

Time course of lung function changes in atypical pneumonia

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ABSTRACT We measured pulmonary function in each of 21 patients suffering from "atypical non-bacterial pneumonia during the acute illness and during convalescence (two to 18 months) to study the course and the nature of functional impairment at different stages of the disease. In six patients, no aetiological agent was found. An aetiological agent was identified in 15 of the patients: *Mycoplasma pneumoniae* (seven patients), influenza A (three patients), parainfluenza 3 (one patient), varicella (two patients), Q fever (one patient), coxsackie B3 (one patient). At the time of admission we observed a restrictive pattern in 52%, an obstructive pattern (decreased FEV₁/FVC ratio) in 52%, abnormalities in distribution of ventilation (abnormal slope of phase 3) in 63%, and abnormalities in gas exchange (increased AaDO₂) in 75% of the patients. The frequency of abnormalities in these pulmonary function tests decreased dramatically after two to four weeks and nearly disappeared in most patients during convalescence. The only major residual abnormality was a decreased FEV₁/FVC ratio in five subjects, four of whom were smokers. However, when MMEF₅₀ and V₇₅ were measured at this stage, their average value for all the groups of patients with the exclusion of the *Mycoplasma pneumoniae* group, was markedly reduced. These data suggest that small airways involvement can be demonstrated during the convalescence of patients recovering from various types of atypical pneumonia other than those caused by *Mycoplasma pneumoniae*.

The development of tests thought to detect obstruction in small airways has led to their use to study the amount and duration of the functional impairment in the lung during uncomplicated viral infections. Thus, frequency dependence of both compliance and total resistance and decreased maximal airflows at low lung volume were observed in subjects suffering from viral upper airway infections or given live attenuated influenza vaccine,¹⁻⁵ whereas abnormalities in more conventional tests were also detected in patients with uncomplicated influenza or common cold.⁶⁻⁸ Other authors have demonstrated abnormalities during influenza⁹ and rhinovirus¹⁰ infections by measuring maximal airflows in patients breathing ambient air and then a 80% helium-20% oxygen mixture. On the other hand, Zeck and co-workers¹¹ analysed the single breath oxygen manoeuvre and were unable to find abnormalities in the slope of phase 3 in subjects who had received live attenuated influenza vaccine. Finally, increased bronchial

reactivity was found in patients suffering from respiratory syncytial virus infection.¹² The prolonged duration of these functional abnormalities was stressed by several authors.^{1 2 4-6 8 12}

In contrast, there are very few reports dealing with the effects of non-bacterial or "atypical pneumonia on respiratory function. Apart from the exhaustive work by Berven¹³ on cardiopulmonary function in the post-infectious phase of atypical pneumonia, only a few studies have assessed lung function in this clinical condition.¹⁴⁻¹⁹ Therefore we studied prospectively patients admitted to hospital with the diagnosis of atypical pneumonia, to characterise the respiratory functional disturbance during the time of acute illness, in the immediate recovery period and from two to 18 months later. This study was meant to answer the following questions. Are there functional alterations specifically related to the nature of the aetiological agent? Is the prognosis related to the initial lung function impairment? And, finally, is there evidence in patients with non-bacterial pneumonia of small airways disease, the main dysfunction in uncomplicated viral illness, and, if so, at which stage?

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Methods

During a nine-month period, 33 patients were admitted to the Hospital Cantonal in Geneva with an initial diagnosis of atypical pneumonia. Twenty-one of these patients were included in our study because they satisfied the following criteria: history of headache, sore throat, myalgia, rhinitis, and fever, in general preceding symptoms of lung involvement (dry cough, pleuritic chest pain); normal breath sounds by physical examination; diffuse lung infiltrates, sometimes with a ground glass-like appearance, seen on the chest radiograph; negative bacterial sputum and blood cultures. Of the 21 patients studied, 12 were smokers (all more than 10 cigarettes per day). The other patients had never smoked.

VIROLOGICAL STUDIES

We performed bedside nasopharyngeal washes with ice-cold phosphate buffered saline²⁰ immediately after admission. The samples were taken without delay to the virus laboratory and a 0.2 ml aliquot of the specimen was inoculated into each of two tubes containing primary human embryonic kidney cells (HEK) and human fibroblast cell strain (FS-9). The tubes were placed on a roller and incubated at 36°C. Eagle's medium complemented with 2% fetal calf serum (FCS) (for HEK) and Dulbecco's medium with 2% FCS (for FS-9) were used for maintenance and changed at least once a week. The tubes were watched at least twice weekly for cytopathic effect. After four weeks, they were challenged with Echovirus 11. Haemadsorption with fresh guinea pig red blood cells was performed at least twice. Identification of viruses was performed using classical methods.²¹

SEROLOGICAL STUDIES

Samples of sera were taken from each patient on admission, at two to three weeks, and at two to 18 months thereafter for complement fixation tests²² for the following antigens: *Mycoplasma pneumoniae*, adenovirus, influenza A and B, ornithosis, Q fever, respiratory syncytial virus, adenovirus, and mumps (kindly performed by Dr MF Paccaud, Institut d'Hygiène, Geneva, Switzerland), *Legionella* and parainfluenza 1, 2, and 3 (kindly performed by the courtesy of Dr W Dowdle, Centre for Disease Control, Atlanta, Georgia). A fourfold or greater titre rise was considered to be diagnostic.

LUNG FUNCTION TESTS

We performed lung function tests on admission

(acute stage or first series), two to three weeks (post-infectious stage or second series), and two to 18 months (convalescent stage or third series) thereafter. Total lung volumes and specific conductance were measured in a constant volume body plethysmograph.^{23 24} We used a Godart bell spirometer to measure FEV₁, FVC, and MMEF. Closing volume and the slope of the alveolar plateau (phase 3) were measured during the single breath-O₂-manoeuvre.²⁵ We measured maximal flow-volume (\dot{V} -V) curves using a wedge spirometer, recorded the signals on an X-Y storage oscilloscope and photographed the screen to obtain a permanent record. We expressed maximal airflows at various lung volumes as the ratio of maximal flow/forced vital capacity (\dot{V} max/FVC). Knudson and co-workers²⁶ have shown that the value of this ratio is essentially age-independent. Gas exchange studies were made in the sitting position and the alveolar-arterial gradient for O₂ (AaDO₂) calculated from the ideal alveolar air equation. Predicted values for lung volumes were taken from Goldman and Becklake,²⁷ for the ratio FEV₁/FVC from Berglund *et al.*,²⁸ for MMEF from Morris *et al.*,²⁹ for the ratio \dot{V}_{75} /FVC from Knudson *et al.*,² for the slope of phase 3 during the single breath O₂ manoeuvre from Buist and Ross.²⁵ The use of pulmonary function equipment, similar or identical to ours, by these authors was the basis for the selection of these predicted values.

Results

Table 1 gives the distribution of the various types

Table 1 Causal agents and age, sex, and smoking habits of patients studied

Aetiology	Patient number	Age (yr)	Sex	Smoker
<i>Mycoplasma pneumoniae</i>	1	42	M	-
	2	22	M	-
	3	21	M	+
	4	37	F	+
	5	48	M	-
	6	30	M	-
	7	34	F	-
Influenza A	8	48	M	+
	9	28	F	-
	10	52	F	-
Varicella	11	32	F	+
	12	32	F	+
Coxsackie B	13	34	F	+
Q fever	14	29	M	+
Parainfluenza A	15	35	M	-
Unknown	16	67	M	+
	17	43	M	+
	18	30	M	+
	19	32	M	+
	20	23	F	+
	21	50	F	-

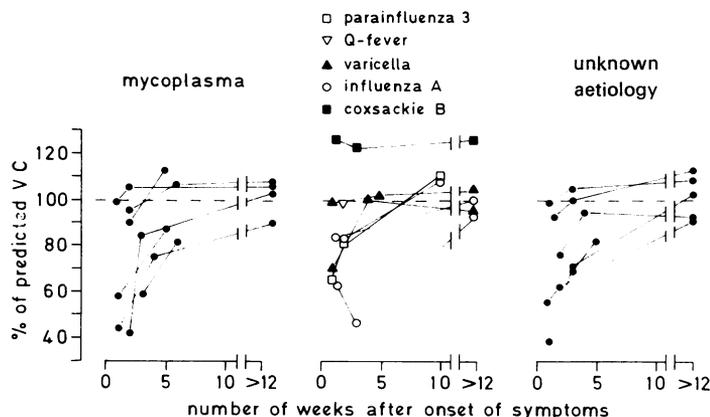


Fig 1 Time course of changes in vital capacity in the three groups of patients classified according to aetiology.

of causal agents, and the age, sex, and smoking habits of each patient. An aetiological agent could not be found in six patients (29%).

In general, VC was decreased during the acute stage and returned to normal values (>80% predicted) during the next five weeks (fig 1). We found that changes in VC were representative of the changes in TLC in all but three patients. A decrease in VC down to 80% or less of the theoretical value could therefore be taken as evidence for the presence of a restrictive lung disease. This was the case for 11 patients (52%) at the time of admission; the values became normal in both the second and third tests.

An obstructive pattern ($FEV_1/FVC < 90\%$ of the predicted value²⁸) was present initially in 11 patients (52%), whereas in four others the value was greater than 110% of predicted value (fig 2). Little change was noted in the second series of tests. In the convalescent stage, five subjects, four

of whom were smokers, had abnormally low values for the FEV_1/FVC ratio.

The slope of the alveolar plateau (phase 3) of the single breath O_2 test was abnormal in 12 out of 19 (63%) of our subjects at the time of admission. However, in the second series of tests only three out of 18 (17%) were abnormal and only one out of 16 (6%) in the third series of tests. Measurements of closing volume were abnormal in only two subjects at the time of admission and in none of the patients at the time of the last examination.

The $AaDO_2$ was abnormal (>2.6 kPa or 20 mm Hg) in 15 out of 20 patients in the first series of tests, in four out of 17 in the second, and in none out of 16 in the third (fig 3).

Two measurements, MMEF and V_{75} (maximal airflow after 75% of FVC), were calculated only in the third series of tests since in view of the normalisation, at this stage, of the other

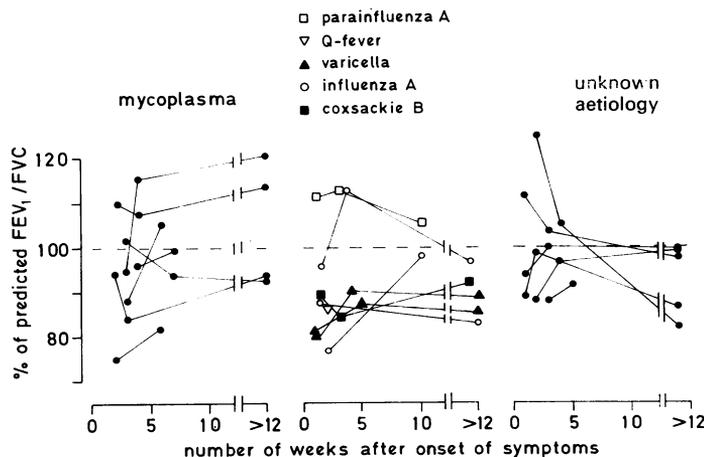


Fig 2 Time course of changes in FEV_1/FVC in the three groups of patients classified according to aetiology.

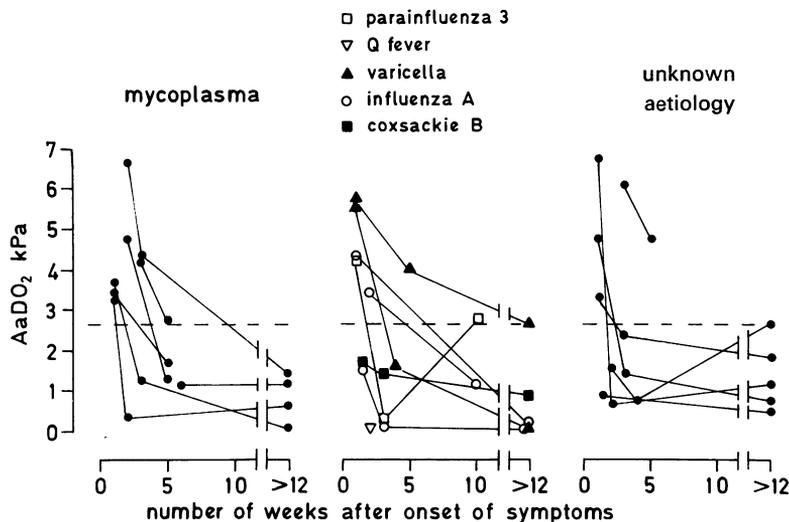


Fig 3 Time course of changes in AaDO₂ in the three groups of patients classified according to aetiology.

conventional tests, we could use them to assess the presence of "small airways disease." The results are given in table 2, together with the values obtained for VC, FEV₁/FVC ratio, and specific conductance. Although few of the measurements of \dot{V}_{75} and MMEF could be considered as significantly abnormal because of the wide range of normal values, the average value of \dot{V}_{75} , expressed as a percentage of predicted, was only 60±29% and that MMEF 80±27% (mean±SD). Patients having recovered from Mycoplasma pneumoniae, however, had normal values for both \dot{V}_{75} (89±12%) and MMEF

(109±18%). If we exclude this group, the average values for the two other groups then became 49±24% for \dot{V}_{75} and 66±22% for MMEF, making both of them significantly different from the values of the Mycoplasma pneumoniae group (p<0.01).

Discussion

There are two factors limiting the conclusions that can be drawn from this study. First, we studied a selected group which excluded patients with acute respiratory distress syndrome and sub-

Table 2 Lung functions in the third series of tests

Aetiology	Patient number	Time after onset of symptoms (weeks)	VC (l)	FEV ₁ /FVC (%)	Slope phase III (% N ₂ /l)	sGaw (s ⁻¹ · kPa ⁻¹)	\dot{V}_{75} ($\bar{M} \pm SD$) [*] (l/s/FVC)	MMEF ($\bar{M} \pm SD$) [*] (l/s)
Mycoplasma pneumoniae	3	18	5.50	80	1.0	1.8	0.43 (0.60±0.17)	4.65 (4.7±1.12)
	4	68	3.85	78	1.0	1.9	0.63 (0.70±0.29)	3.01 (3.3±0.80)
	5	14	4.80	88	1.0	1.5	0.70 (0.71±0.28)	5.20 (4.0±1.12)
Influenza A	7	67	3.45	95	2.0	1.3	0.67 (0.70±0.29)	4.25 (3.65±0.80)
	8	16	4.05	61	2.0	1.4	0.13 (0.71±0.28)	
	9	16	3.70	82	2.0	1.2	0.50 (0.79±0.27)	3.27 (3.72±0.80)
Varicella	10	11	3.20	76	2.5	1.5	0.21 (0.75±0.30)	1.87 (2.79±0.80)
	11	75	3.75	72	2.0	1.7	0.27 (0.70±0.29)	1.70 (3.62±0.80)
Coxsackie B	12	67	3.60	75	1.5	1.6	0.27 (0.70±0.29)	2.42 (3.62±0.80)
	13	16	4.20	77	1.0	1.5	0.35 (0.70±0.29)	3.21 (3.34±0.80)
Parainfluenza A	15	9	5.90	82	0.5	1.4	0.37 (0.59±0.23)	4.60 (4.51±1.12)
Unknown	17	18	5.21	73	1.0			2.50 (3.97±1.12)
	18	16	5.60	80	1.0	1.6	0.39 (0.59±0.23)	2.50 (4.17±1.12)
	19	14	5.40	79	0.75	1.5	0.38 (0.59±0.23)	3.40 (4.42±1.12)
	20	14	3.45	75	1.5	2.2	0.76 (0.79±0.27)	2.54 (3.75±0.80)
	21	19	2.35	63	2.5	1.2	0.10 (0.75±0.30)	0.62 (2.58±0.80)

* Predicted values (±1 SD) for \dot{V}_{75} /FVC were taken from Knudson et al²⁶ and those for MMEF from Morris et al.²⁹

jects with mild illness for whom admission to hospital was not necessary. The second limitation is the small number of cases resulting from each aetiological agent, especially in the mixed group because of its variety of causal agents.

The most obvious conclusion is the variety in the patterns of functional impairment, with evidence in the acute phase of the disease of restriction, obstruction, and abnormalities in the distribution of ventilation and gas exchange in approximately half to two-thirds of the cases. It seems logical, therefore, to infer that several pathophysiological patterns were associated. At this stage, neither smoking nor a particular aetiological agent could be related to a given type of functional abnormality.

Improvement in function was rapid in most cases. The second series of tests, performed two to four weeks after the first series, showed a much reduced prevalence of abnormalities. This was particularly true for the restrictive pattern, the AaDO₂ gradient, and the distribution of ventilation, whereas the frequency of obstruction remained at the same level. This discrepancy might result from the fact that the obstructive pattern was somewhat underestimated in the first series of tests, the coexistence of a restrictive syndrome having prevented its expression in some patients. Airways obstruction, defined conventionally by reduced FEV₁/FVC ratio, was the most common disturbance two months or more after the acute episode, but four of the five subjects with this abnormality were smokers. These patients, however, did not show abnormalities in the slope of phase 3 of the single breath O₂ manoeuvre.

MMEF and \dot{V}_{75} were not analysed in the first two series of tests as the data could not be properly interpreted in view of the coexistence of obstructive or restrictive patterns or both in most subjects. However, at a time when most of the conventional lung function tests returned to normal (two to 18 months after the onset of disease), the analysis of flow-volume curves and the measurement of MMEF suggested abnormalities for the group as a whole. Closer examination of the data, however, indicated that the group of patients with *Mycoplasma pneumoniae* differed from the two other groups by not showing reduced values for \dot{V}_{75} and MMEF. Abnormalities in these tests are generally taken as evidence of small airways disease, and we would like to postulate that, late in the recovery period from atypical pneumonia of various aetiologies, but with the exclusion of *Mycoplasma pneumoniae*, peripheral airways

could be involved as was shown to be the case in the acute phase of uncomplicated viral infections.¹⁻⁵ The different behaviour of the group with *Mycoplasma pneumoniae*, which does not appear to result from a prolonged duration of observation, but might be caused by the different pathophysiology of mycoplasmal and viral pneumonia as proposed by Brunner *et al*,³⁰ is the only finding which separated one aetiological agent from the group as a whole. It is true that strict criteria for pathological (outside 2 SD) reduction in \dot{V}_{75} or MMEF were met only in a few cases, but, as often reported in studies on small airways involvement under various conditions, patients who could not be considered as abnormal on an individual basis, could, as a group, be differentiated clearly from the group of control subjects. By analogy, the mixed and the unknown aetiology groups could be considered as abnormal when compared to the *Mycoplasma pneumoniae* group, which, because of its apparent complete recovery, could be taken as a control.

Out of five patients with the best evidence for small airways involvement (patients 8, 10, 11, 12, 21) at the third series of test, three were smokers. Four presented initially an obstructive pattern, with a mean FEV₁/FVC ratio equal to 87% of predicted value and a sGaw of 1.7 s⁻¹.kPa⁻¹ (0.17 s⁻¹.cm H₂O⁻¹). Out of the 11 other patients, seven were smokers and nine also presented initially an obstructive pattern, with the same FEV₁/FVC ratio (87% of the predicted value) and a sGaw of 1.4 s⁻¹.kPa⁻¹. It appears therefore impossible to predict the occurrence of small airways involvement from the initial measurements of FEV₁/FVC ratio and sGaw. Smoking does not seem to predispose to such functional impairment.

Comparison of our data with those obtained previously by other investigators reveals some discrepancies. Thus Stonehill *et al*¹⁴ found only a slight reduction in VC (89% of the predicted values) in the acute phase of viral respiratory disease with pulmonary infiltrates. Bocles *et al*¹⁵ studied 10 subjects with varicella pneumonia in the acute phase and could not detect any change in VC or FEV₁/FVC ratio. Berven¹³ found the AaDO₂ abnormal in five out of nine patients, 13 to 27 weeks after the onset of atypical pneumonia, whereas none of our 16 patients had an AaDO₂ higher than 2.6 kPa in our third series of measurements. Differences in smoking habits, case selection, time of observation, and severity of disease, could explain these discrepancies at least partially. Because of this variability of

results, some caution is advisable, and our finding of small airways involvement in the late recovery period from all types of atypical pneumonia but *Mycoplasma pneumoniae* deserves confirmation.

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