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Title: Impaired lung compliance and DLCO but no restrictive ventilatory defect in sarcoidosis

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ABSTRACT

Sarcoidosis is a systemic granulomatous disease with predominant manifestation in the lungs, often presenting as interstitial lung disease (ILD). Pulmonary function abnormalities in sarcoidosis include restriction of lung volumes, reduction in diffusing capacity ($D_{L,CO}$), reduced static lung compliance ($C_{L,st}$), and airway obstruction.

The aim of study was to assess various lung function indices including $C_{L,st}$ and $D_{L,CO}$ as markers of functional abnormality in sarcoidosis patients.

We retrospectively analyzed results from 830 consecutive patients referred for lung function tests with a diagnosis of sarcoidosis (223 in stage I, 486 in stage II, and 121 in stage III). The mean age of the patients was 40±11 yrs; 18% were active smokers and 24% were former smokers.

We found normal TLC in 772 patients (93%). Of these cases, 24.5% had a low $C_{L,st}$ and 21.5% had a low $D_{L,CO}$. At least one abnormality was observed in 39.3% of these patients, while in restrictives 88%. Airway obstruction was present in 11.7% of cases.

Lung volumes usually remain within the normal range and measurement of either $C_{L,st}$ or $D_{L,CO}$ will often reveal impaired lung function in sarcoidosis patients, even when their lung volumes are still in the normal range; these two measurements provide complementary information.

Key words: diffusion capacity, lung compliance, pulmonary function tests, restriction, sarcoidosis.

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology characterized by the formation of granulomas in the lungs and intrathoracic lymph nodes [1]. In progressive sarcoidosis, cellular infiltrates in the lung transform into fibrotic changes, causing interstitial lung disease (ILD) [2,3].

Sarcoidosis forms part of a group of ILDs which are characterized by diverse clinical and histopathologic manifestations, sharing a common basic pattern of functional impairment. The basic mechanism of lung function impairment is assumed to be decreased lung compliance (lungs become stiffer, less compliant) so that the static expiratory pressure-volume (P-V) curve of the lung is shifted downward and to the right compared with normal subjects. The P-V curve is contracted along its volume axis, as both total lung capacity (TLC) and vital capacity (VC) decrease [4,5]. The transpulmonary pressure near TLC is increased, which reflects the greater mechanical advantage of the diaphragm, whose force-generating capacity is enhanced at the diminished lung volume in ILD. Static lung compliance ($C_{L,st}$), measured from the P-V curve, is one of the parameters which reflects the mechanical properties of the lung tissue, but it is rarely measured in clinical settings. See Figure 1 for an example of $C_{L,st}$ measurement in a patient with sarcoidosis and a low TLC.

An increased alveolar-arterial oxygen tension gradient and resting hypoxemia also occur with more severe ILD [6]. The arterial carbon dioxide tension ($P_{a,CO2}$) is usually normal but may be reduced at rest in a proportion of patients because of alveolar hyperventilation [6]. The diffusion capacity of the lung ($D_{L,CO}$) is characteristically reduced in ILDs and to a greater extent than the total lung capacity at which it is measured [7]. Spirometry and $D_{L,CO}$ measurements are recommended tests in the initial evaluation of the magnitude of functional lung involvement, but the prognostic value of $D_{L,CO}$ in sarcoidosis is poor [1,8].

Although a "restrictive ventilatory defect", characterized by the reduction in static lung volumes and "impaired gas exchange" expressed as reduced $D_{L,CO}$, is classically considered as the most prevalent pattern of lung function abnormality in ILD, airway obstruction has also been reported [7,9-13].

The National TB & Lung Diseases Research Institute in Warsaw, Poland serves as the regional referral center for patients with sarcoidosis and other ILDs. All patients with chronic interstitial markings on chest x-ray or lung CT scans seen by our pulmonary specialists are referred to the pulmonary function testing (PFT) laboratory for measurement of lung volumes, single-breath $D_{L,CO}$, and static lung compliance measurements. This practice provided the opportunity to describe patterns of lung function abnormality from a much larger group of patients with sarcoidosis than previously reported [7,9,10,12-16]. One study reported about a comparable number of subjects, but pulmonary function tests were not presented [17].

The main purpose of this investigation was to describe lung function abnormalities and to determine the rates of lung function impairment expressed as reduced $D_{L,CO}$ and/or reduced $C_{L,st}$ in patients with sarcoidosis, especially those with no volume restriction.

This study was approved by the local Ethics Committee.

METHODS

The study group consisted of 830 patients with sarcoidosis (387 females, 443 males, all Caucasian) consecutively referred for PFT evaluation at the time of diagnosis or during follow up, over a period of almost four years. Only the first result was considered if the patient was seen several times, usually it was the initial PFT evaluation, so the majority of patients were not treated at the moment of investigation. In the majority (85%) the diagnosis was confirmed by histopathological examination. In most cases, endobronchial biopsy was performed, but mediastinoscopy, transbronchial biopsy, video assisted thoracoscopy or open lung biopsy were also used. In a minority of patients with no histopathological confirmation (15%), clinical features, such as Löfgren's syndrome, regression of the disease without treatment, and exclusion of other causes of hilar lymphadenopathy were used to establish the diagnosis of sarcoidosis with a high degree of confidence, in agreement with the ERS/ATS 1999 statement on sarcoidosis [1]. Radiographic stages were defined in accordance with the same statement [1]. The study group characteristics are presented in table 1.

Table 1.

All patients underwent a standard evaluation that included history, physical examination, chest radiogram, spirometry and flow-volume curve, whole body plethysmography, static lung compliance, and single breath $D_{L,CO}$. All treated patients were asked to not use any inhalers 24 hours before the tests. ERS guidelines for all lung function measurements were followed [18,19]. All PFTs were done using a MasterScreen system (Jaeger, Würzburg, Germany, software version number 4.65).

Semistatic lung compliance was measured from "quasistatic" expiratory pressure-volume curves using the standardized esophageal pressure method [19]. Details are provided in an online depository. This measurement is routine procedure in our lab (approximately 1000 measurements/year), and is only sporadically refused by patients. Adverse effects (*e.g.* nasal and throat bleedings, vomiting, nausea) occurred a few times a year and were not threatening. In general this procedure is safe for patients.

Reference equations for spirometry were taken from Falaschetti [20], ERS for lung volumes and $D_{L,CO}$ [18,21]. For static lung compliance we used references taken from Colebatch *et al.* [22]. $D_{L,CO}$ results were corrected for hemoglobin concentration [23]. Following ATS/ERS 2005 guidelines, the lower limits of normal (LLN) were set at the level of 5^{th} percentile (or mean minus 1.64 SD) of each reference population [24]. Results were conventionally expressed as percent predicted. As the mean predicted value falls with age and the scatter does not fall proportionately, percent predicted leads to an age, height and sex related bias. We therefore also calculated standardized residuals (SR = (observed – predicted)/RSD) [18] which are free of such bias. Results are presented as means and 95% confidence intervals. For each disease stage, the percentage of subjects whose pulmonary function index was below the LLN, was also calculated.

Statistical analysis. Differences between the various disease stages were analyzed using the General Linear Model analysis of variance (ANOVA), with pulmonary function expressed as percent predicted or SR as the outcome variable, disease stage and sex as predictors, and age, height, daily tobacco consumption or years smoked or packyears as confounding variables. Levene's test did not disclose inhomogeneity of variance. A p-value of less than 0.05 was regarded as significant. Group comparisons were made using Student's t-test for independent samples to clarify whether significant differences detected with ANOVA translated into significant differences between all groups; applying Bonferroni correction a p-value of < 0.017 was considered significant. The χ^2 test was used to test for differences in the

prevalence of observations below the LLN. Statistical analyses were performed using STATISTICA, version 8.0. StatSoft, Inc. (2008).

RESULTS

The mean age of the patients was 40.3 (SD 10.9) years (range 19-75). There were 223 (26.9%) patients in stage I, 486 (58.6%) patients in stage II and 121 (14.6%) patients in stage III of the disease. Only six cases were classified as stage IV and their lung function indices were not statistically different from those in stage III, so they were included in stage III for this analysis.

Analysis of variance revealed that, after taking into account age, height and sex, disease stage was a significant ($p<0.01$) predictor for all PFT indices except the FEV_1/FVC and the ratio of residual volume and total lung capacity (RV/TLC), and $FEF_{25-75\%}$. Smoking variables were only related to the $D_{L,CO}$. The most frequent PFT abnormalities in all patients were reduced $C_{L,st}$ (27.8%) and reduced $D_{L,CO}$ (25.7%) (Table 2).

Table 2.

Only 58 of the 830 patients with sarcoidosis had a low TLC (the classic pattern of restriction). In this restrictive group of patients $D_{L,CO}$ and $C_{L,st}$ were reduced in 81% and 72.4% of cases respectively, at least one abnormal finding being observed in 88% of these patients. Another 33 patients had a reduced FVC but a normal TLC (a non-specific pattern). Of the 772 patients with normal lung volumes, figure 2 shows those with a low $D_{L,CO}$ and/or a low $C_{L,st}$. The distributions of $D_{L,CO}$ and $C_{L,st}$ results in the 772 patients are presented in figure 3, showing a shift towards abnormally low values.

Airflow obstruction (FEV_1/FVC below the LLN) was detected in 97 patients (11.7%). Using ATS/ERS guidelines to grade severity, [24] obstruction was mild (FEV_1 >70% predicted) in the majority (77), moderate in 15, and severe in 4 patients. The mean duration of smoking in 153 current smokers and 201 former smokers was 9.0 years.

In the 772 patients with a TLC within normal limits, $C_{L,st}$ identified more subjects with abnormal lung compliance than $D_{L,CO}$ (0.245 (189/772) *vs* 0.215 (166/772), but the difference (0.03, CI 0.072, -0.012) was not significant (χ^2 test). The detailed distribution of patients with different types of lung function disturbances according to stage of the disease is presented in table 3 (figures are in online depository).

Table 3.

We compared patient characteristics of those with normal $D_{L,CO}$ and normal $C_{L,st}$ (n=476) versus those with abnormal $D_{L,CO}$ and/or abnormal $C_{L,st}$, irrespective of a restrictive ventilatory defect. A reduced $C_{L,st}$ was more frequently observed in females and in older patients (Table 4). Ever-smokers with more pack-years of smoking were more likely than other patients to have a low $C_{L,st}$ and low $D_{L,CO}$.

Table 4.

DISCUSSION

The lung function measurements in this large group of patients with pulmonary sarcoidosis revealed that only 7% presented with restriction of lung volumes, despite parenchymal involvement visible on the chest radiograph in about three-fourths of these patients (stages II, III, and IV). Previous investigators have also reported normal lung volumes in the majority of patients with stage I or II sarcoidosis [15,25]. The cause of a

restrictive ventilatory defect in sarcoidosis patients may be more complex and should consider also respiratory muscle weakness [26].

$D_{L,CO}$ and $C_{L,st}$ tests were much more sensitive than lung volumes in detecting functional disturbances in sarcoidosis. This corroborates findings in previous smaller studies [1,16,27-29]. When only hilar lymphadenopathy is seen on the chest x-ray (stage I sarcoidosis), parenchymal involvement is present in some patients and is often noted on high resolution lung CT scans [30]. This may explain the low $D_{L,CO}$ and $C_{L,st}$ in our patients with stage I sarcoidosis (low $D_{L,CO}$ in 13% and a low $C_{L,st}$ in 17% of our patients). In previous studies,a reduced $C_{L,st}$ was frequently observed in ILD patients with reduced lung volumes [31-35]. However, only in one study was lung compliance measured in patients with ILD but normal lung volumes [36]. In our study $C_{L,st}$ was abnormally low in 72.4% of patients with lung volume restriction (TLC < LLN). The proportion of abnormal findings of $D_{L,CO}$ and $C_{L,st}$ correlated well with the clinical staging of the disease (Table 2), underlining that these indices reflect clinically relevant disease related lung damage.

$D_{L,CO}$, a measure of gas transfer in the lungs, is highly dependent on pulmonary vascular blood volume. So a low $D_{L,CO}$ usually suggests alveolitis or vasculitis in sarcoidosis patients [37,38]. Other causes of a low transfer factor (like emphysema or marked uneven ventilation distribution) cannot explain the findings in our patients. On the other hand, a low $C_{L,st}$ may not be solely due to parenchymal pathology. Fibrotic changes or infiltrates in the airway walls may stiffen the bronchi, which act as a supporting frame for lung tissue; thus pathological changes in small airways may contribute to apparent lung stiffness.

Patients with both a low $C_{L,st}$ and low $D_{L,CO}$ were more likely to have airway obstruction, perhaps because of more widespread disease involving both parenchyma and airways. They were also more likely to be ever-smokers with more pack-years of smoking (table 4). ANOVA revealed no relation between PFT results and smoking status (including ever-never smokers as categorical predictor and packyears as continuous predictor). Differences were found between ever-smokers and never-smokers and were statistically significant, but only for TLC and $D_{L,CO}$; however, they were too small to be clinically important. Interestingly, lung function indices attributed to airway obstruction (which are expected to be affected by smoking) were comparable between ever and never smokers (see table in online depository). This observation is in agreement with some data suggesting that smoking may even play a protective role in sarcoidosis [39,40].

$C_{L,st}$ was most frequently reduced in women (35.9 % *vs* 20.7%). This finding is independent of the choice of reference equations; using those from Begin *et al*. [41] the prevalence was 36.4% and 28.5%, respectively. Older patients were also more likely than younger patients to have a low $C_{L,st}$, perhaps because longstanding disease causes more fibrosis.

Airway obstruction is more common in sarcoidosis when compared to other interstitial lung diseases. About 6% of our patients in stage I and 13-16% of those in stages II and III had a low FEV_1/FVC, however statistical analysis (ANOVA) did not confirm the relationship between this index and stage of the disease. These rates are lower than reported by others, perhaps because of differences in the definition of airway obstruction [42,43]. Judged from a low $FEF_{25-75\%}$, as was done in previous studies, airways obstruction was about twice as prevalent as when using FEV_1/FVC. However, current ATS/ERS guidelines for the interpretation of PFTs discourage using $FEF_{25-75\%}$ to define airway obstruction [24]. Moreover, the physiological meaning of a low $FEF_{25-75\%}$ in sarcoidosis patients is unclear.

Other studies may have used FEV_1/FVC below 0.70 to define airway obstruction, but this causes considerable misclassification [24,44].

Study Limitations.

This is a retrospective, cross-sectional analysis based on the group of sarcoidosis patients seen in the lab during a 4 years period. The required number of cases to demonstrate significant differences was not established before. The numbers of cases in each group and proportion of them reflects the actual distribution of patients in our lab and hospital.

Ideally statistical analyses would have made use of matched controls; however, this was not at all feasible for this study, hence reference values were used. Reference values for the various PFTs which we performed do not come from a single source and therefore relate to different samples of healthy subjects. Therefore, the predicted values and LLNs from each of these studies may have caused some misclassification for abnormality rates in our patients. Predicted values for $C_{L,st}$ are poorly established and our techniques may not have exactly matched those used by the reference study. We chose Colebatch's predicted values because they were based on the highest number of healthy subjects (83 males, 40 females) and included information about the scatter of the results (SD). However, our findings on lung compliance are to a minor extent influenced by such a choice. Using prediction equations from Begin *et al.* [41] (based on only 40 healthy men and 26 healthy women), somewhat higher percentages of an abnormally low $C_{L,st}$ were obtained in all groups. Additional reference values for $C_{L,st}$ based on an even higher number of subjects were recently published [45], but they were limited to males and did not include variance data and could therefore not be used in our study. If the true lower limit of the normal range for $C_{L,st}$ was lower for our patients (or the true LLN for TLC was higher), then we have over-estimated the number of abnormal (lowered) $C_{L,st}$ measurements.

The use of specific static lung compliance (*e.g.* $C_{L,st}$/FRC) has the potential advantage that it can be regarded as a parameter of lung mechanics that is independent of lung volumes. However, only very limited data on reference values are available. Moreover the great majority of patients had normal lung volumes, so adjusting for lung volume would have had limited impact on results.

We used "quasistatic" expiratory pressure-volume curves to assess static lung compliance (slow expiration from TLC level, without interruptions forced by a shutter). It may lead to underestimating $C_{L,st}$ in patients with increased airway resistance, particularly if airflow is not very low [19]. However, airway obstruction with increased airway resistance (>0.35 kPa/(L/s)) occurred in only 8 cases (<1% of the group), and expiratory flow during measurements was low (0.3 L/s). Moreover, our comparative studies in some patients showed good agreement between semistatic and static lung compliance (see online data supplement).

This was a cross-sectional study of patients in various stages of the disease. Some patients may have had above average PFT values before the onset of disease and despite having lost lung function, the test results may have remained within normal limits. Measurement of change in lung function over a prolonged period would be more sensitive in such cases.

We believe that lung function assessment in sarcoidosis patients should include static lung compliance measurement as a method of evaluation of mechanical properties of the lungs, as it discloses abnormalities in pulmonary function that are not detected by measurement of lung volumes and gas transfer. Static lung compliance and $D_{L,CO}$ concern

different aspects of respiratory pathophysiology, and they complement rather than overlap each other in revealing lung function disturbances in all stages of the disease. The functional abnormalities are likely to reflect parenchymal involvement and correlate well with clinical staging, but further studies are needed to assess the prognostic value of a low static lung compliance in patients with sarcoidosis.

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TABLES

Table 1. Characteristics of patients with sarcoidosis stratified by disease stage.

	Stage I	Stage II	Stage III	*significance (p-value)*
n =	223	486	121	
Sex (F/M ratio)	45.7%	45.9%	51.2%	0.54
Age (years)	39.1	40.1	43.7	0.001
range (95% CI)	(24; 64)	(24; 63)	(24; 63)	
smoking status				
active:	13.5%	21.6%	14.9%	0.001
ex:	18.4%	25.1%	31.4%	
never:	68.2%	53.3%	53.7%	
Ever-smokers	n = 71	n = 227	n = 56	
median pack-years	4.5	6.0	7.5	0.01
range (95% CI)	0.2; 20.0	0.5; 45.0	0.5; 40.0	

Table 2. Spirometry, plethysmography (TLC and RV/TLC), $D_{L,CO}$, and $C_{L,st}$ results from all 830 patients with sarcoidosis, stratified by disease stage. Values are expressed as mean and 95% confidence interval of percent predicted or standardized residuals (SR), and as percent of patients with abnormal results.

	stage I	**stage II**	**stage III**
n=	223	486	121
FVC %pred.	102.7 (73.9; 127.5)	98.0 (72.7; 122.2)	90.2 (56.2; 112.4)
SR	0.22 (-1.88; 2.30)	-0.15 (-2.25; 1.71)	-0.78 (-3.42; 0.98)
% with low FVC	4.0	8.2	19.8
FEV_1 %pred.	100.8 (71.4; 128.3)	95.4 (64.3; 120.9)	88.2 (50.8; 113.9)
SR	0.07 (-2.21; 2.46)	-0.38 (-2.89; 1.78)	-1.0 (-4.11; 1.09)
% with low FEV_1	8.1	15.8	25.6
FEV_1/FVC %	80.5 (70.3; 91.0)	79.6 (63.8; 92.7)	79.5 (64.7;94.1)
SR	-0.32 (-2.34; 1.26)	-0.44 (-2.95; 1.55)	-0.37 (-2.82; 1.97)
% with obstruction	6.3	13.2	15.7
$FEF_{25-75\%}$ %pred.	87.9 (40.8; 137.6)	81.8 (32.5; 138.9)	74.0 (27.5; 137.3)
SR	-0.50 (-2.48; 1.78)	-0.72 (-2.64; 1.79)	-1.02 (-2.99; 1.69)
% of reduced $FEF_{2575\%}$	13.5	23.0	28.9
TLC %pred.	107.2 (82.4; 134.2)	103.7 (77.7; 129.7)	97.1 (62.3; 121.3)
SR	0.62 (-1.7; 2.97)	0.31 (-2.14; 2.57)	-0.30 (-3.01; 1.77)
% with low TLC	2.7	5.3	21.5
VC %pred.	111.8 (84.1; 144.5)	107.0 (78.5; 138.7)	100.0 (60.6; 128.2)
SR	0.92 (-1.50; 3.30)	0.52 (-2.12; 2.81)	-0.08 (-2.81; 1.94)
% with low VC	1.8	3.9	15.7
RV/TLC %pred.	92.0 (57.3; 124.0)	95.9 (64.3; 130.8)	98.4 (63.9; 142.0)
SR	-0.40 (-2.13; 1.37)	-0.21 (-2.00; 1.66)	-0.1 (-2.19; 2.19)
% with high RV/TLC	1.3	2.9	5.8
$D_{L,CO}$ %pred.	92.4 (69.9; 118.4)	87.1 (59.4; 113.5)	77.9 (42.4; 105.7)
SR	-0.60 (-2.42; 1.41)	-0.97 (-3.13; 1.12)	-1.63 (-4.03; 0.51)
% with low $D_{L;CO}$	13.0	26.7	44.6
$C_{,;st}$ %pred.	77.6 (42.7; 127.6)	69.6 (34.8; 110.0)	62.4 (17.6; 112.4)
SR	-0.88 (-2.35; 0.97)	-1.19 (-2.69; 0.35)	-1.50 (-3.23; 0.45)
% with low $C_{L;st}$	17.0	29.2	42.1
$C_{L,st}$ % pred.	*86.1 (53.0; 126.9)*	*77.9 (41.5; 116.9)*	*70.5 (24.9; 119.6)*
SR	*-0.73 (-2.79; 1.47)*	*-1.15 (-3.25; 0.88)*	*-1.55 (-3.79; 1.07)*
% with low $C_{L;st}$	*21.5*	*33.5*	*46.3*

The last row of the table represents results using reference values from Begin *et al.* [41]

Table 3 – Prevalence of abnormal lung compliance, gas transfer or both in patients in whom the TLC was within normal limits. Numbers in brackets are percentages of (columns) and [rows]

Condition	Stage I	Stage II	Stage III	Total
Normal $C_{L,st}$ and $D_{L,CO}$	158 (72.8) [33.7]	267 (58.0) [56.9]	44 (46.3) [9.4]	469 [100]
Low $C_{L,st}$	31 (14.3) [22.6]	85 (18.5) [62.0]	21 (22.1) [15.3]	137 [100]
Low $D_{L,CO}$	23 (10.6) [20.2]	70 (15.2) [61.4]	21 (22.1) [18.4]	114 [100]
Low $C_{L,st}$ and $D_{L,CO}$	5 (2.3) [9.6]	38 (8.3) [73.8]	9 (9.5) [17.3]	52 [100]
Total	217 (100)	460 (100)	95 (100)	772 (100) [100]

Table 4. Characteristics of 830 patients with sarcoidosis, stratified by $D_{L,CO}$ and $C_{L,st}$ abnormality; standard deviation of mean in brackets.

group / variable	Normal C_{Lst} & normal $D_{L,CO}$	Low $C_{L,st}$	Low $D_{L,CO}$	Low $C_{L,st}$ & low $D_{L,CO}$
n =	476	141	123	90
% cases in stages I/II/III	33.8/56.5/9.7	23.4/61.7/14.9	19.5/61.0/19.5	5.6/66.7/33.3
% female	41.6	68.1	40.7	47.8
age (years)	38.2 (9.5)	48.0 (11.1)	35.9 (8.5)	45.7 (12.9)
weight (kg)	79.8 (15.5)	75.6 (13.6)	77.2 (16.1)	74.6 (14.8)
height (cm)	172.0 (9.3)	163.2 (8.8)	174.6 (9.3)	167.3 (11.0)
ever smokers	40.7%	35.5%	54.5%	47.8%
Pack-years*	7.5 (8.1)	9.6 (9.9)	8.6 (9.0)	15.7 (18.0)
FVC % pred	103.9 (11.3)	95.2 (12.4)	93.4 (10.8)	78.4 (12.2)
VC % pred	112.3 (13.9)	108.2 (17.2)	100.9 (12.9)	87.5 (15.7)
TLC % pred	108.4 (11.8)	102.1 (11.7)	99.7 (12.9)	86.2 (14.1)
RV/TLC % pred	92.9 (16.1)	98.1 (16.2)	95.4 (20.0)	103.1 (20.6)
FEV_1/FVC %abs % abnormal	80.0 (6.4) 11.1%	79.6 (6.7) 7.8%	80.2 (7.2) 12.2%	78.6 (8.2) 20.0%
$FEF_{25-75\%}$ % pred % abnormal	88.1 (25.6) 14.9%	78.8 (29.1) 22.7%	81.6 (25.6) 23.6%	63.4 (31.1) 50.0%

* for ever smokers only;

FIGURE LEGENDS

Figure 1. An example of a set of five pressure-volume curves in a patient with sarcoidosis and restriction of lung volumes. The slopes of the tangent lines on the expiratory limbs of the curves represent static lung compliance. The dashed line represents the expected normal $C_{L,st}$ (3.62 liters per kPa). His lung compliance was very low.

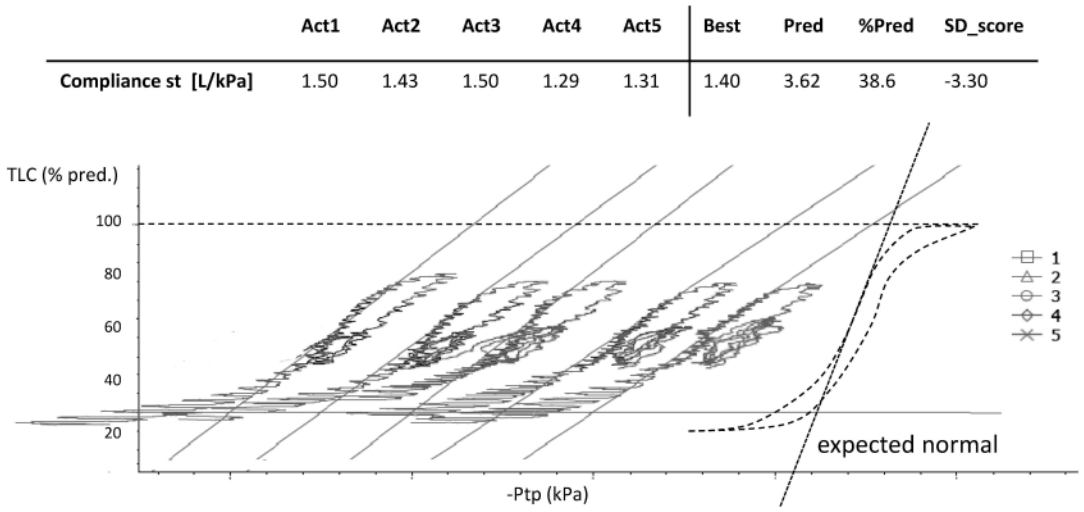
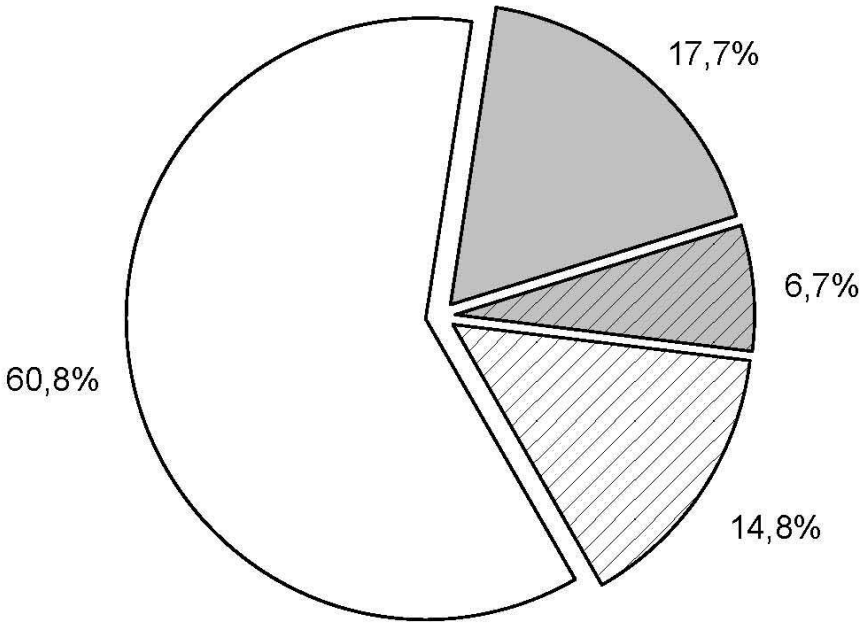
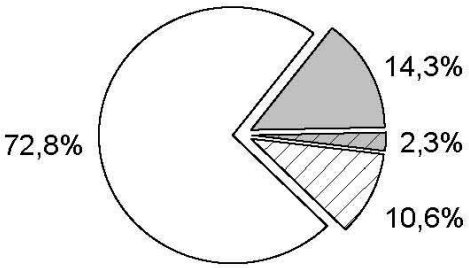


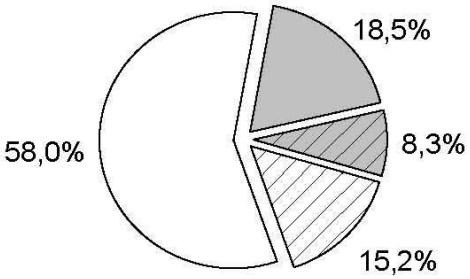
Figure 2. Distribution of abnormally low $C_{L,st}$ and abnormally low $D_{L,CO}$ in 772 patients without restriction of lung volumes in all subjects, and in groups stratified by the stage of sarcoidosis.



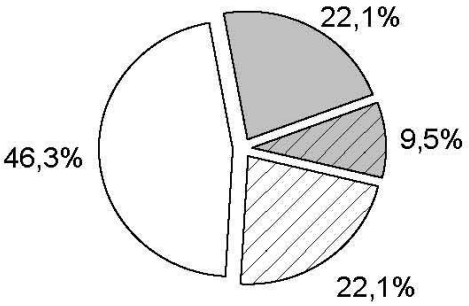
all non restrictive (n=772)



stage I (n = 217)



stage II (n = 460)



stage III (n = 95)

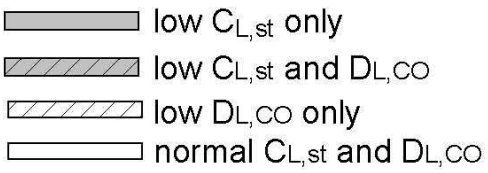
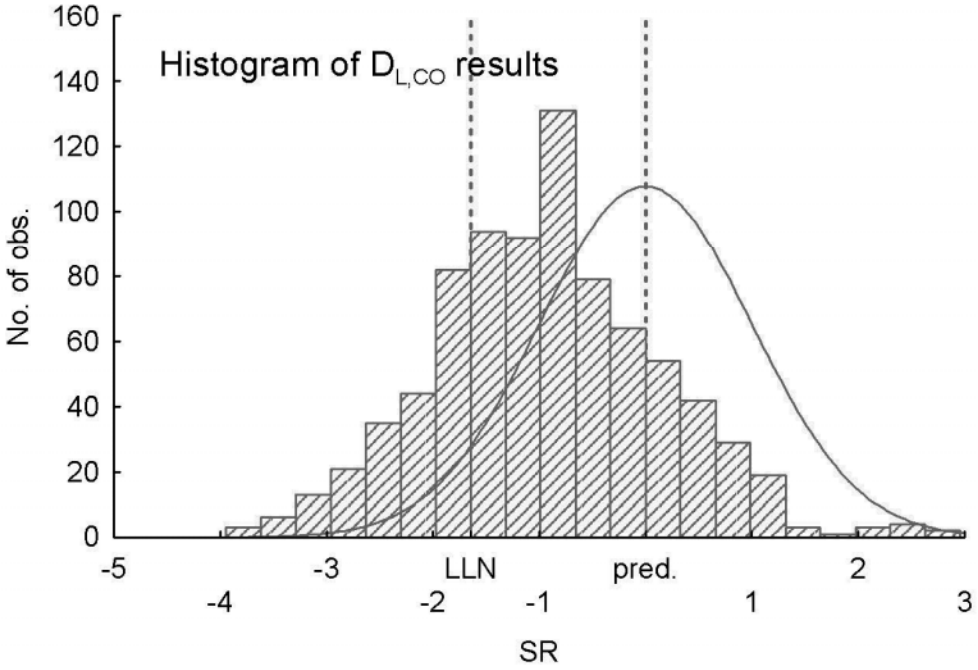
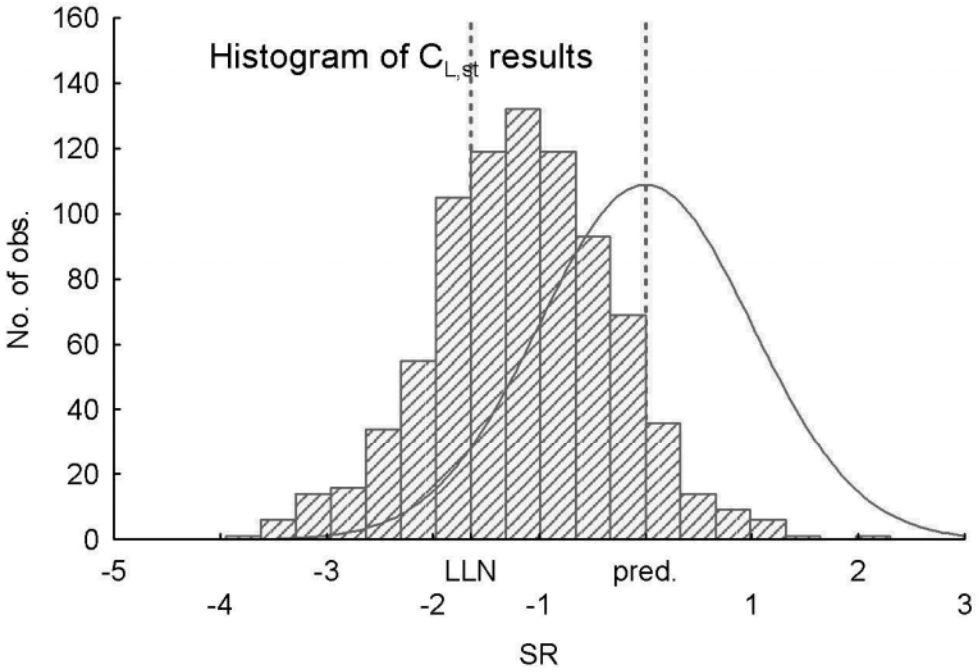


Figure 3. Distribution of $D_{L,CO}$ (upper part) and static lung compliance (lower part) in 772 patients with sarcoidosis but normal lung volumes. The horizontal axis represents the number of standard deviations from the predicted value (SR: standardized residual). The dashed vertical lines show the predicted value and lower limit of normal (LLN) based on SR. The bell-shaped curve shows the expected normal distribution for healthy adults.


Histogram of $D_{L,CO}$ results
No. of obs.
160
140
120
100
80
60
40
20
0
-5
-4
-3
-2
LLN
-1
pred.
1
2
3
SR


Histogram of $C_{L,st}$ results
No. of obs.
160
140
120
100
80
60
40
20
0
-5
-4
-3
-2
LLN
-1
pred.
1
2
3
SR