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Effect on lung function of methotrexate and non-steroid anti-inflammatory drugs in children with juvenile rheumatoid arthritis

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Abstract We evaluated lung function in a group of patients affected by juvenile rheumatoid arthritis (JRA), without clinical and/or radiological signs of respiratory involvement. We compared the effects on pulmonary function of methotrexate (MTX) therapy combined with non-steroid anti-inflammatory drugs (NSAIDs) to those of NSAIDs alone and correlated lung function to subtype onset, disease duration and disease activity. Our patients were 27 JRA children, subdivided into two groups according to the therapy (group A = 14 patients, treated with a low dose of MTX and NSAIDs; group B = 13 patients, treated with NSAIDs alone). Clinical evaluation, haematological data and pulmonary function tests (PFTs) were obtained in each group at baseline (time 0) and at 1 year (time 1). At time 0 and time 1 PFTs were altered in 51.8% of JRA patients. The restrictive pattern (reduced forced vital capacity, FVC) was the most frequent feature, observed in 22.2% of patients. In group A the mean values of FVC, FEV1 (forced expiratory flow in 1 s), FRC (functional residual capacity), TLC (total lung capacity) and DLCO (diffusing lung capacity of carbon monoxide) were significantly lower compared to those of group B, at time 0 and at time 1. No functional parameter was correlated to subtype, duration or activity of the disease. Our study confirms that abnormalities in PFTs may be detected in JRA patients, even in the absence of clinical and/or radiological signs of lung disease; MTX in combination with NSAIDs does not seem to affect lung function at 1 year more than NSAIDs alone.

Key words Juvenile rheumatoid arthritis · Methotrexate · Lung function

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Introduction

Juvenile rheumatoid arthritis (JRA) is an inflammatory joint disease, rarely associated with the involvement of internal organs [1]. The lung is in some cases a target of the disease [2]. Pneumonitis and pleuritis are the most frequent respiratory abnormalities; transient or persistent pulmonary infiltrates have also been reported, especially in systemic JRA. While respiratory function in adults with rheumatoid arthritis (RA) has been extensively investigated, few studies have been carried out in children [2–6]. One-third of RA patients who have no clinical symptoms and/or radiological findings of pulmonary involvement show abnormal pulmonary function tests [7]. The reduction in carbon monoxide diffusing capacity (DLCO) is the most frequent functional alteration, suggesting abnormalities of the alveolar-capillary interface, compatible with diffuse vascular and/or parenchymal lung disease, both in RA and in JRA [3, 7]. It is still unclear whether this pathophysiological finding is due to primary pulmonary involvement and/or to immunosuppressive therapy. Methotrexate (MTX) is the immunosuppressive drug most widely used in JRA; pulmonary toxicity associated with MTX has been reported since the late 1960s, with an incidence estimated at about 7% [8, 9]. The clinical picture is similar to that of hypersensitivity pneumonitis with subacute onset [10]; progressive pulmonary fibrosis may also occur [11].

The aims of our study were:

1) to monitor the lung function in JRA children without clinical symptoms and/or radiological signs of respiratory disease, over 12 months;
2) to compare the respiratory functional data of patients treated with MTX and NSAIDs to those treated with non-steroid anti-inflammatory drugs (NSAIDs) alone;
3) to assess the influence of subtype onset, disease duration and activity on lung function.

Table 1 Anthropometric and clinical data of JRA patients at baseline

	n	M/F	Age (years)	Height (cm)	Disease duration (months)	Disease activity (active/ inactive	Type onset pauci/poly/ syst	Haemo-globin (g/dl)
Group A	14	5/9	11.3±2.8	140.6±19.7	89.6±45.0	8/6	1/11/2	12.1±1.2
Group B	13	9/4	12.9±3.6	156.6±18.2	67.4±39.3	6/7	11/2/0	12.9±1.0

Materials and methods

Subjects

Thirty-one consecutive outpatients fulfilling the American College of Rheumatology (ACR) criteria for the diagnosis of JRA [12], were prospectively evaluated. Of these patients, only 27 (14 females, 13 males; mean age 12.1±2.4 years, range 8–20 years) were able to carry out the complete set of respiratory tests required by our protocol and entered the study.

Patients' charts were reviewed in order to assess disease duration, type of disease onset (pauciarticular, polyarticular and systemic) and drug schedule. Physical examination was performed before the patients entered the study; the extent of joint involvement was assessed using the Steinbrocker functional stage [13]. Disease activity was defined by the presence of active synovitis (joint swelling or pain with limitation of motion) in pauciarticular cases, and by increased erythrocyte sedimentation rate (ESR, Westergreen) and/or C-reactive protein (CRP) values in systemic and polyarticular cases [14].

Disease duration ranged from 6 to 144 months (mean disease duration 78 months). The disease onset was polyarticular in 12, pauciarticular in 12 and systemic in 3 patients. Fifteen patients were in stage 1, 8 in stage 2 and 4 in stage 3 according to the Steinbrocker classification. The disease was defined as active in 14 patients and inactive in 13 patients.

Patients and/or parents were asked to answer a complete respiratory questionnaire, derived from a previous paper [15], requesting information about dry or productive cough, dyspnea, cyanosis, chest pain and about their smoking habits. No patient fulfilled the diagnostic criteria for asthma, chronic bronchitis or emphysema as suggested by the American Thoracic Society [16]. All patients were non-smokers and did not complain of respiratory symptoms before starting the study. Chest X-ray was performed in all patients at baseline.

Subjects were subdivided into two groups according to the treatment regimen, chosen on clinical evaluation: Group A included 14 patients (5 boys and 9 girls, mean age 11.3±2.8 years, range 8–15 years) treated with NSAIDs (flurbiprofen 5 mg/kg per day or naproxen 15 mg/kg per day or tolmetin 20 mg/kg per day) and weekly oral low-dose MTX (10 mg/m^2) for at least 1 year (mean treatment period 2 years 3 months). The mean cumulative dose of MTX received, at baseline evaluation, was 1.610 mg (range 950 to 2.800 mg). Group B included 13 patients (9 boys and 4 girls, mean age 12.9±3.6 years, range 8–20 years) treated with NSAIDs alone (mean treatment period 5 years 9 months). Informed consent was obtained from both children and parents.

Respiratory function tests

Flow volume curves were obtained by means of a heated pneumothacograph (Fleisch no. 4) while subjects breathed room air, in a seated position, according to standard methods. The best of three determinations was used to calculate forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and maximal expiratory flow rates at 50% and 25% of FVC (V_{max50} and V_{max25}, respectively). Functional residual capacity (FRC) was determined by the helium dilution method, by means of a water-sealed spirometer (Pulmonet III Gould, Godard, Bilthoven, The Netherlands), and vital capacity (VC) was obtained to calculate total lung capacity (TLC) and residual volume (RV).

The predicted values for the above measurements were those proposed by the European Community for Coal and Steel for two patients over 18 years [19], and by Cotes et al. [20] for those under 18 years of age. No patients turned 18 during the follow-up. The single-breath carbon monoxide diffusing capacity (DLCO) was measured with a 4004 TC (Sensormedics, Menheim, Calif., USA) and the values corrected for haemoglobin concentration (DLCO) according to the formula proposed by Clark et al. [21]. The predicted values for each subject were derived from the regression equation proposed by Cotes et al. [22]. Values less than –1.64 SD were considered significantly reduced; values more than +1.64 SD were considered significantly increased. Lung function measurements, along with ESR, CRP and haemoglobin values were obtained in each group of subjects at baseline (time 0) and after 12 months (time 1).

Statistical analysis

Results are presented as means±1 SD in Table 2, and as individual absolute values in Table 3. T-test for paired samples was used to compare baseline and post-treatment functional indices within each group of subjects, and T-test for unpaired data to compare results between groups. The relationships between pulmonary function parameters and type of onset, duration and activity of the disease were assessed with univariate linear regression. Significance was established at $P<0.05$.

Results

Anthropometric, clinical and functional data for patients of group A and group B are reported in Tables 1 and 2. At baseline, the two groups were matched for age, anthropo-

Table 2 Mean values (SD) of functional respiratory parameters in groups A and B at baseline and at time 1

	Group A		Group B	
	Baseline	Time 1	Baseline	Time 1
FVC (l)	2.22±0.78	2.33±0.84*	3.35±1.24**	3.43±1.11**
FEV1 (l/s)	1.97±0.7	2.03±0.8	2.98±1.12**	2.99±1.12**
V_{max} 50% (l/s)	3±1.04	2.78±1.18	4.18±2.22	3.92±2.22
V_{max} 25% (l/s)	1.4 ±0.6	1.38±0.69	2.19±1.39	2.08±1.35
TLC (l)	3.09±0.98	3.26±1.06*	4.34±1.7	4.71±1.6*
RV (l)	0.87±0.27	0.90±0.26	0.97±0.57	1.15±0.54*
FRC (l)	1.52±0.54	1.68±0.56*	2.11±0.9	2.36±0.9*
DLCOc (ml/mmHg per min)	17.75±3.53	19.11±4.8	25.7 ±7.9	26.3 ±8.5

* $P<0.05$: time 1 vs baseline within groups
** $P<0.05$: between groups

Table 3 Individual values of FVC, FEV1, V_{max50}, V_{max25}, TLC, RV, FRC, DLCO measured at time 0

Patients	Therapy	FVC (l)	FEV1 (l)	V_{max50} (l/s)	V_{max25} (l/s)	TLC (l)	RV (l)	FRC (l)	DLCOc
1	NSAIDs	4.99	4.99	7.79[b]	6.18[b]	7.26	2.27[b]	3.98[b]	39.31
2	NSAIDs	4.23[a]	4.23	9.61[b]	3.37	6.34	1.82	3.30	24.62[a]
3	NSAIDs	6.22[b]	5.02[b]	5.25	2.74	7.91[b]	1.46	3.51	42.92[b]
4	NSAIDs	2.42	2.08	2.50	1.31	2.96[a]	0.54[a]	1.64	20.02
5	NSAIDs	3.43	3.07	3.35	1.99	4.56	1.18	2.49	24.59
6	NSAIDs	3.63[b]	3.01[b]	3.18	2.03	4.07	0.54[a]	1.44[a]	25.05
7	NSAIDs	2.50	2.12	2.44	1.13	3.08	0.85	1.91[b]	19.47
8	NSAIDs	3.73	3.04	3.63	1.43	4.40	0.67[a]	1.83[a]	33.35[b]
9	NSAIDs	2.15	1.83	2.14[a]	0.96[a]	3.17	0.99	1.47	20.44
10	NSAIDs	3.55	3.18	4.24	1.97	3.85[a]	0.3[a]	1.55[a]	22.64
11	NSAIDs	2.06	2.02	3.56	2.11[b]	2.74	0.66	1.46	16.5
12	NSAIDs	2.44	2.33	4.4[b]	2.34[b]	3.15	0.71	1.55	22.27
13	NSAIDs	2.26	1.89	2.31	0.94	2.98	0.66	1.35	23.15[b]
14	MTX/NSAIDs	1.37[a]	1.36[a]	2.54	1.67	2.21[a]	0.84	1.46	16.74
15	MTX/NSAIDs	1.05	0.82[a]	1[a]	0.51[a]	1.71	0.66[b]	0.84	14.12[b]
16	MTX/NSAIDs	1.94[b]	1.5[b]	1.39[a]	0.50[a]	2.69[b]	0.8[b]	1.18[b]	16.76[b]
17	MTX/NSAIDs	3.23[a]	2.83	4.01	1.6[a]	4.34[a]	1.11	1.98[a]	21.57
18	MTX/NSAIDs	2.92	2.71	3.97	2.40	3.88	0.96	1.82	17.5
19	MTX/NSAIDs	1.96[a]	1.68[a]	4.11	0.85	3.19[a]	1.23[b]	1.98	22.82
20	MTX/NSAIDs	2.23	1.89	2.32	1.11	2.88	0.62	1.45	15.22
21	MTX/NSAIDs	1.26[a]	1.17	2.42	0.98	1.56[a]	0.3[a]	0.48[a]	12.39
22	MTX/NSAIDs	3.26	2.77	3.24	1.93	4.67	1.41	2.31	24.41
23	MTX/NSAIDs	1.75	1.62	2.74	1.40	2.55	0.79	1.13	13.3
24	MTX/NSAIDs	1.98[a]	1.82	3.16	1.10	2.82	0.81	1.25[a]	19.54
25	MTX/NSAIDs	2.99	2.70	4.13	1.81	4.05	1.06	1.76	19.44
26	MTX/NSAIDs	1.84	1.78	2.93[b]	1.76[b]	2.63	0.79	1.28	18.07[b]
27	MTX/NSAIDs	3.30	3.04	4.14[b]	2.17	4.16	0.84	2.40	27.87

[a] Value < –1.64 SD
[b] Value > +1.64 SD

metric indices (weight and height), disease duration or activity, and haemoglobin values. Chest X-ray was normal in all patients at baseline. During the follow-up, no patient complained of respiratory symptoms suggesting the occurrence of pulmonary disease. The individual absolute values of FVC, FEV1, V_{max50}, V_{max25}, FRC, RV, TLC and DLCO, measured at baseline and at time 1, are reported in Table 3.

At baseline, 14/27 patients (51.8%) showed abnormal pulmonary function tests, taking into account the alterations in any of the pulmonary function tests (PFTs): 7 belonged to group A (50%) and 7 to group B (53.8%). In particular, the following parameters were significantly reduced: FVC in 6/27 patients (22.2%), 5 of group A (35.7%) and 1 of group B (7.7%); FEV1 in 3/27 (11.1%), all of group A (21.4%); V_{max50} in 3/27 (11.1%), 2 of group A (14.3%) and 1 of group B (7.7%); V_{max25} in 4/27 (14.8%), 3 of group A (21.4%) and 1 of group B (7.7%); FRC in 6/27 (22.2%), 3 of group A (21.4%) and 3 of group B (23.7%); and TLC in 6/27 (22.2%), 4 of group A (28.6%) and 2 of group B (23.7%). FRC was significantly increased in 3/27 (11.1%) 1 of group A (7.1%) and 2 of group B (15.4%) and TLC in 2/27 (7.4%), 1 of each group.

Nine patients (33.3%) showed abnormal values of RV: RV was reduced in 5/27 patients (18.5%), 1 of group A (7.1%) and 4 of group B (30.8%), while it was significantly increased in 4 (14.8%), 3 of group A (21.4%) and 1 of group B (7.7%). One out of 27 patients (3.7%), belonging to group B, showed significantly reduced DLCO.

At time 1, 14/27 patients (51.8%) showed altered PFTs: 7 belonged to group A (50%) and 7 to group B (53.8%). FVC was reduced in 7/27 patients (26%), 5 of group A (35.7%) and 2 of group B (15.4%); FEV1 in 5/27 (18%), 4 belonging to group A (28.6%) and 1 to group B (7.7%); V_{max50} in 8/27 (29.6%), 4 for each group (28.6% group A, 30.8% group B); V_{max25} in 7/27 (26%), 4 of group A (28.6%) and 3 of group B (23%); FRC in 2/27 (7.4%), 1 of each group (7.1% group A, 7.7% group B) and TLC in 5/27 (18%), 4 of group A (28.6%) and 1 of group B (7.7%).

FRC was significantly reduced in 4/27 (14.8%), 1 of group A (7.1%) and 3 of group B (23%) and TLC in 2/27 (7.4%), 1 of each group. Six patients (22%) showed an abnormal RV: in particular, RV was reduced in 1 patient belonging to group B (7.7%), while it was significantly increased in 5 (18%), 3 of group A (21.4%) and 2 of group B (15.4%). Only 1/27 patients (3.7%) showed significantly reduced DLCO value. Between the treatment groups, no significant difference was found in terms of V_{max50}, V_{max25}, and RV values both at baseline and at time 1. In contrast, the mean values of FVC, FEV1, FRC, TLC and DLCO of group A were significantly lower than those of group B, either at baseline or at time 1.

Within group A, FVC, TLC and FRC at time 1 were significantly increased when compared to the baseline values. Within group B, TLC, FRC and RV mean values at time 1 were significantly increased in comparison to baseline values. No functional respiratory parameters correlated sig-

Table 4 Individual values of FVC, FEV1, V_{max50}, V_{max25}, TLC, RV, FRC, DLCO measured after a year (T1)

Patients	FVC (l)	FEV1 (l)	V_{max50} (l/s)	V_{max25} (l/s)	TLC (l)	RV (l)	FRC (l)	DLCO
1	5.03	4.77	6.52	4.24[b]	7.58[b]	2.55[b]	4.32[b]	39.64
2	4.34[a]	4.32	9.66[b]	5.54[b]	6.37	1.99	3.49	37.45
3	5.63[b]	5.23	5.54	2.53	7.88	1.23	3.8[b]	40.86
4	2.41[a]	1.84[a]	1.59[a]	0.99[a]	3.51	0.90	1.91	21.68
5	3.70	2.94	3.00	1.63	4.97	1.27	2.56	25.5
6	3.84[b]	2.76	2.64[a]	1.55	4.54	0.7[a]	1.75[a]	27.46
7	2.47	2.12	2.23[a]	1.12[a]	3.34	0.87	2.04[b]	18.76
8	3.92	3.21	3.58	1.92	4.97	0.97	2.30	35.81[b]
9	2.29	1.93	2.2[a]	1[a]	3.49	1.1[b]	1.63	16.7
10	3.60	3.19	4.37	2.03	4.61[a]	0.97	2.18	21.21[a]
11	2.21	2.08	4.1[b]	1.83	3.11	0.86	1.53	17.61
12	2.78	2.57	3.27	1.81	3.75	0.91	1.90	23.22
13	2.36[b]	2.03	2.30	0.86	3.18	0.69	1.36	18.92
14	1.46[a]	1.32[a]	2.44	1.04	2.2[a]	0.74	1.30	16.65
15	1.10	0.7[a]	0.71[a]	0.37[a]	1.82	0.72[b]	1.00	9.99
16	2.14[b]	1.55	1.42[a]	0.5[a]	3.05[b]	0.9[b]	1.4[b]	16.06
17	3.29[a]	2.72[a]	3.3[a]	1.3[a]	4.54[a]	1.18	2[a]	24.37
18	2.98	2.65	3.78	2.07	4.10	1.03	2.12	24.17
19	1.87[a]	1.35[a]	1.35[a]	0.44[a]	3.41[a]	1.39[b]	2.25	20.02
20	2.17	1.88	2.62	1.06	2.79	0.62	1.37	17.44
21	1.25[a]	1.25	2.53	1.17	1.86[a]	0.58	1.07	14.28
22	3.34	2.95	3.39	2.27	5.06	1.42	2.85	23.82
23	1.96	1.84	3.00	1.74[b]	2.35	0.78	1.09	15.22
24	2.08[a]	1.94	2.76	1.35	3.00	0.91	1.70	18.19
25	3.19	2.89	4.01	2.17	4.12	0.87	1.68	25.4
26	2.01	1.81	2.35	1.42	2.71	0.70	1.35	16.63
27	3.78	3.53	5.31[b]	2.52	4.63	0.84	2.44	25.39

[a] Values < –1.64 SD
[b] Values > +1.64 SD

nificantly to the onset subtype, duration and activity of the disease, neither at baseline nor at time 1.

Discussion

Our data show that respiratory function abnormalities are present in 51.8% of JRA patients, even in the absence of clinical and/or radiological evidence of pulmonary involvement. The prevalence of lung involvement does not change over a period of 12 months. In our study, MTX does not seem to affect lung function after 1 year of weekly low-dose administration. The subtype of onset, disease duration and activity are not correlated with lung function impairment.

Pulmonary involvement, including pleurisy, parenchymal nodules, interstitial fibrosis, airways disease and, rarely, vasculitis is frequently observed in RA; reduced lung volumes, airflow limitation and impaired diffusing capacity are the most common pulmonary function abnormalities [7, 23–25]. The true prevalence of pleuro-pulmonary involvement in JRA is still unknown, ranging from 4% [2] to 62% [5]. The few available data show that pleural involvement occurs more commonly than parenchymal, and that rheumatoid pulmonary nodules and Caplan's syndrome are extremely rare in JRA. The relatively low incidence of JRA and the difficulty for children in carrying out all manoeuvres required in lung function tests may account for this lack of information. Furthermore, it should be taken into account that, due to extensive muscular and/or skeletal impairment, pulmonary function tests may not be routinely obtained in all children affected in JRA. In fact, in our study 4 out of the 31 initially selected patients (13%) were unable to complete functional evaluation due to their young age.

The total prevalence of pulmonary impairment observed in our population (51.8%) is consistent with that reported by Wagener et al. [5], who found those respiratory function abnormalities in 12/16 JRA patients (62%). In our study, the most frequently altered parameters were FVC and TLC, both reduced in 22.2% of children; RV and FRC were both reduced in 18.5% and 22.2%, and increased in 14.8% and 11.1% of patients, respectively. Unlike the previous studies [4, 5], which revealed a significant reduction of uncorrected DLCO in about 35% to 45% of JRA children, we found reduced DLCO values only in 3.7% of patients. These results may be explained by considering that our population included only out-patients, with no severe disease, and that our values are already corrected for haemoglobin levels.

Furthermore, it is still a contentious issue whether small-airways disease can develop as a specific complication of JRA. In our population, airflow reduction in the last part of expiratory flow-volume curve (V_{max50} and V_{max25}) was noted in 4 out of 27 patients (14.8%) at baseline; most

of them belonged to group A. Despite the absence of respiratory symptoms and the good course of the disease, the prevalence of these abnormalities doubled after 12 months, with equal distribution into two groups. Decreased airflows have been frequently described in adults with RA [26, 28] and in children with JRA [4] as a direct effect of peripheral airway disease or as abnormal lung recoil. The study of airway reactivity and the responsiveness to bronchodilators, as well as high-resolution computed tomography, might provide additional insights into the underlying mechanisms [29].

Methotrexate may affect the respiratory system, inducing an immunologic hypersensitivity response. Drug-induced pneumonitis, characterized by subacute onset and by systemic and respiratory symptoms (fever, cough and dyspnea), occurring 1–5 months from the beginning of therapy, is the most frequent feature [30]. Progressive pulmonary fibrosis has also been described [11]. Risk factors for the development of MTX-related pulmonary abnormalities have not been defined, although preliminary data suggest that the presence of previous lung disease may increase patient susceptibility [31]. Other risk factors include male sex, renal insufficiency and concurrent use of corticosteroids, NSAIDs and aspirin [32]. However, recent studies do not support these findings [33, 34].

The comparison of PFTs between the two treatment groups shows that FVC and FEV1 in group A were significantly lower than in group B, either at baseline or at time 1. The difference between the two groups at baseline may be explained considering that group A included mostly patients with polyarticular and systemic onset; these patients showed a greater severity of the disease and a higher disease activity – either when starting MTX treatment or at enrollment – than patients of group B. We cannot exclude the possibility that MTX treatment over 2 years before the beginning of the study could have influenced pulmonary function, although no further progression of lung disease was demonstrated in the 1-year follow-up period.

After 1 year, a significant increase of TLC, RV and FRC values was observed within group B when compared to baseline. This finding may reflect an improvement of the static volumes in these patients; a significant increase of FVC, TLC and FRC was also recorded within group A, suggesting an improvement in the assessment of the volumes also in these patients. Thus, our study, which prospectively evaluated the respiratory effects of long-term low-dose MTX therapy in JRA children failed to demonstrate any significant difference in pulmonary function within group A after 1 year of MTX treatment.

To our knowledge, only one study, by Pelucchi et al. [3], has investigated the effects of long-term low-dose MTX on pulmonary function in 61 JRA patients. Their data show that the impairment of lung function in JRA is mostly related to the clinical subtypes of the disease instead of to MTX therapy. Our results are in agreement with the conclusion of Pelucchi's group that low-dose MTX can be safely employed in JRA. However, their study does not provide a prospective evaluation of pulmonary function during MTX treatment. A previous retrospective study on morbidity associated with low-dose MTX showed that its side effect are mainly hepatic, without alteration in respiratory diffusing capacity or development of restrictive pattern [35].

References

1. Cassidy JT, Petty RE (1991) Juvenile rheumatoid arthritis. In: Textbook of pediatric rheumatology, 2nd edn. Churchill Livingstone, Tokyo, pp 113–219
2. Athreya BH, Doughty RA, Bookspan M (1980) Pulmonary manifestations of juvenile rheumatoid arthritis: a report of eight cases and review. Clin Chest Med 1:361–374
3. Pelucchi A, Lomater C, Gerloni V (1994) Lung function and diffusing capacity for carbon monoxide of patients with juvenile chronic arthritis: effect of disease activity and low dose of methotrexate therapy. Clin Exp Rheum 12:675–679
4. Cerveri I, Bruschi C, Ravelli A et al (1992) Pulmonary function in childhood connective tissue diseases. Eur Respir J 5:733–738
5. Wagener JS, Taussig LM, DeBenedetti C et al (1981) Pulmonary function in juvenile rheumatoid arthritis. J Ped 99:108–110
6. Lovell D, Lindsley C, Langston C (1984) Lymphoid interstitial pneumonia in juvenile rheumatoid arthritis. J Ped 105:947–950
7. Anaya JM, Diethelm L, Ortiz LA et al (1995) Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum 24:242–254
8. Acute Leukemia group B (1969) Acute lymphocytic leukemia in children: Maintenance therapy with methotrexate administered intermittently. JAMA 207:923–928
9. Cooper JAD Jr, White DA, Matthay RA (1986) State of the art: drug-induced pulmonary disease. Am Rev Respir Dis 133:321–340
10. Robbins KM, Gribetz I, Strauss L et al (1973) Pneumonitis in acute lymphatic leukemia during methotrexate therapy. J Pediatr 82:84–88
11. Phillips TJ, Jones DH, Baker H (1987) Pulmonary complications following methotrexate therapy. J Am Acad Dermatol 16:373–375
12. Brewer EJ, Bass J,Baum J et al Current proposed revision of JRA criteria. Arthritis Rheum 20:195–199
13. Steinbrocker O, Traeger CH, Batterman RC (1949) Therapeutic criteria in rheumatoid arthritis. JAMA 140:659–662
14. Kvien TK, Hoyeraal HM, Kass E (1982) Diagnostic criteria of rheumatoid arthritis in children. Scand J Rheumatol 11:187–191
15. Lebowitz MD, Knudson RJ, Burrows B (1975) Tucson epidemiological study of obstructive lung disease: methodology and prevalence of disease. Am J Epidemiol 102:348–356
16. American Thoracic Society (1962) Chronic bronchitis, asthma and pulmonary emphysema: a statement by the committee on diagnostic standards for non-tuberculous respiratory disease. Am Rev Respir Dis 85:762–768
17. Zapletal A, Paul T, Samanek M (1977) Die Bedeutung heutiger Lungenfunktiondiagnostik zur Feststellung einer Obstruktion der Atemwege bei Kindern und Jugendlichen. Z Erkrank Atm Org 149:343–371
18. Zapletal A, Samanek M, Paul T (1982) Upstream and total airway conductance in children and adolescents. Bull Eur Physiopathol Respir 18:31–37
19. European Community for Coal and Steel (1983) Standardization of lung function tests. Bull Eur Physiopathol Respir 19:1–95
20. Cotes JE, Dabbs JM, Hall AM et al (1979) Sitting height, fat free mass and body fat as reference variable for lung function in healthy British children: comparison with stature. Ann Hum Biol 6:307–314
21. Clark EH, Woods RL, Hughes JB (1978) Effect of blood transfusion on the carbon monoxide transfer factor in man. Clin Sci 54:627–631

22. Cotes JE, Dabbs JM, Hall AM (1973) Lung volumes, ventilatory capacity and transfer factor in healthy British boy and girl twins. Thorax 28:709–715
23. Anaya JM, Diethelm L, Ortiz LA (1995) Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum 24:242–254
24. Kelly CA (1993) Rheumatoid arthritis: classical rheumatoid lung disease. Bailliere's Clin Rheum 7:1–16
25. Kelly CA (1993) Rheumatoid arthritis: other rheumatoid lung problems. Bailliere's Clin Rheum 7:17–29
26. Mountz JD, Turner RA, Collins RL et al (1984) Rheumatoid arthritis and small airways function: effects of disease activity, smoking and α_1-antitrypsin deficiency. Arthritis Rheum 27:728–736
27. Hyland RH, Gordon DA, Broder I (1983) A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. J Rheumatol 10:395–405
28. Epler GR, Snider GL, Gaensler EA et al (1979) Bronchiolitis and bronchitis in connective tissue disease: a possible relationship to the use of penicillamine. JAMA 242:528–532
29. Du Bois RM (1994) College lecture: Diffuse lung disease. Combined clinical and laboratory studies. J Roy Coll Phys London 28:338–346
30. Zitnik RJ, Cooper AD (1990) Pulmonary disease due to antirheumatic agents. Clin Chest Med 11:139–150
31. Searles G, McKendry RJR (1987) Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. J Rheumatol 14:1164–1171
32. Kaplan RL, Waite DH (1978) Progressive interstitial lung disease from prolonged methotrexate therapy. Arch Dermatol 114:1800–1802
33. Carson CW, Cannon GW, Egger MJ et al (1987) Pulmonary disease during the treatment of rheumatoid arthritis with low-dose pulse methotrexate. Semin Arthritis Rheum 16:186–195
34. Golden MR, Katz RS, Balk RA et al (1995) The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. J Rheumatol 22:1043–1047
35. Graham DL, Myones BL, Rivas Chacon RF et al (1992) Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediat 120:468–473