Lung function in the aging Swedish cystic fibrosis population

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Summary
Swedish Cystic Fibrosis (CF) care follows international guidelines in general. The only difference in our CF care package since 25 years is the physiotherapy regimen. Airway clearance therapy has since the early 1980s, from the day of diagnosis, been based upon daily physical exercise in conjunction with techniques for transporting and evacuating mucus. Postural Drainage ± percussion and vibration has not been used in any age. The aim of this study was to evaluate our CF care package.

Lung function data from the start of the study and with a 3-year interval were collected in the entire Swedish CF population ≥7 years old. Data were analysed for the age groups 7–17 and ≥18 years of age. Change of lung function over the study period was calculated. The impact of chronic Pseudomonas aeruginosa (Pa) colonisation and basal FEV1%p was also evaluated in a linear mixed model.

Data from 99% of the country-wide CF population were available at inclusion. Mean FEV1%p was 90 ± 21 vs 73 ± 26 in the different age groups and mean VC%p was 94 ± 18 vs 91 ± 20. Forty
Introduction

Patients with Cystic Fibrosis (CF) is an aging population. This is the result of the development within many areas of the CF care regimen and that patients are being referred to centralised CF centre care as soon as possible. CF is a multi-organ system disease that requires qualified care by a multi-disciplinary team. In spite of this development, CF is still a progressive, lethal disease. Reports show continuous annual deterioration of lung function and progressive lung disease accounts for more than 90% of the deaths in CF. CF is not yet screened for in Sweden. In 2002 the median age of diagnosis was reported to be 9 months. A previous study describes the frequency of DF508 among CF alleles in Sweden to be 68%, 47% of the patients are homozygous and 41% heterozygous. The DF508 frequency in our population is similar to that in other European countries, where the DF508 frequency is reported to 51%. Centralised CF care has been the situation in Sweden since the beginning of the 1980s, and the care is organised into four CF centres where 97% of all diagnosed CF patients are seen. Swedish CF care follows the European standards of care for patients with CF, which directs at all components of the disease.

The cornerstones of treatment are active nutritional support, aggressive antibiotic therapy, psycho-social support and physiotherapy. The physiotherapy includes inhalation therapy, airway clearance therapy (ACT) and physical exercise. The ACT aim is described as to compensate for the impaired mucociliary transport, and a number of different techniques are nowadays available. One of the most often used techniques in the world, especially among pre-school children, is still the Postural Drainage ± percussion and vibration. This technique has not at all been used in Sweden since 1983, an effect of the results from the long-term study by Andreasson et al. Instead, the airway clearance therapy based upon daily physical exercise has replaced the Postural Drainage ± percussion and vibration, in all ages. This technique is based upon immediate physiological effects from moderate intense physical handling/activity/exercise on lung volumes and respiratory patterns, in order to loosen and mobilize secretions. The physical exercise is carried out in conjunction with techniques for transporting and evacuating mucus from the airways. The primary aim of this treatment regimen is to avoid hypoxia by maintaining all parts of the lungs aerated and possible to ventilate.

Recent discussions have emphasised the importance of evaluating therapy in long-term studies (more than 1 year observation period) where basic treatment is deemed to be optimal. End-points or expected outcomes must be stable lung function and physical status or a decrease in the rate of decline of lung function. The aim of this study was to evaluate the CF care package used since 25 years in Sweden.

Material and methods

This study was based on longitudinal individual data that were collected and prospectively evaluated to calculate the lung function evolution during a 3-year period in the whole Swedish CF population. The study was approved by the local research ethics committees at the University Hospitals in Göteborg, Lund, Stockholm and Uppsala. All individuals with CF ≥ 7 years old who had performed an annual expanded lung function control at least once during the 3-year period at one of the four Swedish CF centres during the study period were included. Information was collected on Pancreatic insufficiency (PI), Body Mass Index (BMI) and chronic Pseudomonas aeruginosa (Pa) colonisation defined as positive sputum cultures on at least two consecutive sputum samples within six months. Chronic Pa colonisation is expressed as Pa+ and not chronically colonised as Pa−. Patients who were lung or heart/lung transplanted prior to the study start were excluded.

Lung function data

Individual Forced Expiratory Volume in 1 s (FEV1) and Vital Capacity (VC) were collected at the 1st and the 3rd year of the study. The individual lung function data were collected from the mandatory annual expanded lung function tests at the Swedish CF centres. The annual expanded lung function tests are always carried out with patients in a stable condition, essentially at the same time of the year for each individual. The lung function test technique is well known to them since simple spirometries are carried out at each out-patient clinic from early age and the annual expanded tests have been carried out since the end of the 1970s. All annual lung function measurements are always performed in a body plethysmograph box by certified laboratory technicians, according to standardised procedures at each centre’s accredited Department of Clinical Physiology. FEV1 and VC were used as end-points. FEV1 and VC are expressed as percentage of predicted normal values (%p), obtained from Solymar et al. for patients 7–17 years old and from Quanjer et al. for patients ≥ 18 years old. For those individuals who passed the age of 18 years during the study period, the predicted values from Solymar et al were used for the calculations at the end of the study. Stratification was made due to chronic P. aeruginosa (Pa) colonisation and basal FEV1%p.

Statistical analysis

Mean ± SD and median (range) FEV1%p and VC%p when entering the study was summarised for the two age groups 7–17 (young) and ≥ 18 years old (adult), and selectively for percent of the adult group was ≥ 30 years old. Overall, 41% were chronically Pa colonised. Mean annual FEV1%p rate of decline was 0.77 and 0.64 in the different age groups.

Lung function among Swedish CF patients is good and annual rate of decline low, even in an old cohort. The large proportion of adult patients emphasises future demands on CF care.
the ≥30 year olds. Lung function was also summarised separately for the Pa+ and Pa− groups.

Mean annual rate of change in FEV1%,p and VC%p were calculated for the two age groups. The mean annual rate of change was calculated for the Pa+ and Pa− groups, divided into <80% (subnormal) or ≥80% (maintained) FEV1%,p when entering the study. In some of the calculations, patients ≥30 years old were selected for additional analyses.

Continuous data are presented as mean values with standard deviation and median values with range. Categorised variables are described using frequency table. Linear mixed regression models were used for the assessment of changes in lung function over time using subjects as random variables and age, Pa status and FEV1%,p above or below 80% when entering the study as fixed variables when applicable. The calculations were performed using the mixed regression procedure in SAS (nr 8.2, SAS, Institute, Cary, NC, www.sas.com/).

Results

At the start of the study, 371 individuals fulfilling the inclusion criteria were defined. Data from two patients of the 371 were not available at all, one due to multi-handicap and the other due to his decision never to participate in the expanded annual controls. Data was supplied only the 1st year from 53 individuals (14%). Of these, four patients died during the studied period (30, 30, 32 and 43 years old) and six had lung transplantations (24, 27, 30, 33, 38 and 39 years old). The remaining 43 (12%) had not participated in the expanded annual controls. Data was supplied only the 1st year from 53 individuals (14%). Of these, four patients died during the studied period (30, 30, 32 and 43 years old) and six had lung transplantations (24, 27, 30, 33, 38 and 39 years old). The remaining 43 (12%) had not participated in the expanded annual lung function test the 3rd year due to unspecified reasons. During the studied period, data from 31 individuals were added. These individuals (age span 7–50 years) were either <7 years old or not diagnosed when the study started.

Baseline characteristics at the start of the study period for the 369 individuals divided into the two different age groups are shown in Table 1. The proportion ≥30 year olds at inclusion was 40% within the adult group. The mean lung function data for the ≥30 year olds alone was FEV1%,p 65 ± 28, median 63 (18–131) and mean VC%p was 89 ± 23, median 89 (37–140). Within the whole population studied the proportion Pa+ was 41%. The Pa− group showed a mean FEV1%,p of 84 ± 25, and the Pa+ group 74 ± 24.

The overall mean annual rate of decline of FEV1%,p was 0.77% and 0.64% within <18 and ≥18 years olds, p = 0.008, respectively, p = 0.0008. When analysing the ≥30 year olds separately, the mean annual rate of decline of FEV1%,p was 0.54%, p = 0.08.

Fig. 1a and Table 2 demonstrates that the two young groups with maintained FEV1%,p at inclusion, either Pa+ or Pa− and the Pa− with low FEV1%,p, proved to have a slow annual rate of decline. Fig. 1b and Table 2 shows that the adult group with maintained FEV1%,p and Pa− at inclusion had a slightly slower annual rate of decline. Independently of age, the two groups with subnormal FEV1%,p and Pa+ at inclusion demonstrated the fastest annual rate of decline in the study, p = 0.04, respectively, p = 0.0002 (Fig. 1a and b, Table 2).

The annual rate of change of VC%p was slightly positive for all the young subgroups (Fig. 2a and Table 3) and close to zero for the two adult groups with maintained FEV1%,p either Pa+ or Pa− at inclusion (Fig. 2b and Table 3). For the two adult groups with subnormal FEV1%,p at inclusion, either Pa+ or Pa−, the annual rate of decline of VC%p was significant, p = 0.045 and p = 0.015, respectively (Fig. 2b and Table 3). Mean annual rate of decline of VC%p for all the ≥30 year olds alone was 0.45%, p = 0.11.

Discussion

The aim of this study is to evaluate a 25-year-old CF care package aiming at preventing lung function decline, not to evaluate a rehabilitation intervention.

Data from almost the entire Swedish CF population ≥7 years old were collected. The study shows that lung

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics for the CF population (7–62 years old) when divided due to age at the start of the 3-year study period (n = 369).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7–17 years old (n = 176 (48%))</td>
</tr>
<tr>
<td>F/M (%)</td>
<td>48/52</td>
</tr>
<tr>
<td>Pancreatic insufficient (PI), %</td>
<td>94</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>18.8 ± 3.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>18.6 (13.0–30.9)</td>
</tr>
<tr>
<td>Chronically colonised with Pseudomonas aeruginosa, %</td>
<td>35</td>
</tr>
<tr>
<td>FEV1, %predicted</td>
<td>90 ± 21</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>92 (24–139)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>96 (35–145)</td>
</tr>
<tr>
<td>VC, %predicted</td>
<td>96 ± 18</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>96 (35–145)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.93 ± 0.13</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.96 (0.46–1.15)</td>
</tr>
</tbody>
</table>
function as measured by FEV1%p in the Swedish CF population is good compared to recently published reports.4,5,15–17 It is even more encouraging that the relative number of females within the older group is unchanged and that the big proportion >30 years old in our country-wide study also shows a relatively well preserved lung function. Other studies have shown mean rate of decline of FEV1%p from 1.1 to 3.9%.5,17–20 In contrast to the study of Konstan et al. in 2007 we found that patients with a maintained FEV1%p had equal or reduced rate of decline than those with a subnormal FEV1%p at inclusion.5 The present study also shows that the good VC%p at inclusion was well maintained for the whole population and that the young cohort even increased their VC%p slightly during the studied period, which was unexpected.

CF lungs are reported morphologically normal at birth.21 But, studies have shown that even clinically asymptomatic infants with CF have obstructed airways and air trapping within the first months of life.21,22 This peripheral airway obstruction decreases ventilation distribution gradually and moreover poorly aerated, plugged and hypoxic areas of the lungs may act as a source where micro-organisms such as Pa survive and grow.23,24 The permanent bacterial growth and prevailing inflammation further affects lung function and ventilation distribution, resulting in an increasing proportion of non-aerated and hypoxic parts of the lungs. Thereby a vicious circle is started.

In hypoxic parts of the lungs, a commonly used Pa antibiotic has shown to have a reduced efficacy due to the anaerobic conditions.24 This may have been the reason for the results in a study by Bosworth and Nielsen, where intravenous antibiotic courses when combined with intensified airway clearance therapy gave better results than when combined with only “routine” physiotherapy.23 Trying to maintain all parts of the lungs ventilated by the help of ACT based upon physical exercise has constituted one major aim of our physiotherapy regimen since the beginning of the 1980ies. This study confirmed to a certain extent the findings from other studies that Pa+ patients show a faster decline than the Pa−.4,26–28 Our prevalence of Pa+ turned out to be low compared to similar populations.4,16 Our preventative ACT regimen aiming to maintain all parts of the lungs ventilated could play a major role in postponing a rich environment for growth of Pa.23,24,29 The lower prevalence could partly explain the better outcome in Swedish CF patients than in corresponding CF populations. Surprisingly, our study showed that in patients with maintained FEV1%p,
Pa+ does not necessarily influence the rate of decline, which to our knowledge is not seen in any previous study. However, we do not know for how long these patients have been colonised, therefore, this study does not say whether >3 years Pa+ would affect the rate of decline or not. Another factor brought up in discussions is the importance of aging, which has been deemed to influence the FEV1%p rate of decline for individuals with CF. But our study reports that increasing age not necessarily is a confounding factor influencing the rate of decline. A previous study based on data in a national registry (Swedish Death Cause Registry), showed low death rate due to CF in Sweden (0.9%) during 1991–1999 and median age at death 26 years.1 Bias due to high mortality must be considered little during these years, but an unknown survival selection from previous decades must be considered.

It is well known that physical exercise causes immediate physiological changes in breathing pattern, lung volumes and ventilation distribution in obstructed airways.30–32 The degree of changes is dependent on the severity of airway obstruction, and is different to changes in healthy individuals. Especially the increased End Expiratory Lung Volume (EELV) and the reduced Trapped Air Index (TAI) may be of interest when discussing aerating hypoxic parts of the lungs and getting air behind sputum clogs and plugs, preparatory and in conjunction with ACT. Added to that, a decreased re-absorption of Na+ from airway epithelia during physical exercise in CF has been described.13 This may improve the sol phase defect of the airway surface liquid, which may help to loosen secretions from the mucosa. Patients report and studies have shown increased mucus expectoration after physical exercise.34–37 In our physiotherapy regimen, respiratory physiological effects of moderate intensive physical exercise are utilized as the airway clearance therapy in conjunction with assisted autogenic drainage (AAD) in all infants and toddlers, with autogenic drainage (AD) or forced expiration technique (FET) and directed coughing for children, adolescents and adults.9–11 This combination is replacing, not added to Postural Drainage±percussion and vibration which is still the most commonly used technique for infants, toddlers and preschool children in a global perspective. Alternative airway clearance techniques may be used in the more severely ill, as well as in adolescents and adults, whereas physical exercise always is added to the airway clearance therapy.9 Physical exercise programmes are not specific or standardised in the Swedish physiotherapy approach. However, there is a standardised principle that the physical exercise programmes are tailored to the capacity and interest of each individual. The programmes are build upon agreements with

<table>
<thead>
<tr>
<th>Subgroup 7–17 years</th>
<th>Annual VC%p change with age</th>
<th>95%CI</th>
<th>( p = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa− and FEV(_1) ≥ 80%p</td>
<td>+0.12%</td>
<td>−0.36 to +0.60</td>
<td>0.6309</td>
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<tr>
<td>Pa+ and FEV(_1) ≥ 80%p</td>
<td>+0.22%</td>
<td>−0.26 to +0.69</td>
<td>0.3736</td>
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<tr>
<td>Pa− and FEV(_1) &lt; 80%p</td>
<td>+0.28%</td>
<td>−0.70 to +1.26</td>
<td>0.5749</td>
</tr>
<tr>
<td>Pa+ and FEV(_1) &lt; 80%p</td>
<td>+0.68%</td>
<td>−0.49 to +1.86</td>
<td>0.2520</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Subgroup ≥18 years</th>
<th>Annual VC%p change with age</th>
<th>95%CI</th>
<th>( p = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa− and FEV(_1) ≥ 80%p</td>
<td>+0.01%</td>
<td>−0.29 to +0.31</td>
<td>0.9666</td>
</tr>
<tr>
<td>Pa+ and FEV(_1) ≥ 80%p</td>
<td>−0.02%</td>
<td>−0.38 to +0.33</td>
<td>0.8937</td>
</tr>
<tr>
<td>Pa− and FEV(_1) &lt; 80%p</td>
<td>−0.45%</td>
<td>−0.88 to −0.01</td>
<td>0.0455</td>
</tr>
<tr>
<td>Pa+ and FEV(_1) &lt; 80%p</td>
<td>−0.57%</td>
<td>−1.02 to −0.11</td>
<td>0.0147</td>
</tr>
</tbody>
</table>
the patients and involve (1) physiological cardio-respiratory aims and immediate consequences on the respiratory pattern and ventilation distribution, (2) musculoskeletal aims (posture, chest and chest wall mobility, muscle strengthening exercises and bone mass density). The programmes are frequently up-dated. With the help of this regimen included in the treatment package from the very beginning, all these aims can be achieved at the same time as the ACT, which makes the daily treatment more stimulating and time efficient for patients and families. This 25 years old regimen may have contributed to the good lung function and low rate of decline presented in this study.

There are limitations of the design in this study. The most important is the absence of a control group. This study is not an intervention study, but an evaluation of 25 years of CF care where the biggest difference from international guidelines is the physiotherapy approach. Analyses and interpretation of the results has to rely on historical data and similar populations. Without a control group it is difficult to establish the exact role of our physiotherapy regimen. One previous randomised controlled study noticed a more slow decline in lung function in the exercise group than in the control group.16 Our study is based on results from already performed annual expanded standardised lung function tests during a 3-year interval, which does not allow bias. With the help of statistical analysis the study evaluates 25 years of clinical work in the Swedish CF centres. We regard the low proportion of missing data of minor importance compared to the obvious advantage of this country-wide study containing data from almost all known Swedish CF patients, which avoids bias. Previous studies seldom report data from a total CF population.15,16 The spirometry data for the 43 patients (median age 26 years 11–58) who did not provide data at the end of the study due to unspecified reasons showed similar lung function (VC 84%p and FEV1 70%p) collected at corresponding time for the expanded annual control. However, these lung function tests were obtained in the non-accredited out-patient clinic and were, therefore, not included in the study.

Conflict of interest
No conflict of interests declared.

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References