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Pulmonary function in adolescents with childhood asthma

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The aim of this study was to determine the pulmonary function in former and present asthmatics. We examined 77 persons aged 12–24 years, classified into four groups: 1) healthy subjects (controls) ($n = 19$), 2) former asthmatics ($n = 19$), 3) present mild asthmatics ($n = 20$), and 4) present severe asthmatics ($n = 19$). Although exhibiting no respiratory symptoms, former asthmatics had reduced airflow values measured by FEV_1 (median (range) 89.7 (83–99) vs 101.4 (91–110)) and MEF_{25} (76.5 (68–94) vs 103.0 (97–124)), as compared with controls. Furthermore, former asthmatics had significantly increased PEF variability, as compared with controls, whereas no significant differences were found in static lung parameters, i.e. total lung capacity and residual volume, as compared with controls. In conclusion, former asthmatics, although now exhibiting no respiratory symptoms, were found to have obstructive airflow limitation, increased bronchial responsiveness, and normal lung volumes.

Clinical aspects

We found that persons from an outpatient clinic with former asthma in childhood, although now exhibiting no respiratory symptoms, showed signs of persisting obstructive airflow limitation and increased bronchial responsiveness. This airflow limitation might be due to present subclinical asthma, a supposition supported by the demonstrated increase in bronchial responsiveness. However, it might also be an expression of lung fibrosis, a supposition supported by the demonstrated irreversibility in lung function after β_2-agonist treatment. These findings lead to the following clinical questions regarding the treatment of former and present asthmatics. Would former asthmatics benefit from treatment with appropriate antiasthmatic medication, i.e. steroids, in order to normalize their pulmonary function and would this treatment minimize the risk of developing irreversible lung damage or recurrence of asthma in adulthood? Have former asthmatics suffered from earlier undertreatment and therefore developed lung fibrosis already? In the latter case, antiasthmatic medication would be without effect.

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Bronchial asthma is found in 2.4–12% of children and adolescents, and its frequency seems to have increased during the last decade (9, 19, 3, 4).

Cross-sectional studies of both children and adults with current symptoms of asthma have consistently showed signs of reduced lung function (6, 12, 14, 16–18), but few investigations deal with pulmonary function in young, asymptomatic adults who have had childhood asthma. Cade & Pain (8) showed that the presence of obstructive airflow limitation and normal static lung volumes may be the rule rather than the exception during remission of asthma. These findings agree with other studies, although there is some discrepancy concerning static lung volumes (6, 7, 15, 16). Furthermore, earlier investigations have shown a correlation between increased bronchial responsiveness and an accelerated decline in lung function independent of the presence of clinical symptoms of asthma (3, 5, 6, 25). Thus, our knowledge of lung function level, bronchial responsiveness, and the correlation between these two factors in adolescents with childhood asthma is limited.

Bronchial asthma is clinically defined as attacks of dyspnea, prolonged expiration with audible wheezing, and respiratory symptoms being relieved after β_2-agonist treatment. Furthermore, all affected patients had symptoms after the age of 5 years. Bronchial hyperresponsiveness is defined as in-

creased bronchial responsiveness resulting in either $PC_{20} \leq 8$ mg/ml of histamine (9), PEF variability $\geq 20\%$ (10, 13), or β_2-reversibility in $FEV_1 \geq 15\%$ (22).

The aim of this study was to determine the static and dynamic pulmonary function in adolescents with former and with persistent asthma.

Material and methods

All patients with former and present bronchial asthma had been referred to the Paediatric Department GGK at Rigshospitalet, State University Hospital, Copenhagen.

All patients with the diagnosis of asthma and birthday within the 10 years 1964–74 were selected from the archives of the pediatric allergy unit ($n = 253$, aged 12–23 years). Of the 253 patients, 224 (89%) were interviewed by telephone about their present respiratory symptoms. The remaining patients could not be found. Of the 224 patients interviewed, only 29 (13%) claimed neither to have any symptoms of bronchial asthma nor to have taken any antiasthmatic medication during the last 2 years or more. Of these 29 persons, 10 (35%) were not able to participate: two were living abroad; four were planning to go abroad; and four did not wish to participate – one refused because he did not want to be reminded of his earlier illness, another refused because of preoccupation with anorexia, and the other two did not explain their refusal.

The remaining 19 patients completed the investigation trial and were included in *group 2*: former asthmatics. Thus, the number of persons in each group was determined by the maximum obtainable number of persons in group 2.

Group 3 comprised mild asthmatics selected in random, successive order from the original group of 224 patients. Twenty-two persons with occasional asthmatic symptoms were selected, but two persons did not complete the investigation trial and were excluded. All showed considerable improvement in asthmatic symptoms since they had earlier had daily asthmatic symptoms and daily need of antiasthmatic medication, but they now had symptoms of asthma weekly, monthly, or in the pollen season, and their use of antiasthmatic medication was considerably reduced.

Group 4 comprised severe asthmatics also selected in random, successive order from the original group of 224 patients. Twenty-one patients with daily asthmatic symptoms were selected, but two did not complete the investigation trial and were excluded. Ten were taking inhaled steroids regularly, and all showed either $\geq 20\%$ daily variation in PEF or $\geq 15\%$ increase in FEV_1 after β_2-agonist inhalation.

Group 1 comprised the normal control group selected from an earlier investigation of bronchial hyperresponsiveness in a random population performed 2 years before this study (2). Nineteen healthy persons were selected. They were matched by age, sex, and height to the group of former asthmatics (group 2). They had never exhibited symptoms of asthma, rhinoconjunctivitis, or atopic dermatitis, and they had no family history of any of these diseases. In addition, they had shown PC_{20} values > 8 mg/ml 2 years earlier.

To summarize, the material consisted of 77 subjects divided into four different groups:

Group 1: normal control group (controls). $n = 19$, median age 16.4, range 14–27 years; 15 males, 4 females.

Group 2: former asthmatics (FA). $n = 19$, median age 17.0 years, range 13–23 years; 15 males, 4 females.

Group 3: mild asthmatics (MA). $n = 20$, median age 18.0 years, range 13–21 years; 15 males, 5 females.

Group 4: severe asthmatics (SA). $n = 19$, median age 17.7 years, range 12–23 years; 12 males, 7 females.

All 77 persons included in the study were seen twice in the outpatient clinic. At their first visit, they were interviewed about 1) age at asthma debut; 2) duration of asthma, number of attacks per day, and provoking factors of the asthmatic disease, including exercise-induced asthma; 3) number of hospitalizations; 4) antiasthmatic medication (β_2-agonist, steroid, or other); 5) family history of allergic diseases; 6) rhinitis; 7) smoking habits; and 8) recent respiratory infections. Furthermore, a skin prick test with nine common allergens (1, 11) and a complete lung function test were performed. At the second visit in the outpatient clinic, a β_2-agonist reversibility test was performed. During the 28 d between the two visits, all participants monitored their daily morning and evening PEF (Mini-Wright®), and they graded daily the intensity of their respiratory symptoms by a visual analog scale (20).

Lung function test. All lung function tests were performed between the hours of 1400 and 1700 and consisted of 1) ventilatory capacity: FEV_1 (Vitalograph®) and maximal expiratory flow at 25% of vital capacity (MEF_{25}), measured with a pneumotachograph (Vitalograph®), and 2) static lung volumes and capacities, i.e. total lung capacity (TLC), residual volume (RV), and vital capacity (VC), which were measured with a closed-circuit helium-dilution technique (Godard Bell spirometer). The diffusing capacity ($T_{L,CO}$) was measured by the single-breath technique (Morgan spirometer). All lung function

indices were measured as recommended by Quanser (22), and the lung function values were, with regard to sex and height, recorded as percentages of predicted values (% pred.) (27).

Diary card. The diary card consisted of daily recordings of PEF and respiratory symptoms (dyspnea, wheezing, and coughing) by a visual analog scale (grades 0–3). All participants kept their antiasthmatic medication unchanged during the registration period. Any other supportive antiasthmatic medication was recorded.

Reversibility test. FEV_1 was measured before and 15 min after inhalation of 7.5 mg salbutamol delivered by a nebulizing system. The change in lung function after inhalation of the bronchodilator was calculated as the percent increase of FEV_1 (21). Significant reversibility of FEV_1 was defined as $\geq 15\%$ increase or an absolute increase of ≥ 200 ml (26). All subjects refrained from smoking for 2 h before the test; furthermore, all were advised to avoid antiasthmatic medication, as recommended by Cockcroft et al. (9). Inhalation of steroids was continued if used.

This study was approved by the local ethics committee, and informed consent was obtained from all participating subjects and from their parents if subjects were under the age of 18.

Calculations and statistics

The variability of PEF was measured by means of the differences between the highest and the lowest values during 28 d of registration divided by the highest PEF value (10). Variability of $\geq 20\%$ was defined as significant variability (13). The Spearman rank correlation test (r_s) was used for correlation analysis. The differences in lung function between groups were analyzed by the Mann-Whitney rank test, and the Jonckheere-Terpstra test was used to analyze the trend in symptom scores. Fisher's exact test was used to analyze differences in the number of respiratory symptoms between groups.

Results

Minor differences were found in comparing the three groups of asthmatic patients ($n = 29$, $n = 22$, $n = 21$) and the group of unexamined asthmatics, i.e. those interviewed but not examined in the outpatient clinic ($n = 224 - 72 = 152$). The duration of asthma was significantly shorter in FA, and the number of hospitalizations was approximately doubled in SA (Table 1).

Within the groups good agreement was found between the interview concerning asthmatic symptoms (Table 2), the total of asthmatic symptom score registration (Table 3), and the consumption of antiasthmatic medication (Table 4). Four persons with former asthma now had occasional cough; however, no difference was found in the frequency of occasional cough between FA ($n = 4$) and controls ($n = 0$) ($P = 0.1$, Table 2). In each group, from five to six

Table 1. Information from case records of median age, first appearance of asthma, duration of asthma, and hospitalization in former asthmatics (FA), mild asthmatics (MA), severe asthmatics (SA), and the unexamined asthmatic group

	FA Group 2 $n=19$	MA Group 3 $n=20$	SA Group 4 $n=19$	Not selected asthmatics $n=152$
Age (median)	18	18	19	18 years
(range)	(14–22)	(13–21)	(14–24)	(13–25)
Asthma debut before 5 years	68%	75%	79%	67%
Asthma duration (median)	9*	16	14	15 years
(range)	(4–16)	(12–21)	(8–22)	(7–24)
Hospitalized u.d. **asthma	53%	45%	89%	50%
Death from asthma	0	0	0	0

* $P<0.001$ compared to all the other groups.
** Under diagnosis.

Table 2. Results of questionnaire regarding respiratory symptoms in groups 1, 2, 3, and 4

	Controls Group 1 $n=19$		FA Group 2 $n=19$		MA Group 3 $n=20$		SA Group 4 $n=19$	
	Before	Now	Before	Now	Before	Now	Before	Now
Asthmatic symptoms:								
Never	–	19	0	19	0	0	0	0
Rare	–	0	5	0	6	8	1	3
Frequent	–	0	6	0	7	12	14	16
Dyspnea	–	0	19	0	18	18	18	19
Wheezing	–	0	19	0	20	18	19	18
Cough	–	0	10	4*	12	5	12	8
Rhinitis	–	0	9	7	9	19	10	14

Before: according to hospital journal.
Now: according to present interview.
* $P=0.1$, as compared with controls without cough.

Table 3. Cumulative lung symptom score (diary card) recording dyspnea, cough, wheezing, and results of the skin prick test in groups 1, 2, 3, and 4

	Controls Group 1 $n=19$	FA Group 2 $n=19$	MA Group 3 $n=20$	SA Group 4 $n=19$
Symptom score	0	0.1	7.8	21
(range)	(0–0)	(0–26)	(0–81)	(8–87)
Positive skin prick test	0	16	19	15

$P<0.0001$: Jonckheere-Terpstra test (increasing score from group 1 to group 4).
P: NS: group 1 vs group 2 (Mann-Whitney).

Table 4. Use of antiasthmatic medication in groups 2, 3, and 4

	FA Group 2 $n=19$		MA Group 3 $n=20$		SA Group 4 $n=19$	
	Before	Now	Before	Now	Before	Now
β_2-agonist	16	0	18	10	17	8
Steroids	3	0	5	2*	9	10
Others	-**	0	-**	1	-**	1

Before: according to hospital journal.
Now: according to present interview.
* Seasonal use of steroids.
** Insufficient information.

persons smoked, except for the SA, in which only two persons smoked.

No difference was found in the number of asthmatics in groups 2, 3, and 4 with positive skin prick test, and the controls still had negative skin prick test (Table 3).

The impairment of the patients' lung function increased with the severity of their asthmatic symptoms. The FA group had no asthmatic symptoms, but did show a significantly reduced FEV_1 % pred. ($P<0.05$), Tiffenau index = FEV_1/VC % pred. ($P<0.05$), MEF_{25} % pred. ($P<0.01$), and increased PEF variability ($P<0.05$), as compared with controls (Table 5). However, FA patients were indistinguishable from MA patients by all these airflow parameters except possibly MEF_{25}, which was not measured in MA (Table 5).

Table 5. Median values and (95% confidence interval) of FEV_1, VC, Tiffenau index, MEF_{25} in percentage of predicted value (% pred.), and PEF variability in groups 1, 2, 3, and 4

	Controls Group 1 $n=19$	FA Group 2 $n=19$	MA Group 3 $n=20$	SA Group 4 $n=19$
FEV_1 % pred.	101.4 (91–110)	89.7 (83–99)	89.6 (80–93)	84.5 (70–91)
VC % pred.	100.7 (89–110)	99.9 (90–103)	92.2 (85–98)	93.3 (83–101)
Tiff. % pred.	104.0 (97–106)	93.7 (88–106)	96.6 (87–103)	87.9 (76–99)
PEF variability	12.6 (4–26)	20.2 (6–32)	23.1 (11–39)	35.2 (11–44)
MEF_{25} % pred.	103.0 (97–124)	76.5 (68–94)	-	-
P values:				
	2 vs 1	3 vs 1	4 vs 1	2 vs 3
FEV_1	$P<0.05$	$P<0.001$	$P<0.001$	NS
VC	NS	NS	NS	NS
Tiff.	$P<0.05$	$P<0.05$	$P<0.005$	NS
PEF variability	$P<0.05$	$P<0.01$	$P<0.01$	NS
MEF_{25}	$P<0.01$	-	-	-

Table 6. Median values and (95% confidence interval) of TLC, FRC, RV, and diffusion capacity (DIFF) in percentage of predicted value (% pred.) in groups 1, 2, 3, and 4

	Controls Group 1 $n=19$	FA Group 2 $n=19$	MA Group 3 $n=20$	SA Group 4 $n=19$
TLC % pred.	102.4 (89–113)	99.5 (89–107)	94.2 (87–102)	103.9 (90–110)
FRC % pred.	102.3 (88–118)	105.8 (90–119)	98.4 (89–107)	108.9 (103–130)
RV % pred.	106.4 (90–126)	115.5 (88–136)	120.1 (86–131)	138.5 (115–177)
DIFF % pred.	129.7 (111–144)	132.7 (120–146)	136.9 (129–147)	132.1 (125–140)
P values:				
	2 vs 1	3 vs 1	4 vs 1	2 vs 3
TLC	NS	NS	NS	NS
FRC	NS	NS	$P=0.08$	NS
RV	NS	NS	$P<0.05$	NS
DIFF	NS	NS	NS	NS

Static lung parameters, i.e. TLC, FRC, RV, and VC, were within the normal range in all four groups except for RV, which was significantly higher in SA than in controls (Table 6). The diffusion capacity $T_{L,CO}$ was within normal range in all groups (Table 6).

No significant differences were shown in the increase of FEV_1 after inhalation of β_2-agonist in FA, as compared with controls and MA (Table 7). However, the increase of FEV_1 in FA was found to be between the increase in FEV_1 in MA and controls. Compared with controls, those with asthma (MA and SA) were found to have a significantly increased FEV_1 to bronchodilator inhalation (SA: $P<0.001$; MA: $P<0.05$).

Table 7. Bronchial response to inhaled β_2-agonist, reported as the percent increase in FEV_1 following bronchodilator (95% confidence interval)

	Controls Group 1 $n=19$	FA Group 2 $n=19$	MA Group 3 $n=20$	SA Group 4 $n=19$
Increase of FEV_1 following ventolin	2.0% (0–5)	4.5% (2–8)	5.5% (3–12)	11.0% (4–22)
P values:				
	2 vs 1	3 vs 1	4 vs 1	2 vs 3
FEV_1 %-ventolin	$P=0.09$	$P<0.05$	$P<0.001$	NS

Discussion

Our study showed that subjects with a history of asthma in childhood who had no clinical symptoms of asthma for at least 2 years (range 2–15 years) showed decreased dynamic lung function to the same degree as patients with mild asthmatic symptoms. Four subjects reported approximately yearly episodes with cough. However, these four subjects were not significantly different from the remaining former asthmatics in dynamic lung function and β_2-agonist reversibility, and we therefore assumed that their cough was not asthmatic.

Our findings differ from those of Martin et al. (18). They showed that children who ceased wheezing in adolescence were indistinguishable from healthy controls in lung function, whereas persons who had persistent but infrequent wheezing in early adult life had minor abnormalities in lung function. However, our findings are supported by those of Cade & Pain (8), who showed persistent abnormalities in forced expiratory flow indices and ventilation distribution in former asthmatic patients. Our results could also agree with those of Jones & Jones (15) and Blackhall (4), who all found that the lung function of former asthmatics normalized with time. These findings are beyond the conclusions to be drawn in this study.

Although we were unable to demonstrate any relation between the duration of the symptom-free period and the degree of abnormalities in lung function, long-term investigations in our group will make it possible to verify this hypothesis. Yet, despite difficulties in comparing these studies because of differences in selection criteria and definition of asthma, it seems that persons with a history of childhood asthma still have signs of airflow obstruction, as their FEV_1, MEF_{25}, and FEV_1/VC-index are reduced years after their clinical symptoms have vanished. Furthermore, former asthmatics showed signs of increased bronchial reactivity, as they showed increased PEF variability. We found no correlation between smoking and reduced lung function (data not shown); thus, it seems that the reduced lung function was caused by former or present subclinical asthma and not by smoking. The numbers of patients with positive skin prick test were equal in the three groups of asthmatics. Likewise, the numbers of positive skin reactions in each patient were equal among the groups (data not shown).

In our study, patients with former asthma were found to have static lung volumes within normal range (27), and these were similar to the findings in the controls and the MA. The only significant difference regarding static lung parameters was found in SA, who had increased RV, as compared with controls, a finding which could be expected.

The bronchial response to inhaled β_2-agonist in FA was found to be between the bronchial response of MA and that of controls, but it did not increase their lung function to values within normal range. This might reflect acute airway obstruction caused partly by mucosal inflammation and partly by muscle contraction in the bronchial tree. This would agree with an increased degree of bronchial responsiveness as shown by the increased PEF variability. However, we were unable to demonstrate a relation between increased PEF variability and β_2-agonist reversibility in each subject. The PEF variation was of minor clinical importance, and the reduced lung function might reflect chronic injuries such as pulmonary fibrosis caused by chronic airway obstruction, which in turn was probably due to earlier undertreatment. Whether optimal bronchodilator therapy affects the rate of growth and development of lung function among asymptomatic asthmatics is still unclear (8).

As the material in this study was selected from an outpatient clinic and not from general practitioners, the implication of these results for the clinician is that laboratory measurements are essential for the assessment of the functional status of the asthmatic patient regardless of symptoms. Clinical assessment based only on symptoms can be misleading and may underestimate the severity of pulmonary dysfunction. Furthermore, if treatment is directed solely towards relieving symptoms without considering functional abnormalities, many patients with few or no symptoms could remain undertreated. Whether asymptomatic patients with a history of childhood asthma would benefit from antiasthmatic medication must be a subject for further investigation. Our results indicate that at least some former asthmatics who have more pronounced signs of airflow limitation and increased bronchial responsiveness might benefit from antiasthmatic therapy.

We conclude that although the questionnaire concerning childhood asthma in this study is retrospective and could be biased by preferential recall of childhood events, our observations are compatible with the hypothesis that childhood asthma represents an important risk factor for persistent impaired lung function, i.e. obstructive airflow limitation and increased bronchial responsiveness. We do not know whether the obstruction is reversible, and further investigations are needed to determine whether these abnormalities disappear spontaneously with time. If not, it is important to determine whether normalization of lung function may be brought about or accelerated by appropriate steroid treatment.

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