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Total respiratory impedance and early emphysema

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ABSTRACT: It can be postulated that patients in early stages of pulmonary emphysema have normal values of total respiratory resistance and reactance. The purpose of this study was to investigate whether pulmonary emphysema, detected functionally by a decrease of the single breath diffusing capacity (DLCO) by at least 25% of predicted, and an increase of the static lung compliance (CLst) by at least 50% of predicted, can be accompanied by normal values of respiratory resistance (Rrs) and reactance (Xrs), measured between 2 and 24 Hz by the forced oscillation technique.

In a prospective study, we determined CLst in 26 patients, who had been selected on the basis of normal values of Rrs and Xrs, and a DLCO of less than 75% of predicted.

In 17 of these patients, CLst was more than 150% of predicted. Since there were only minor abnormalities on routine lung function tests and chest X-ray, it is likely that these patients presented early emphysema. In the nine other patients, CLst was within normal limits: four suffered from interstitial lung disease; the remaining five were probably in a preliminary stage of early emphysema.

In conclusion, early emphysema should systematically be considered as the first diagnosis in patients with normal values of Rrs and Xrs, and a decrease of DLCO. Onset of interstitial lung disease is a possible alternative.

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Although emphysema is a pathological diagnosis [1], several studies have shown that pulmonary function tests are sensitive noninvasive indicators of this condition. Specifically, a reduction of diffusing capacity for carbon monoxide (DLCO) associated with a loss of lung elastic recoil (to exclude interstitial diseases) strongly suggests emphysema, in the absence of clear-cut airways obstruction [2–7].

Maximal forced expiratory volume in one second (FEV_1), depends not only on airway dimensions but also on the elastic recoil of the lungs. One expects that, for the same reduction of FEV_1, patients with emphysema will demonstrate a lesser increase in airway resistance than patients suffering from asthma or chronic bronchitis. This was, indeed, the finding of Van Noord *et al.* [8], who compared the values of total respiratory resistance (Rrs) and reactance (Xrs), obtained by means of a forced oscillation technique [9], in 75 patients with airways obstruction (27 asthmatics, 28 patients with chronic bronchitis and 20 subjects with emphysema). In the latter subjects, the diagnosis of emphysema was based on a decrease of DLCO of at least 30% of predicted, and an increase of static lung compliance (CLst) by at least 50% of predicted. For a similar degree of obstruction (FEV_1 on average 56% of predicted) the patients with emphysema were, as a group, the least impaired in terms of Rrs and Xrs: there was less negative frequency dependence of Rrs, and less decrease of the average Xrs. In fact, among the latter patients, five demonstrated completely normal values of Rrs and Xrs.

We wondered how often the finding of normal values of Rrs and Xrs in patients with reduced DLCO can be attributed to emphysema.

In a prospective study, we selected all patients referred to the lung function laboratory, who demonstrated normal values of Rrs and Xrs and a significant decrease of DLCO. We investigated, by measuring CLst, whether these subjects suffered from pulmonary emphysema, and how these functional abnormalities related to routine lung function tests.

Patients

Among the patients presenting with normal values of Rrs and Xrs and a reduction of DLCO of at least 25% of predicted, in the absence of anaemia, 26 consented to a measurement of static recoil pressures by the oesophageal balloon technique. In 17, CLst was more than 150% of predicted.

The general characteristics of these 17 patients (15 males, 2 females) mean age 56 yrs (Group 1) are summarized in table 1. All patients except one were current or exsmokers. Six patients had been exposed to occupational hazards. There was no α_1-antitrypsin deficiency (one unknown). Most subjects presented with exertional dyspnoea, one suffered from chronic cough with white phlegm, whereas the remaining three patients had no respiratory complaints. On clinical examination, we noticed reduced lung sounds (nine patients), basal crackles (seven patients), wheezing and prolonged expiration (four patients). Chest X-rays, performed in 14 patients, showed in all but one patient at least one sign suggesting emphysema: enlarged retrosternal space [10–12], bullae [14], decreased or irregular vascular markings [10–12], enlarged right lung length [11, 14], flattened diaphragm in lateral or anteroposterior view [10–12, 14].

Table 1. – General characteristics of the 26 subjects (Group 1 and Group 2)

Patient No.	Sex	Age yrs	Height cm	Weight kg	Cig·day^{-1}	X-ray	Hazard	Presenting symptom(s)	Ausc.	Associated or previous lung pathology
Group 1										
1	M	44	169	65	8	NA	-	1	0	Haemopneumothorax (pr.)
2	M	70	164	65	10	2,3	-	1	1	Left ventricular failure
3	M	53	167	66	40	1,4,5	Glass-grinder	0	2	Systemic herpes+candid (pr.)
4	M	62	166	61	25	2	-	1	1	-
5	M	60	166	63	20	1	-	1	1,3	-
6	M	56	186	76	20	1,2,3,4,5	-	1	1	-
7	M	64	172	72	(12)*	1.2,3,5	Copper founder	1	2,3	Tuberculosis (pr.)
8	M	50	169	65	20	2,3	Welder	1	1,2	-
9	M	36	177	59	10	NA	-	1	1	-
10	M	73	167	52	20	1,3	-	1	1,2	-
11	M	63	159	47	25	1,3	Coal miner	2	0	-
12	M	50	182	70	10	NA	-	1	1	Pneumothorax (pr.)
13	M	62	179	88	10	1,3	Copper founder	0	1	-
14	M	68	169	57	20	3	-	1	2,3	-
15	M	58	172	73	6	1,2,3	Coal miner	0	0	-
16	F	47	163	70	0	0	-	1	2	-
17	F	41	154	60	(50)*	1	-	1	2,3	-
Group 2										
1	M	48	176	74	25	NA	-	4	0	Systemic sclerosis
2	M	43	164	62	30	0	Coal miner	3	1	Chronic bronchitis
3	M	67	169	55	2	1	-	1,2	1,2	-
4	M	44	163	60	7	1	-	6	0	-
5	M	57	163	57	20	1,3,5	Coal miner	7	0	-
6	F	43	150	47	15	0	-	0	3	-
7	M	73	163	49	-	1,3,4,5	Coal miner	1	1,2,3	Anthracosilicosis
8	M	75	167	63	(6)*	2,3	-	1,2	2	Idiopath. lung fibr. chron. bronch.
9	M	55	171	58	15	0	-	5,6	1	Sarcoidosis

*: ex-smokers; Chest X-ray: 0) normal; 1) enlarged retrosternal space; 2) bullae; 3) decreased or irregular markings; 4) enlarged right lung length; 5) flattened diaphragm. Presenting symptoms; 0) none; 1) exertional dyspnoea; 2) cough, mucous secretions; 3) purulent secretions; 4) arthralgia, Raynaud's phenomenon; 5) arthritis; 6) fever; 7) angina pectoris. Ausculations: 0) normal; 1) reduced lung sounds; 2) basal crackles; 3) wheezing and prolonged expirations. NA: not available; pr.: previous; idiopath. lung. fibr.: idiopathic lung fibrosis; candid: candidiasis; chron. bronch.: chronic bronchitis.

The general characteristics of the remaining nine patients (eight males, one female), mean age 56 yrs (Group 2) are also found in table 1. All patients except one were current or ex-smokers. Three patients had been exposed to occupational hazards. Four suffered from interstitial lung disease (systemic sclerosis, idiopathic lung fibrosis, sarcoidosis and anthracosilicosis). On clinical examination, we observed reduced lung sounds (four patients), basal crackles (three patients) and wheezing (two patients). Chest X-rays were performed in eight patients, five presented signs suggesting emphysema.

Fifteen (out of 20) patients with emphysema and abnormal values of Rrs and Xrs of the study of Van Noord *et al.* [8] were used for comparison (Group 3).

Methods

Vital capacity (VC), and FEV_1, were measured with a water-sealed spirometer. DLCO was determined with the single breath method of Ogilvie *et al.* [15]. Peak expiratory flow (PEF), and maximal expiratory flow at 50% of VC (MEF_{50}), were obtained from expiratory flow-volume curves, measured at the mouth with a pneumotachograph. Airway resistance (Raw) and thoracic gas volume (TGV) were measured during quiet breathing in a constant volume body plethysmograph. By subtracting expiratory reserve volume from TGV, residual volume (RV), was obtained. Static transpulmonary pressure-volume (PL-V) curves were determined during apnoeas at several expiratory lung volumes. The oesophageal pressure was recorded by means of an oesophageal balloon (length 10 cm, containing 1 ml of air) positioned in the oesophagus at about 38 cm from the nares; CLst was calculated as the slope of the expiratory PL-V curve in the vicinity of functional residual capacity (FRC).

VC, FEV_1, DLCO, PEF, MEF_{50}, RV, total lung capacity (TLC), (the sum of VC and RV), and PL at TLC, $P_{L,TLC}$, were related to the prediction equations of Quanjer [16], CLst to those of Yernault *et al.* [17], Raw to the reference values of Amrein *et al.* [18] and specific airway conductance (sGaw), calculated from the prediction equations of Pelzer and Thomson [19] for TGV, and from those of Amrein *et al.* [18] for Raw.

Rrs and Xrs were measured with the technique described by Landser *et al.* [9], and in accordance with the recommendations for this method [20]. The equipment was calibrated by means of a known impedance, consisting of two layers of 400-mesh wire screen fitted into a 2 cm ID perspex tube. The seated subject, wearing a noseclip and supporting his/her cheeks, breathed quietly through a Lilly-type pneumotachograph. A pseudo-random noise signal, containing all harmonics of 2 Hz up to 24 Hz was applied at the mouth *via* a loudspeaker. Pressure and flow were recorded at the mouth using two differential transducers (Validyne MP45) and led into a Fourier Analyser, which calculates the real and imaginary parts of the respiratory impedance at each of the investigated frequencies. A coherence function was computed in order to assess the amount of noise and alinearities at each frequency. A perfect coherence was indicated by 1. Only values with a coherence function of 0.95 or more were accepted. As reference parameters for Rrs and Xrs we used data obtained in 417 healthy nonsmoking subjects (291 females, 126 males) by means of the same technique [21, 22]. Four indices were used to express the measurements: Rrs at a frequency of 6 Hz, (Rrs_6); the mean Rrs value between 6 and 24 Hz ($\overline{Rrs}$); the slope of Rrs *vs* frequency, (Rrs^{-1}); and the mean Xrs value between 6 and 24 Hz ($\overline{Xrs}$). These indices were obtained from fourth degree polynomials fitted on the individual data [22]. To be normal, Rrs_6 and $\overline{Rrs}$ had to be below the predicted Rrs_6 or Rrs+1.65 SD and Rrs^{-1} as well as $\overline{Xrs}$ had to be, respectively, above the predicted values of Rrs^{-1}-1.65 SD and of Xrs-1.65 SD, 1.65 SD, corresponding to the 95% confidence interval for one-tailed t-test.

Results

Table 2 shows the mean values of the functional indices in the two groups of subjects.

The first 17 patients (Group 1) were, as a group, characterized by a slight reduction of FEV_1/VC associated with a decrease of PEF and MEF_{50}. Raw and sGaw were normal in all subjects. TLC was slightly increased in one subject, whereas RV was increased in five patients. VC was abnormally low in one moderately obstructive patient. Eight patients showed an abnormally decreased PL,TLC. CLst varied between 151 and 406% predicted, DLCO between 8.7 and 74.7% predicted. PEF was decreased in eight patients, MEF_{50} in all patients with reduced FEV_1/VC ratio, as well as in one patient with normal spirometric values. The 17 patients could be divided into three subgroups on the basis of FEV_1 and VC: four patients had no spirometric abnormalities, three patients showed a decreased FEV_1/VC ratio of less than 10% of the predicted value, the remaining 10 patients were obstructive (eight mildly, with FEV_1 between 65–80% of predicted, two moderately with FEV_1 between 50–65% of predicted).

The nine patients of Group 2 were, as a group, characterized by minor bronchial obstruction and a decreased DLCO (between 22.5 and 68.9% of predicted), similar to Group 1 but with values of CLst within normal range (between 80 and 148.9% of predicted). One subject had normal spirometric values, five had a decreased FEV_1/VC ratio, two were mildly and one moderately obstructive. VC and TLC were normal in all nine patients. RV was increased in one subject (148.5% of predicted), whereas Raw was slightly above normal in another patient. sGaw was normal in this particular patient. PL,TLC was decreased in one patient. An unpaired t-test between Groups 1 and 2 showed that, except for CLst (used as selection criterion between both groups), no other measurement differed significantly between the two groups.

As mentioned previously, 5 of the 20 patients with emphysema in the study of VAN NOORD *et al.* [8] showed normal values of Rrs and Xrs. The 15 patients with abnormal values of Rrs and Xrs (fig. 1) (Group 3 of table 2) were compared to our 17 patients of Group 1. Group 3 differed significantly from Group 1 (table 2): FEV_1, PEF, MEF_{50}, sGaw, Xrs and Rrs^{-1} were less, whereas RV, TLC, TGV, Raw, Rrs were larger in Group 3, indicating more obstruction in the latter. DLCO and CLst do not differ between the two groups,

Table 2. – Biometric and functional data (mean±1 SD) in subjects with a static lung compliance, > (Group 1) or < (Group 2) than 150% of predicted, compared with 15 subjects from the study of VAN NOORD *et al.* [8] (Group 3)

	Group 1 n=17	Group 2 n=9	Group 3 n=15	p 1 *vs* 2	p 1 *vs* 3
Age yrs	56±10.5	56±12.8	62±9.5	NS	NS
VC % pred	105±18.6	100±8.0	96±20.9	NS	NS
FEV_1 % pred	82±20.8	79±10.8	47±15.3	NS	0.0001
FEV_1/VC %	60±10.1	61±6.5	37±6.9	NS	0.0001
RV % pred	121±45.6	103±24.5	178±50.5	NS	0.0024
TLC % pred	109±12.5	101±13.2	122±10.9	NS	0.0032
PEF % pred	69±17.7	69±22.3	50±12.0	NS	0.0011
MEF_{50} % pred	49±22.8	47±18.6	17±6.4	NS	0.0001
CLst % pred	226±72.7	123±26.9	214±58.1	0.0001	NS
PL,TLC % pre	68±26.6	83±14.7	47±14.9	NS	0.0091
DLCO % pred	54±19.0	49±17.5	58±15.9	NS	NS
Raw % pred	89±31.3	108±27.2	145±51.3	NS	0.0012
TGV % pred	113±18.7	107±18.9	147±27.4	NS	0.0005
sGaw % pred	115±44.7	94±27.4	56±26.4	NS	0.0001
Rrs_6 $kPa \cdot l^{-1} \cdot s$	0.202±0.044	0.204±0.046	0.430±0.107	NS	0.0001
$\overline{Rrs}$ $kPa \cdot l^{-1} \cdot s$	0.218±0.047	0.218±0.048	0.367±0.091	NS	0.0001
$\overline{Xrs}$ $kPa \cdot l^{-1} \cdot s$	0.033±0.021	0.036±0.020	-0.084±0.061	NS	0.0001
Rrs^{-1} $kPa \cdot l^{-1} \cdot s^2$	0.001±0.001	0.001±0.001	-0.006±0.003	NS	0.0001

NS: nonsignificant; VC: vital capacity; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; PEF: peak expiratory flow; MEF_{50}: maximal expiratory flow at 50% of VC; CLst: static recoil pressure; PL,TLC: recoil pressure at 100% TLC; DLCO: diffusing capacity of the lungs for carbon monoxide; Raw: airway resistance; TGV: thoracic gas volume; sGaw: sirway specific airway conductance; Rrs_6: respiratory resistance at 6 Hz; $\overline{Rrs}$, $\overline{Xrs}$: respectively, mean respiratory resistance and reactance; Rrs^{-1}: slope of the Rrs-frequency curve.

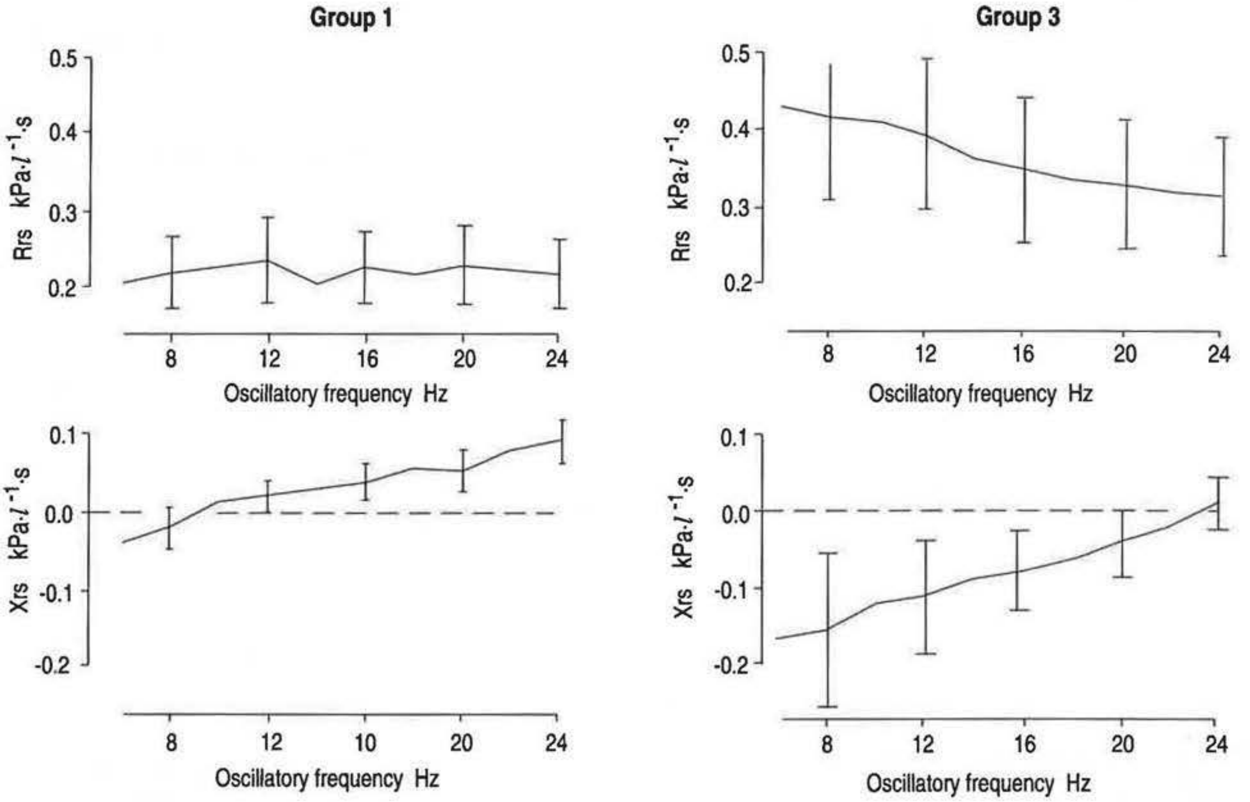

Fig. 1. – Mean values (±1 SD) of total respiratory resistance (Rrs), and reactance (Xrs), as a function of oscillatory frequency in Groups 1 and 3. As compared to Group 1, the group 3 subjects demonstrate a negative frequency dependence of Rrs, and more negative values of Xrs.

whereas PL,TLC was significantly lower in Group 3. All but two Group 3 patients had abnormally low values of sGaw.

In three patients, confirmatory evidence for emphysema was obtained: by means of computerized tomographic (CT) scan (presence of bullae) in one Group 1 patient and, one Group 2 patient, and by means of pathological examination (panlobular emphysema) in one Group 2 patient, who died one year after the measurements.

Discussion

In this prospective study, we selected, from the patients referred to the clinical pulmonary function laboratory, 26 patients characterized by normal values of Rrs and Xrs and a decrease of DLCO. Seventeen of these demonstrated an increase of CLst exceeding 150% of predicted (Group 1). These subjects probably suffered from pulmonary emphysema. Indeed, the occurrence of a reduction of DLCO, associated with an increase of CLst strongly suggests this diagnosis [5]. This was confirmed in most subjects by the clinical symptoms and signs, the fact that all subjects, but one, were current or ex-smokers and the finding on chest X-rays of signs suggesting emphysema. It is known that chest X-rays, though insensitive, are accurate for the diagnosis of emphysema [12]. In recent years CT scan has been applied to evaluate pulmonary emphysema, either by visual examination [23], or by density measurements [24]. This technique appears to have some limitations, however: it lacks sensitivity for the detection of the earliest lesions of emphysema [5, 25], and for distinguishing hyperinflation without (*i.e.* asthma) and with parenchymal destruction (*i.e.* emphysema) [26]. In the few patients investigated by this technique, the presence of emphysema was confirmed.

The presence of emphysema in Group 1 subjects did not affect Raw or sGaw. FEV_1, was often within normal limits, but the ratio FEV_1/VC was moderately reduced. This type of emphysema with minor airway obstruction is referred to as "early or subclinical emphysema" in previous studies [2, 3, 27–29]. The fact that the forced oscillation indices were normal (fig. 1) is in keeping with the finding of normal values of Raw or sGaw; the geometry of the airways is not noticeably modified during quiet breathing. During forced expirations, however, minor abnormalities were observed on spirometry and expiratory flow-volume curves. This was possibly due to collapse of the airways secondary to a loss of interstitial support: MEF_{50}, was decreased in 14, and PEF in 8 patients. This is consistent with the observation of GELB *et al.* [3] that a decreased DLCO in association with abnormal expiratory flow-volume curves, especially at lower lung volumes, is suggestive for early emphysema. The mean value of TLC in our patients (109% of predicted) was between the mean values of 117% of predicted, found by PETTY *et al.* [28], SILVERS *et al.* [29] and DEMEDTS *et al.* [27], and the mean value of 100% of predicted, found by GELB *et al.* [3].

In their study of the evolution of early emphysema, DEMEDTS *et al.* [27] concluded that DLCO and CLst vary little over a 10 yr period, whereas PL,TLC and FEV_1 decrease significantly. Accordingly, if the patients of Group 1 suffered from early emphysema, it is likely that the 15 patients of VAN NOORD *et al.* [8] were representative of a further stage of the disease, the latter being characterized by similar values of DLCO and CLst but more obstruction, increased resistance values, larger RV and TLC values, and more pronounced decrease of PL,TLC.

Among the nine patients of Group 2, four (Nos. 1, and 7–9 in table 1) showed a clinical history of interstitial lung disease. Although the reduction of DLCO may reflect interstitial pathology, these patients did not demonstrate a restrictive disorder (normal value of TLC). In addition, MEF_{50}, was decreased in all patients, and in three of them FEV_1/VC was reduced. It is likely that, in addition to the interstitial disease, these subjects also suffered from airway pathology. The latter is not unusual in sarcoidosis, anthracosilicosis or systemic sclerosis, and might also be related to their smoking habits [4, 30–31]. The mean value of CLst in these four patients was 104% of predicted, compared with 138% of predicted in the remaining five patients of the group. In the latter five subjects, the combination of pulmonary function abnormalities, chest X-ray features, auscultation and smoking habits suggests that these patients were in a preliminary stage of early emphysema ("nearly early emphysema"?).

In these series, none of the patients presented with pulmonary vascular disease (*e.g.* pulmonary embolism). However, it is conceivable that this may also cause an isolated decrease in DLCO, with normal values of the other pulmonary function tests including Rrs and Xrs.

As a conclusion of this prospective study, we submit that early emphysema should be considered systematically in the differential diagnosis of patients with normal values of Rrs and Xrs (or sGaw) and a decrease of DLCO. Commencement of interstitial lung disease is a possible alternative. Chest X-ray, clinical history, physical examination and measurement of CLst could be used for a differential diagnosis.

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