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Pulmonary function in childhood connective tissue diseases

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ABSTRACT: The term connective tissue diseases (CTD) defines a group of illnesses characterized by the presence of immune abnormalities and by widespread inflammation involving various organs and tissues including the lung. These diseases are not frequent in the paediatric age group. Very few data on pulmonary function are available in paediatric CTD.

We investigated possible early lung function abnormalities and any likely relationship with clinical activity of the disease in a group of 81 paediatric CTD patients, without clinical or radiological evidence of pulmonary involvement. Measurement of lung volumes and diffusion lung capacity were performed. A sample of 65 subjects, defined as normal on the basis of history and clinical examination, and matched by age and height with the group of patients, was chosen as control group.

CTD patients did not show significant deviations from the control distribution with respect to functional residual capacity (FRC) and maximal expiratory flow at 75% of the forced vital capacity (MEF_{75}) values. On the contrary, both vital capacity (VC) and diffusing capacity of the lungs for carbon monoxide (DLCO) were quite impaired in most CTD during the active phase of the disease.

Our results show a functional lung impairment in most children with clinically active CTD, even in absence of abnormalities on chest X-ray pictures. *Eur Respir J., 1992, 5, 733–738.*

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The term connective tissue diseases (CTD) defines a group of illnesses with immune abnormalities and widespread inflammation involving different organs and tissues. Interstitial lung injury, although with different frequency and severity, represents one of the most common features of CTD and is supposed to be secondary to a common pathogenetic mechanism [1–3]. In adults the frequency of the reported abnormalities is variable in the different studies, principally depending on the diagnostic tools: from 5% using radiographic evaluation [4] up to 30–40%, when functional respiratory impairment is considered [5, 6]. Respiratory function studies in adult patients with CTD are numerous [5, 7–13], whilst there are few in a paediatric population [14–16], where these diseases are less frequent.

In childhood CTD, lung involvement is almost never clinically apparent in juvenile rheumatoid arthritis (JRA), rare in juvenile dermatomyositis (JDM), but more common in systemic lupus erythematosus (SLE), especially in overlap syndrome (OS) [17].

To check possible early lung function abnormalities and any likely relationship with clinical activity of the disease, we studied respiratory function parameters in a group of paediatric patients with CTD and without clinical or radiological evidence of pulmonary involvement.

Methods

Among the 81 patients selected on the basis of clinical criteria, only 62 were capable of carrying out at least part of the respiratory function tests according to our protocol, and entered the study.

Of these 62 patients (age range 5–18 yrs, height range 118–170 cm), 34 fulfilled the criteria for the diagnosis of JRA [18], and had been categorized with regard to the form at the onset according to the criteria of the JRA Criteria Subcommittee of the American Rheumatism Association (ARA) [18]: 11 patients presented a systemic form, 7 a seronegative polyarticular form and 16 a pauciarticular form. Fifteen patients satisfied the revised ARA criteria for the classification of SLE [19].

In seven patients a diagnosis of JDM was made according to the criteria of BOHAN *et al.* [20]. Six cases who showed clinical features of more than one of the CTD were categorized as having an overlap syndrome (OS). All of the CTD patients were divided, according to clinical and laboratory parameters, into active disease and remission; in particular, in JRA and JDM patients the disease activity was assessed as described previously [21, 22]; the "lupus activity criteria count" (LACC) was used to estimate disease activity in SLE patients [23]. All patients had a

complete clinical examination before undergoing the respiratory function tests. None of them presented abnormalities on chest X-ray pictures. The main features of the patients are summarized in table 1.

Measurements of lung volumes were taken using a water-sealed spirometer and He-analyser (Jaeger, Wuerzburg, West Germany): functional residual capacity (FRC) and residual volume (RV) were obtained by means of the dilution technique by helium; the best of two vital capacity (VC) manoeuvres and the best of three forced vital capacity (FVC) expiratory curves were registered; forced expiratory volume in one second (FEV_1), maximum medium expiratory flow (MMEF), maximum expiratory flow at 75% of the FVC (MEF_{75}) and total lung capacity (TLC) were calculated. Diffusion capacity of the lung for carbon monoxide (DLCO) was then determined using the single-breath method (Diffusion-test Jaeger, Wuerzburg, West Germany). In seventeen of the 62 patients undergoing the study (12 JRA, 1 SLE, 3 OS, 1 JDM) DLCO measurement was unreliable.

Table 1. – Main features of the 62 patients

	Sex		Age	Disease duration	A	R	SY	PO	PA
	M	F	yrs	yrs					
JRA	15	19	12 (5–20)	5.4 (0.7–16.7)	23	11	12	7	15
SLE	1	14	15 (8–20)	2.7 (0.3–12.7)	11	4			
OS	3	3	16 (8–23)	2.4 (0.6–4.2)	6	-			
JDM	-	7	9 (8–13)	7.3 (1.8–12.6)	5	2			

The table shows the number of males (M) and females (F), of patients with active disease (A) and remission (R), of JRA patients classified into systemic (SY), polyarticular (PO) and pauciarticular (PA) forms. Mean and range (in brackets) are given for age and disease duration. JRA: juvenile rheumatoid arthritis; SLE: systemic lupus erythematosus; OS: overlap syndrome; JDM: juvenile dermatomyositis.

A sample of 65 subjects, defined as normal on the basis of history and clinical examination and matched by age and height with the group of patients, was chosen as a control group and underwent the same protocol. Forty four of these children (age range 7–18 yrs, height range 127–179 cm) were found to be reliable in performing pulmonary function test and their data analysed.

None of the patients and normal subjects was admittedly a smoker. Informed consent was obtained from both children and parents.

In order to obtain reference values, a preliminary study was carried out on the control sample. A logarithmic transformation was applied to the variates to normalize their distributions and a stepwise multiple regression analysis was performed on the eight functional variables using age, height and weight as independent variables. In all but the case of DLCO, height was the first variable to enter into the analysis, and it explained most of the variability of the dependent variables. For DLCO, body surface area (BSA= $\sqrt{height \cdot weight/3600}$) turned out to be the best independent variable in linear regression, as suggested by other authors [24].

Individual deviations (residuals) from the regression lines of table 2 were then used as pulmonary variables, corrected either for stature or body surface area. The analysis of these residuals showed that they were normally distributed: the standard deviation of the distributions is also shown in table 2. All distributions were then standardized to normal N(0.1), in order to render them more easily comparable. These are the distributions against which the individual values of the patients were tested after they had been log-transformed, the deviations from the regression-lines of the normal subjects had been computed and then standardized.

Because of the high degree of association between some of the spirometric variables, both in the control and in the affected samples, they could be grouped into three main clusters, namely VC-FEV_1, FRC-RV, MMEF-MEF_{75}, TLC being highly associated with the first four variables. The study was, therefore, limited

Table 2. – Regression lines and unexplained standard deviations (SD) of the control sample

					SD
VC ml	ln(VC)	=	5.1751 + 0.01855	× H	0.125
FRC ml	ln(FRC)	=	4.7797 + 0.1811	× H	0.216
RV ml	ln(RV)	=	4.1129 + 0.01731	× H	0.416
TLC ml	ln(TLC)	=	5.4990 + 0.01811	× H	0.141
FEV_1 ml	ln(FEV_1)	=	4.9802 + 0.01905	× H	0.132
MMEF $ml \cdot s^{-1}$	ln(MMEF)	=	5.2303 + 0.01885	× H	0.236
MEF_{75} $ml \cdot s^{-1}$	ln(MEF_{75})	=	3.7858 + 0.02430	× H	0.378
DLCO $ml \cdot min^{-1} \cdot mmHg^{-1}$	ln(DLCO)	=	1.6654 + 1.02402	× BSA	0.127

H: height in cm; BSA: body surface area in mq; VC: vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in one second; MMEF: maximal mid-expiratory flow; MEF_{75}: maximal expiratory flow at 75% forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide.

to the most informative variables, *i.e.* VC, FRC and MEF_{75}, along with DLCO. All statistical analyses have been performed irrespective of sex, since no significant differences were found between sexes. Mann-Whitney (MW) U-test was applied to test the difference between patient and control group and one-tailed binomial probabilities were computed to compare observed and expected proportions. Significance levels have been corrected according to Sidak' multiplicative inequality: type 1 error rate is obtained applying the correction $a' = 1-(1-a)^{1/11}$, "a" being the experiment-wise error rate and 11 the number of subgroups since no remission cases were found among OS patients [25].

Statistical Package for the Social Sciences (SPSS)/PC+ statistical package was used to perform the statistical analysis.

Results

The sample of normal individuals examined in the present work is substantially consistent, as far as the relationship between the spirometric variables and height is concerned, with data in the literature [26], in particular those of COLOMBO *et al.* [27] obtained on a sample of Italian subjects of comparable age. For DLCO the only available equation for the paediatric population, drawn out of a large sample representative of the general population, is reported in the paper by PAOLETTI *et al.* [28]; however, the comparison with our data has not been carried out since BSA was not considered in their paper. However, we observed that DLCO values of our normal group (25.7±6.46 $ml \cdot mmHg^{-1} \cdot min^{-1}$) were set within the normal range calculated in that study (29.2±9.99 $ml \cdot mmHg^{-1} \cdot min^{-1}$). The normal individuals have thus been taken as a satisfactory control sample to test the pulmonary function of the affected individuals.

None of the CTD groups showed significant deviations from the control distributions with respect to FRC and MEF_{75} values. On the contrary, both VC and DLCO were quite impaired in most CTD subgroups with active disease.

Figure 1 shows the dispersion of VC individual values (corrected for height and standardized) in JRA, SLE, OS and JDM patients, divided according to the activity of the disease into active disease (A) and remission (R). Most of the individual values were negative; in particular, about 70% of JRA and SLE patients, and all OS and JDM patients were below the expected values. For most diseases the Mann-Whitney non-parametric test showed a decreased mean VC value in patients with active disease, the significance level of the one-tailed test (MW) is indicated in figure 1. It should also be noted that in several groups with active disease a much higher than expected percentage of individuals is in the 2.5% left tail of the distribution of residuals obtained with the controls, as shown by the significance of the binomial test (BIN) (fig. 1). Conversely, all patients in remission were within the 95% area of the distribution.

The results obtained for DLCO are shown in figure 2. Most JRA patients (81%) with active disease were below the expected values, while all SLE, OS and JDM patients had negative values, irrespective of disease activity. DLCO was found to be significantly lower with respect to controls in patients with active systemic JRA, SLE, OS or JDM (fig. 2). Moreover, among patients with active disease, a significant proportion of systemic JRA (4 out of 5), SLE (8 out of 10), OS (2 out of 3), and JDM (2 out of 4)

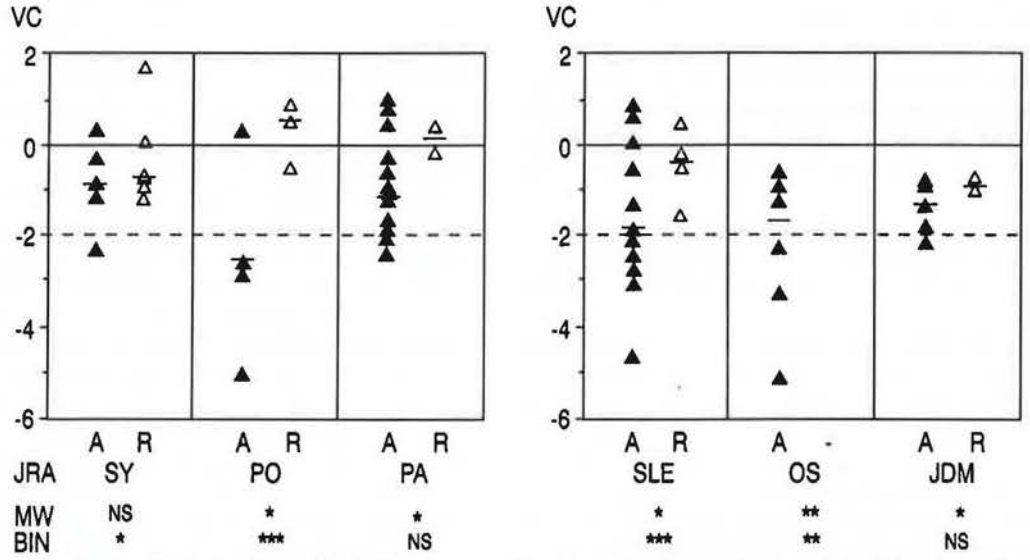

Fig. 1. – Dispersion of VC individual values (triangles) and mean values for each subgroup (horizontal bars) in JRA patients, classified into systemic (SY), polyarticular (PO) and pauciarticular (PA) forms, SLE, OS and JDM patients. Each disease entity is divided according to the presence of active disease (A) (solid triangles) or remission (R) (open triangles). VC values are deviations from the values expected according to the equation of table 2. MW: Mann-Whitney test; BIN: binomial test; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; NS: nonsignificant; SLE: systemic lupus erythematosus; OS: overlap syndrome; JDM: juvenile dermatomyositis; VC: vital capacity; JRA: juvenile rheumatoid arthritis.

patients showed a strong reduction of DLCO, being in the 2.5% left tail of the corresponding control distribution. It should be stressed that when JRA patients were considered as a whole, statistical significance was not generally reached for functional parameters, even in the active phase of the disease. No significant association of the variables, either with age at onset or disease duration, was found.

Our results showed that pulmonary function tests in children in all CTD groups during disease remission did not significantly differ from normal controls. Conversely, different lung function defects were observed during active disease.

Neither large nor small airway obstruction was ever detected. The presence of small airway obstruction in adult CTD and particularly in rheumatoid arthritis is

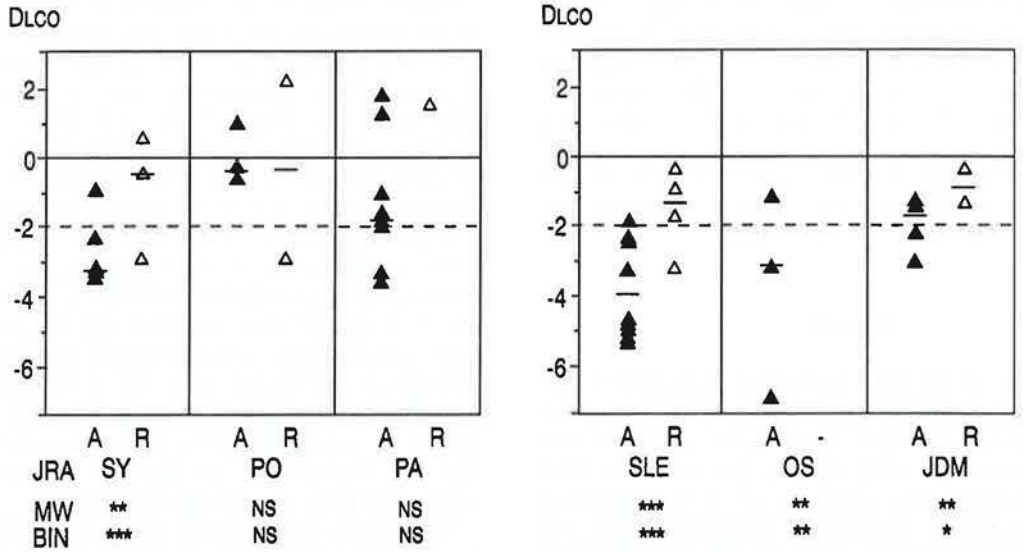

Fig. 2. – Dispersion of DLCO individual values (triangles) and mean values of subgroups (horizontal bars), in JRA patients, classified into systemic (SY), polyarticular (PO) and pauciarticular (PA) forms, SLE, OS and JDM patients. Each disease entity is divided according to the presence of active disease (A) (solid triangles) or remission (R) (open triangles). DLCO values are deviations from values expected according to the equation of table 2. MW: Mann-Whitney test; BIN: binomial test; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; NS: nonsignificant; DLCO diffusing capacity of the lung for carbon monoxide. For further abbreviations see legend to figure 1.

Discussion

There are very few studies on pulmonary function in childhood CTD [14, 15, 29, 30]; in addition, they are based on small samples and are not easily comparable. This could depend on several factors: a relatively low frequency of such diseases in childhood; the difficulty for children to carry out function tests; the insufficient reference values of some parameters; and problems arising from statistical analysis of the results.

A quarter of our selected patients was unable to carry out the tests correctly and this proportion was even higher for the DLCO test, mainly due to their young age.

As far as the reference values are concerned, adult regression equations are based on large population samples, whilst data for children are based on small samples unrepresentative of the general population, particularily for DLCO [26]. All of these problems stress the need for proper statistical analysis. Our control group was represented by clinically normal subjects, matched by age and height and admitted to the hospital for minor surgery. Since this sample was not, however, representative of the general population and not so large for the difficult selection of reliable subjects, we chose a statistical analysis that allowed us to interpret data very cautiously.

debated [3, 6, 9, 13]. In fact, SASSOON *et al.* [9] did not find significant alterations, and attributed those detected by previous authors to factors not related to the underlying disease, such as current or past smoking habit, use of unsuitable criteria for detecting abnormal values, or unreliable measurement of forced expiratory flows at low pulmonary volumes. On the contrary, VITALI *et al.* [3] in a subsequent paper, confirmed the presence of small airway obstruction, having considered all of these points.

The evaluation of pulmonary function tests in the different CTD groups showed that VC and DLCO were impaired in most patients with active disease.

JRA patients taken as a whole did not present, even in the active phase, significant alterations of any functional parameter. However, when the single JRA subtypes were analysed a significant reduction of VC in the polyarticular, and to a lesser degree in the pauciarticular form, and a significant impairment of DLCO in the systemic form were found. The first abnormality, in the absence of FRC and DLCO alterations that exclude an increased parenchymal stiffness caused by interstitial damage, might be mostly ascribed to chest joint involvement and to the subsequent reduction of the intercostal and/or accessory muscles mobilization; a similar picture has previously been documented for ankylosing spondylitis [12]. On the contrary, the impairment of DLCO in the systemic form

seems to support a prevalent interstitial lung damage, which might be explained by the presence of a diffuse vascular or parenchymal lung involvement related to the systemic nature of the inflammatory process. In a previous study on JRA patients WAGENER *et al.* [15] found the presence of pulmonary function abnormalities in 62% of cases; the most impaired tests were DLCO and MEF_{75}. The main difference between our study and that of WAGENER *et al.* [15] is that we could not detect any alteration of MEF_{75} in our JRA patients. This discrepancy seems not to be due to late-onset small airway obstruction, since WAGENER *et al.* [15] did not find a correlation between pulmonary function and time since diagnosis.

DLCO tests were also abnormal in patients with JDM and particularly in those with OS (who also showed a significant impairment of VC), thus suggesting the presence of an early interstitial lung involvement. However, the reliable cases are only six for JDM and three for OS and, thus, definitive conclusions are not possible. Similar data for paediatric [29, 30], as well as for adult patients [10], have been reported in the literature. It should be noted, however, that clinical lung involvement is one of the most relevant features of childhood OS and that, although rare, interstitial pneumonia or fibrosis may occur in JDM [17].

Finally, in our SLE patients we found a significant alteration of VC and particularly of DLCO. In a previous study DE JONGSTE *et al.* [14] reported similar findings in children with SLE.

The findings of a remarkable defect of the DLCO test in our children with SLE is also in agreement with functional studies performed in adults patients [3]. Moreover, dysfunction of the diaphragm and other respiratory muscles, as well as interstitial pulmonary fibrosis, have been reported in adult SLE [31–34].

In conclusion, our results show the presence of functional lung abnormalities in most children with CTD in the active phase of the disease, even in the absence of abnormalities on chest X-ray pictures, stressing the need for performing functional tests for early detection of pulmonary involvement.

References

1. Walport MJ. – Respiration and connective tissue diseases. *Br Med J,* 1987; 294: 392–393.
2. Hunninghake GW, Fauci AS. – Pulmonary involvement in the collagen vascular diseases. *Am Rev Respir Dis,* 1979; 119: 471–503.
3. Vitali C, Viegi G, Tassoni S, Tavoni A, Paoletti P, Bibolotti E, Ferri C, Bombardieri S. – Lung function abnormalities in different connective tissue diseases. *Clin Rheumatol,* 1986; 5: 181–188.
4. Walker WC, Wright V. – Diffuse interstitial pulmonary fibrosis and rheumatoid arthritis. *Ann Rheum Dis,* 1969; 28: 252–258.
5. Frank ST, Weg JG, Harklerad LE, Fitch RF. – Pulmonary dysfunction in rheumatoid disease. *Chest,* 1973; 63: 27–34.
6. Popper MS, Bogdonoff ML, Hugues RL. – Interstitial rheumatoid lung disease: a reassessment and review of the literature. *Chest,*1972; 62: 243–249.
7. Shwarz MI, Matthay R, Sahn SA, Standford RE, Marmostein BL, Scheinhorm DJ. – Interstitial lung disease in polymyositis and dermatomyositis: analysis of six cases and review of the literature. *Medicine (Baltimore),* 1976; 55: 89–104.
8. Segal I, Fink G, Machtey I, Gura V, Spitzer SA. – Pulmonary function abnormalities in Sjogren's syndrome and the sicca complex. *Thorax,* 1981; 36: 286–289.
9. Sassoon CSH, McAlpine SW, Tashkin DP, Baydur A, Quisimoro FP, Mongan ES. – Small airways function in nonsmokers with rheumatoid arthritis. *Arthritis Rheum,* 1984; 27: 1218–1226.
10. Derderian SS, Tellis CJ, Abbrecht PH, Welton RC, Rajagopal KP. – Pulmonary involvement in mixed connective tissue disease. *Chest,* 1985; 88: 45–48.
11. Ploysongsang Y, Foad BSI. – Lung function test in connective tissue diseases associated with Raynaud's phenomenon. *Respiration,* 1984; 46: 222–230.
12. Vanderschueren D, Decramer M, Van Den Daele P, Dequeker J. – Pulmonary function and maximal transrespiratory pressures in ankylosing spondylitis. *Ann Rheum Dis,* 1989; 48: 632–635.
13. Hyland RH, Gordon DA, Broder I. – A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. *J Rheumatol,* 1983; 10: 395–405.
14. De Jongste JC, Neijens HJ, Duiverman EJ, Bogaard JM, Kerrebijn KF. – Respiratory tract disease in systemic lupus erythematosus. *Arch Dis Child,* 1986; 61: 478–483.
15. Wagener JS, Taussig LM, De Benedetti C, Lemen RJ, Loughlin GN. – Pulmonary function in juvenile rheumatoid arthritis. *J Pediatr,* 1981; 99: 108–110.
16. Lovell D, Lindley C, Langston C. – Lymphoid interstitial pneumonia in juvenile rheumatoid arthritis. *J Pediatr,* 1984; 105: 947–950.
17. Cassidy JT, Petty RE. – *In*: Textbook of pediatric rheumatology. 2nd edn. New York, Churchill Livingstone, 1990.
18. Brewer EJ, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, Hanson V, Levinson JE, Schaller J, Sidney Stillman J. – Current proposed revision of JRA criteria. *Arthritis Rheum,* 1977; 20 (Suppl. 2): 195–199.
19. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. – The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum,* 1982; 25: 1271–1277.
20. Bohan A, Peter JB, Bowman RL, Pearson CM. – A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine,* 1977; 56: 255–286.
21. Martini A, Ravelli A, Notarangelo LD, Maccario R, Lanfranchi A, Rondena D, Ugazio AG, Burgio R. – Enhanced interleukin 1 and depressed interleukin 2 production in juvenile arthritis. *J Rheumatol,* 1986; 13: 598–603.
22. Montecucco C, Ravelli A, Caporali R, Viola S, De Gennaro F, Albani S, Martini A. – Auto-antibodies in juvenile dermatomyositis. *Clin Exp Rheumatol,* 1990; 8: 193–196.
23. Urowitz MB, Gladman DD, Tozman ECS, Goldsmith CH. – The lupus activity criteria count (LACC). *J Rheumatol,* 1984; 11: 783–787.
24. Weng Tzong-Ruey, Levison H. – Standards of pulmonary function in children. *Am Rev Respir Dis,* 1969; 99: 879–894.
25. Rohlf FJ, Sokal RR. – Statistical tables. New York, Wh. Freeman and Co., 1981.
26. Quanjer PH, Stocks J, Polgar G, Wise M, Kalberg J,

Borsboom G. – Compilation of reference values for lung function measurement in children. *Eur Respir J,* 1989; 2 (Suppl. 4): 1945–2615.
27. Colombo B, Amaducci S, Rampulla C, Mandelli V, Zappa C. – Le principali grandezze respiratorie nell'infanzia e nell'adolescenza: valori di riferimento. *Med Thor,* 1979; 1: 16–23.
28. Paoletti P, Viegi G, Pistelli G, Fazzi P, Polato R, Saetta M, Zambon R, Carli G, Giuntini C, Lebowitz M, Knudson R. – Reference equations for the single-breath diffusing capacity. A cross-sectional analysis and effect of body size and age. *Am Rev Respir Dis,* 1985; 132: 806–813.
29. Singsen BH, Bernstein BH, Kornreich HK, King KK, Hanson V. – Mixed connective tissue disease in childhood. *J Pediatr,* 1977; 90: 893–900.
30. Oetgen WJ, Boice JA, Lawless OJ. – Mixed connective tissue disease in children and adolescents. *Pediatrics,* 1981; 67: 333–337.
31. Martens J, Denedts M, Van Maenen MT, Dequeder J. – Respiratory muscle dysfunction in systemic lupus erythematosus. *Chest,* 1983; 84: 170–175.
32. Gibson GJ, Edmonds JP, Hughes GRV. – Diaphragm function and lung involvement in systemic lupus erythematosus. *Chest,* 1983; 84: 926–932.
33. Thompson PJ, Dhillon DP, Ledingham J, Turner-Warwick M. – Shrinking lungs, diaphragmatic dysfunction and systemic lupus erythematosus. *Am Rev Respir Dis,* 1985; 132: 926–928.
34. Miller LR, Greenberg P, McCarthy JW. – Lupus lung. *Chest,* 1985; 88: 265–269.