B (incomplete diagnostic criteria for FES) with pulmonary infiltrates due to aetiologies other than FES and an increased number of BAL oil red O positive cells, it is not clinically possible to exclude a mild form of FES in spite of the presence of associated pulmonary disorders.

Our results are in agreement with those of VEDRINNE *et al.* [8] who found high numbers of BAL oil red O positive macrophages in 41% of 22 trauma patients without full clinical evidence of FES. By contrast, CHASTRE *et al.* [7] showed that all patients with FES had a high percentage of oil red O positive lavage cells, whereas trauma patients without the syndrome had a normal lavage. They concluded that BAL could be a specific and sensitive tool for the diagnostic evaluation of FES. VEDRINNE *et al.* [8] suggested that the presence of oil red O positive macrophages may also be explained by parenteral nutrition, multiple organ failure, sepsis or hypertriglyceridaemia. High percentages of oil red O positive macrophages can also be found in patients with aspiration of gastric contents [17], a common condition in trauma patients [18]. Although patients with clinical evidence of pulmonary aspiration were excluded from our study, it has been shown that subclinical aspiration can be a common event in intubated patients [19]. However, we failed to find an increased percentage of oil red O positive macrophages in nontrauma patients with severe respiratory failure and all of them were intubated and under mechanical ventilation. Thus, our results agree with those of CHASTRE *et al.* [7], in which BAL oil red O positive cells are not present in nontrauma patients with acute respiratory failure.

In two patients with FES, sequential BAL showed that the percentage of positive macrophages decreased

substantially when the clinical and pulmonary manifestations had disappeared. Furthermore, we found an increased number of BAL macrophages with fat droplets in two trauma patients without evidence of FES, after long-bone surgical intervention. These findings therefore confirm that the presence of high numbers of oil red O positive macrophages in BAL could be indicative of pulmonary fat embolization.

Bronchoalveolar lavage differential cell counts showed an increased percentage of neutrophils in all groups of patients, including those with no diagnostic criteria of FES and normal chest radiograph. In addition to FES [7], an increased percentage of neutrophils in BAL fluid can be found in patients with pulmonary infections or with adult respiratory distress syndrome. The presence of neutrophils in BAL fluid in patients with no pulmonary disease can be due, at least in part, to mechanical ventilation [20]. Except for the controls, all but one patient included in our study needed mechanical ventilation.

In summary, this study shows that BAL oil red O positive macrophages are frequently observed in trauma patients. Although it may be indicative of FES, high numbers of oil red O positive macrophages can also be found in patients without clinical evidence of the syndrome and could, therefore, be related to clinically silent fat embolization. Conversely, BAL cells with fat droplets are not present in nontrauma patients.

Acknowledgements: The authors are indebted to M. Carrión and M.T. Solé for their technical expertise.

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