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Lung function changes following Legionnaires' disease

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ABSTRACT: Eleven out of thirteen patients hospitalized because of severe pneumonia caused by *Legionella Pneumophila* were evaluated over a period of 53 months. During the acute phase, all but one patient manifested severe hypoxaemia, needing either supplementary oxygen or, in the case of three, mechanical ventilation and one died. Following recovery, two patients complained of mild shortness of breath alone. However, most of the individuals showed subclinical mild to moderate ventilatory and/or gas exchange abnormalities a few months after discharge (<6 months). Despite the fact that some of these functional findings in part persisted at long-term (6–33 months), a significant overall improvement in lung function was noticed. The main pulmonary functional sequelae following Legionnaires' Disease might include a restrictive ventilatory defect, a low transfer factor and hypoxaemia.

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Legionella Pneumophila causes a pneumonic form of infection, called Legionnaires' Disease (LD) [5]. It has been reported that up to 15% of the cases of community-acquired pneumonia requiring hospitalization are secondary to Legionella Pneumophila [12, 13]. Until recently, few studies have been carried out in order to evaluate the respiratory clinical, radiographic [6] and functional condition during and after the acute phase of LD [1, 9, 11, 17]. In an attempt to document such data, thirteen patients suffering from LD admitted to our hospital over a period of 53 months were studied early and late stages after LD. A better understanding of the outcome of LD may be helpful in the knowledge of the lung function sequelae which can occur following the resolution of pneumonia.

Methods

The records of thirteen male patients, aged ($X \pm SD$) 41 ± 15 yr, admitted to our hospital from July, 1981 to December, 1985 were included. The diagnosis of LD was based either on a fourfold increase in serogroup I of *Legionella Pneumophila* antibodies (microagglutination) or in *Legionella* growth in specific culture medium in patients with pneumonia. The main clinical and radiographic findings are summarized in table I. Patients were hospitalized over a period of 19 ± 6 days. All but one patient (No. 13) survived. Pulmonary function tests were carried out in eleven patients (No. 12 refused to collaborate). In eight cases (No. 2 and Nos 5–11), pulmonary function tests were performed a few months after discharge (less than 6 months: early follow-up) and were evaluated again between 6 and 33 months following the recovery from LD in all but one patient (No. 2). In addition, in three others (Nos 1, 3 and 4), pulmonary function was only determined after 9, 32 and 29 months of discharge (late follow-up), respectively.

Arterial blood gases were measured using an IL-1023. The alveolar-arterial O_2 difference (A_aDO_2) was calculated according to the simplified form of the alveolar gas equation ($P_{AO_2} = P_{IO_2} - P_{aCO_2}/R$) (where P_{AO_2} is alveolar oxygen partial pressure; P_{IO_2} is pressure of inspired oxygen and P_{aCO_2} is arterial carbon dioxide tension), assuming an exchange respiratory ratio (R) of 0.8. Forced spirometry with bronchodilator response (tested after 15 minutes of two puffs (200 μg) of inhaled salbutamol) and slow spirometry were measured according to the European Community Coal and Steel (ECCS) recommendations [14] using an HP 47804 System. Both thoracic gas volume (functional residual capacity) and airway resistance were determined using a constant volume plethysmograph (Body test, E. Jaeger). The single-breath CO transfer factor (DLCO) was measured with a Respirometer Morgan PK 4. Except for specific airway conductance (sGaw) (normal values, equal or higher than 0.13 $s^{-1} \cdot cmH_2O^{-1}$) [3], predicted values were obtained from our own laboratory [15, 16]. Ventilatory and gas exchange abnormalities were defined as follows: obstructive ventilatory pattern (ratio of forced expiratory volume to forced vital capacity (FEV_1/FVC)% <70% and sGaw $< 0.13\ s^{-1} \cdot cmH_2O^{-1}$); restrictive ventilatory pattern (FVC and total lung capacity (TLC) <80% predicted and $FEV_1/FVC\% \geq 70\%$); mixed ventilatory pattern (similar abnormal percentages, but without previous criteria for obstructive or restrictive pattern); and, gas exchange impairment (arterial oxygen tension (Pa_{O_2})

Table I. - Main clinical and radiographic findings during the acute episode

Case No.	Age	Smoking data pks/yr	Associated respiratory conditions	Fever	Dyspnoea	Cough	Thoracic pain	ARF	Pulmonary radiographic involvement
1	29	Ex-Sm (15)	–	+	+	+	+	NA	RLL, PE
2	66	51	–	+	+	–	–	+	RLL
3	65	0	–	+	+	+	–	+	Bil
4	44	25	CB	+	+	+	–	+	RLL
5	31	20	–	+	+	+	+	+	DLL, PE
6	40	Ex-Sm (15)	CB	+	+	+	–	+	LLE, PE
7	28	Ex-Sm (8)	–	+	+	+	+	+	Bil
8	40	15	–	+	+	–	+	+	Bil
9*	39	20	–	+	+	+	–	+	Bil, PE
10	28	8	–	+	+	+	+	+	DLL
11	64	70	CB	+	+	+	–	+	LLL
12*	36	8	–	+	+	–	–	+	DLL
13*	24	0	–	+	+	+	–	+	Bil

+: present; –: absent; CB chronic bronchitis; ARF acute respiratory failure (Pa_{O_2}<8 kPa (60 torr) while breathing room air); RLL right lower lobe; Bil bilateral involvement; DLL diffuse left lung; LLL left lower lobe; LUL left upper lobe; PE pleural effusion; NA Pa_{O_2} not available on admission; *: under mechanical ventilation.

<10.7 kPa), $A_aD_{O_2}$ >2.7 kPa, and/or DLCO <80% predicted.

Wilcoxon's tests were used to test differences between separated measurements when appropriate.

Results

Assessment during the acute phase (fig. 1)

Measurements in this period included arterial blood gases in all but one patient (No. 1). On admission, arterial P_{O_2} was reduced while $A_aD_{O_2}$ was increased. Nine patients had respiratory failure (Pa_{O_2} <8 kPa) and two others (Nos 5 and 11) rapidly progressed into this condition after a few hours. Patient No. 12 was admitted on mechanical ventilation. Twelve patients needed supplementary oxygen and three of them (Nos 9, 12 and 13) mechanical support. There was progressive gas exchange improvement throughout hospitalization, which paralleled the clinical and radiographic recovery. Yet, on discharge, patients showed mild hypoxaemia and widened $A_aD_{O_2}$.

Early follow-up (less than 6 months) (table II)

Mid-term assessment was available in eight of the twelve survivors (Nos 2 and 5–11). Chest X-ray films were normal in all the patients. Only two subjects (Nos 5 and 9) complained of moderate dyspnoea on exertion alone. Only patient No. 2 exhibited an $A_aD_{O_2}$ slightly elevated and patient No. 6, a normal forced spirometry. Three patients (Nos 5, 8 and 10) exhibited ventilatory defects together with gas exchange impairment. Patient No. 5, with a minimal pleural effusion, showed a mild restrictive ventilatory impairment along with a low DLCO, patient No. 8 a mixed ventilatory defect, and patient No. 10 a mild obstructive ventilatory pattern. Hypoxaemia was present in the latter two. Three other patients (Nos 7, 9 and 11), one of whom had chronic bronchitis, had only gas exchange impairment. No significant positive bronchodilator response was elicited in these patients. Overall, arterial blood gases did not show a significant improvement in comparison with measurements made on discharge.

Table II. - Early (less than 6 months) and late (8–33 months) individual pulmonary function tests in 11 patients with Legionnaires' disease.

Patients No.	Months	FVC *l*	FEV_1/FVC %	FEF_{25-75}% $l \cdot s^{-1}$	TLC *l*	RV *l*	FRC *l*	RV/TLC %	sGaw $s^{-1} \cdot cmH_2O^{-1}$	DLco $ml \cdot min^{-1} \cdot mmHg^{-1}$	Kco $min^{-1} \cdot mmHg^{-1}$	PaO_2 kPa	$AaDO_2$ kPa
1	9	3.9(95)	81	3.0(82)	5.2(94)	1.0(59)	2.7(94)	18	0.21	28.2(97)	5.6(95)	10.9	2.3
2	4	3.7(90)	77	2.4(99)	7.1(101)	3.3(119)	3.9(115)	46	0.26	29.2(118)	6.0(119)	10.7	2.8
3	32	5.1(129)	66	1.5(65)	6.5(95)	1.3(45)	4.0(103)	19	0.23	24.1(102)	3.6(76)	9.3	5.9
4	29	4.3(86)	63	1.8(49)	7.2(95)	2.7(109)	4.1(113)	38	0.08	30.1(96)	5.0(91)	9.7	4.7
5	3	3.0(65)	79	2.6(61)	5.4(75)	1.9(89)	3.0(88)	35	0.16	28.7(74)	6.1(109)	ND	ND
	8	3.5(69)	83	3.2(76)	5.6(77)	2.0(91)	3.1(90)	34	0.17	31.3(92)	7.2(120)	ND	ND
6	1	4.4(93)	70	2.2(60)	ND	ND	ND	ND	ND	ND	ND	ND	ND
	29	5.8(123)	62	2.3(65)	9.6(141)	3.8(170)	5.3(163)	40	0.10	27.2(90)	4.1(71)	10.4	2.8
7	2	4.4(94)	77	3.0(74)	ND	ND	ND	ND	ND	24.5(76)	4.5(73)	ND	ND
	33	4.8(103)	77	3.2(79)	6.2(98)	1.3(74)	3.8(128)	22	0.20	34.7(110)	5.9(98)	10.5	3.7
8	1	3.0(71)	76	2.5(72)	5.4(89)	1.9(101)	3.1(135)	36	0.15	22.3(78)	5.0(80)	9.3	4.0
	8	3.4(80)	74	2.1(64)	6.1(101)	2.6(137)	3.1(135)	43	0.16	32.4(115)	6.7(102)	9.3	3.9
9	1	4.4(84)	77	3.5(85)	7.0(93)	2.6(104)	3.3(86)	36	0.17	22.9(68)	3.9(71)	11.6	2.3
	8	4.8(92)	74	2.9(72)	7.6(100)	2.8(112)	3.9(102)	36	0.13	30.8(92)	5.0(91)	12.8	0.8
10	1	4.4(87)	61	1.4(32)	7.1(105)	2.4(129)	3.5(112)	34	0.06	34.3(102)	6.1(101)	10.3	3.7
	8	4.7(94)	59	1.4(32)	7.8(116)	3.0(163)	3.8(122)	38	0.07	34.3(102)	6.2(102)	10.7	2.7
11	2	3.1(87)	81	2.5(73)	4.4(92)	1.2(91)	2.2(92)	27	0.18	17.8(76)	4.2(73)	13.1	0.9
	8	3.2(90)	79	2.5(72)	4.6(96)	1.4(107)	2.2(92)	30	0.14	22.3(93)	6.2(107)	12.7	1.7

Data are expressed as actual and percent of predicted values (between brackets), except for FEV_1/FVC % and RV/TLC % ratios, and PaO_2 and $AaDO_2$ (actual values) ND not done. FEV_1 forced expiratory volume in one second; FVC, forced vital capacity; FEF 25–75%, forced expiratory flow between 25–75% of FVC; TLC total lung capacity; RV residual volume; FRC, functional residual capacity; sGaw, airway conductance; DLco, Carbon monoxide transfer factor; Kco, transfer coefficient, Normal values for PaO_2 10.7-13.3 kPa; $AaDO_2$ equal or less than 2.7 kPa.

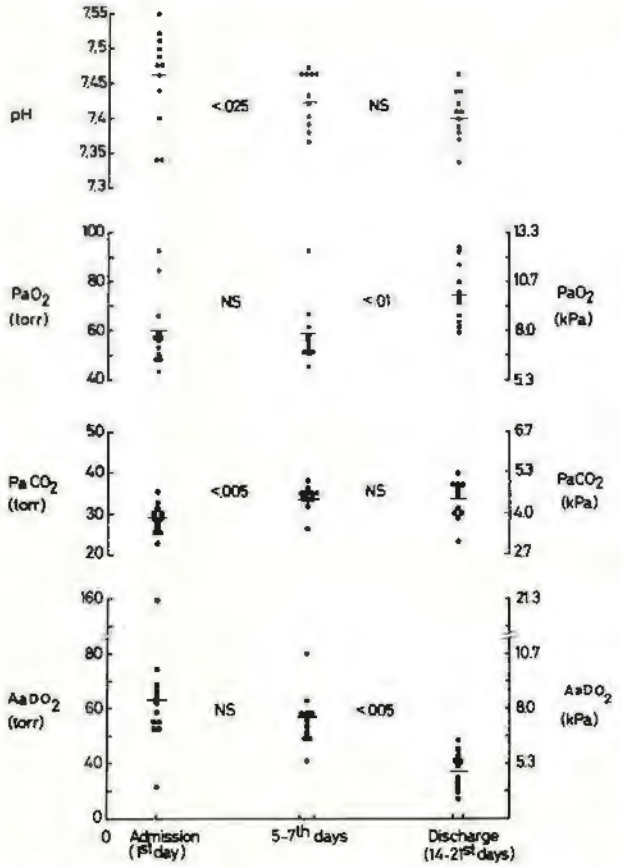

Fig. 1. Arterial blood gases in patients with Legionnaires Disease during hospitalization. While mean pH and Pa_{CO_2} returned to normal values during the first week, mean Pa_{O_2} and $A_aD_{O_2}$ improvement was more evident between the 7th and the 14th day (bars represent mean values).

Late follow-up (between 6 and 33 months) (table II)

Among the ten patients in the long-term assessment, only one (No. 11) gave up smoking tobacco. Nos 5 and 9 still complained of moderate dyspnoea on exertion. Seven individuals (Nos 5–11) had been evaluated a few months after recovery from LD. Two of them (Nos 9 and 11) showed normal pulmonary function with DLCO increased up to normal values. Even though, patient No. 7 (with a reduced ratio of residual volume to total lung capacity (RV/TLC%) and patient No. 8 (with air trapping) normalized their DLCO, both had mild hypoxaemia. Three subjects showed a ventilatory defect. Patients No. 5 and 10 remained with the same ventilatory impairment formerly seen, but DLCO and blood gases were within normal range. The third patient (No. 6), a chronic bronchitic with normal spirometric values in the previous evaluation, disclosed a mild obstructive ventilatory pattern, probably as a consequence of the increase in FVC, with mild gas exchange impairment.

Among the three individuals (Nos 1, 3 and 4) with a single long-term evaluation, patient No. 1 had a low RV/TLC% ratio alone. In contrast, the other two patients had an obstructive ventilatory defect (No. 4 had chronic bronchitis) associated with hypoxaemia. Patient No. 3 also showed a reduced RV and a low RV/TLC% ratio. No positive bronchodilator response was shown in these three subjects either.

In summary, analysis of the individual pulmonary function data found at the end of the study was as follows: three patients (Nos 2, 9 and 11) had normal lung function tests; one (No. 1), a reduced RV/TLC% ratio alone; one (No. 5), a mild restrictive defect alone; one (No. 10), a moderate obstructive defect alone; one (No. 7), a low RV/TLC% ratio with mild hypoxaemia; one (No. 8), air trapping with mild hypoxaemia; and the three remaining (Nos 3, 4 and 6) an obstructive ventilatory pattern with slight hypoxaemia. Among the latter three patients, there was one non-smoker and two heavy smokers with chronic bronchitis. Despite the existence of these mild individual ventilatory and/or gas exchange abnormalities more than half a year after discharge, there was on the whole a significant improvement in pulmonary function tests in comparison with data from mid-term follow-up (table III). However, arterial blood gases significantly improved when compared with values determined on discharge. No correlation was found between the severity of hypoxaemia during the acute phase and pulmonary function sequelae.

Discussion

Our study documents the outcome of both mid-term and long-term lung function disturbances following LD. During the early follow-up most of the patients showed subclinical functional abnormalities, mainly characterized by a mild to moderate impairment in gas exchange and various abnormal ventilatory patterns. At the end of the follow-up, however, DLCO and carbon monoxide transfer coefficient (KCO) values returned toward normal in all but one patient and only five individuals had slight hypoxaemia. In addition, seven patients showed several mild to moderate ventilatory defects but, only two complained of shortness of breath on exertion. The most interesting finding, however, was the overall improvement in static and dynamic lung volumes, without accompanying changes in $FEV_1/FVC\%$ ratio, and in DLCO, KCO, Pa_{O_2} and $A_aD_{O_2}$. These data therefore suggest that LD may be responsible for reduction in lung volume along with gas exchange impairment. No bronchial hyperreactivity, at least measured using a conventional bronchodilator test, was shown in these patients.

Despite the absence of pulmonary function tests before the acute episode of LD, the presence of smoking habits in the majority of the patients and chronic bronchitis in some of them, several characteristics suggesting that these functional abnormalities are likely to be related to the episode of LD should be pointed out. Firstly, most of the patients did not show previous signs and/or symptoms of respiratory disease. Secondly, smoking data were present in all but one patient and it is of interest that those with the heaviest smoking history showed normal pulmonary function values at the end of the follow-up. Thirdly,

Table III. - Pulmonary function tests, mean± SD values at early and late follow-up

	FVC *l*	FEV_1 *l*	FEV_1/FVC, %	TLC *l*	RV *l*	RV/TLC, %	D_{LCO} $ml \cdot min^{-1} \cdot mmHg^{-1}$	K_{CO} $min^{-1} \cdot mmHg^{-1}$	Pa_{O_2} kPa	$A-aD_{O_2}$ kPa
Early	3.8±0.7(83±11)	2.8±0.5(78±11)	74±7	5.9±1.2(91±11)	2.0±0.5(103±16)	86±7	25.1±6(79±12)	5.0±0.9(84.5±16)	11.1±0.7	2.7±1.5
	*	*	NS	*	*	*	*	*	NS	NS
Late	4.3±1.0(93±17)	3.1±0.5(84±13)	73±9	6.3±1.3(98±14)	2.3±0.7(122±28)	77±4	31.0±5(100±10)	6.2±0.7(100.3±10)	11.3±1.6	2.3±1.3
n	7	7	7	5	5	5	6	6	4	4

Data are expressed as actual and percent of predicted values (between brackets), except for FEV_1/FVC, % and RV/TLC, % ratios, and Pa_{O_2} and $A-aD_{O_2}$ (actual values); n, number of patients who had both early and late pulmonary function measurements; (*), $p<0.05$; NS, non significant.

seven individuals were evaluated twice, therefore allowing for better assessment of their changes. Finally, no other major factors usually known to influence lung function tests were present. However, our comments need to be tempered because it is not possible to completely rule out pre-existing lung function abnormalities.

So far few studies have reported lung function changes following pneumonia [4]. Respiratory function abnormalities have been occasionally shown after successful antibiotic treatment in LD [1, 9, 11]. LATTIMER *et al.* [11] documented that LD may lead to persistent functional abnormalities such that, as many as 50% of survivors had a reduced DLCO two years later. Similarly, BERTOYE *et al.* [1] reported a group of eleven patients with severe LD who persisted with reduced lung volumes and low DLCO four months later. In contrast, pulmonary functional abnormalities were more reversible in our series. The question arises, however, whether these pulmonary function abnormalities are specifically related to the damage caused by Legionella or to the lung injury itself, regardless of the causative nature [10]. Both specimens from open lung biopsy and post-mortem histological studies in LD have confirmed the presence of acute interstitial disease and alveolar inflammation [19]. Neutrophils, macrophages, proteinaceous debris and extensive deposits of fibrin were present in these infiltrates, and were similar to those found in both classical pneumonia and gram-negative pneumonia [18]. In some cases, these changes can lead to permanent structural abnormalities in the form of pulmonary fibrosis [2]. Bronchii and bronchioles were variously involved by this process, with some airways obliterated or collapsed by fibrous tissue. This early fibrosis due to LD would be potentially reversible because capillary and epithelial basement membranes were often intact [8]. However, the alveolar damage may further progress to interstitial fibrosis, even with intact membranes [8], and this was probably the underlying pathological substract in the patients reported by BERTOYE *et al.* [1] and LATTIMER [11]. While the reversible changes in lung volumes, DLCO and Pa_{O_2} seen in our patients were probably linked to areas of lung fibrosis, the obstructive ventilatory defects were rather related to tobacco smoking. Nevertheless, preliminary data prospectively collected over one full year by us in 25 previously healthy patients with community-acquired bacterial pneumonia showed similar reversible lung function abnormalities to those observed in the present study, irrespective of the causative agent [7]. Hence, it is possible that the functional changes found in our series were not specifically related to *Legionella per se*. The diffuse alveolar damage caused by a nonspecific injury may play a key role in the observed lung function sequelae.

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RÉSUMÉ: De 13 patients hospitalisés pour une pneumonie à Legionella Pneumophila sévère, 11 ont été suivis pendant une période de 53 mois. A la phase aiguë tous les patients sauf un présentaient une hypoxémie sévère nécessitant soit une oxygénothérapie soit une ventilation mécanique (3 cas), et l'un d'entre eux mourut. A la phase de récupération 2 patients ne se plaignent que de légère dyspnée. Cependant dans les quelques mois après l'hospitalisation (< 6 mois) chez la plupart des individus existent des anomalies ventilatoires subcliniques et/ou des anomalies des échanges gazeux. Quoique certaines anomalies fonctionnelles persistent partiellement à long terme (6-33 mois), une amélioration progressive est manifeste. Les séquelles principales de la maladie des Légionnaires incluent un deficit ventilatoire restrictif, une capacité de transfert du CO abaissée et une hypoxémie.