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Improvements in lung function of a pediatric cystic fibrosis population in a developing country

Brenda M. Morrow,[1] Andrew C. Argent,[2] Heather J. Zar,[2] Anthony T. R. Westwood[2]

Abstract

Objective: To document the change in pulmonary function of a pediatric cystic fibrosis population managed at the Red Cross War Memorial Children's Hospital, Cape Town, South Africa, between January 1999 and December 2006.

Methods: Retrospective review of the medical records and best spirometry results within 3-monthly intervals.

Results: A total of 1,139 pulmonary function tests from 79 patients showed a significant improvement over the 8 years studied. When comparing the first quarter of 1999 with the last quarter of 2006, 78 pulmonary function tests were performed on 65 patients with equal patient numbers in both groups and similar in terms of gender, age, age at diagnosis, ethnicity, cystic fibrosis genotype and number of patients colonized with either *Staphylococcus aureus* or *Pseudomonas aeruginosa*. In 2006, 15 patients (38.5%) were on azithromycin treatment compared to one (2.6%) patient in 1999 (p = 0.0003). Median (interquartile range) forced expiratory volume in 1 second, forced vital capacity, and average expiratory flow between 25 and 75% of forced vital capacity increased from 61% (51-73), 63% (52-89), and 40% (27-57), predicted in the first quarter of 1999, to 81% (69-100, p = 0.004), 82% (70-98, p = 0.007), and 62% (41-87, p = 0.01), predicted during the last quarter of 2006, respectively.

Conclusions: Pulmonary function tests increased by 20% over 8 years in comparable patient groups. This likely reflects improved care of South African children with cystic fibrosis.

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Introduction

Cystic fibrosis (CF) is a common, serious inherited disease in South Africa,[1,2] occurring in all population groups.[3] Lung disease is responsible for much of the presenting morbidity and mortality,[4] with a predictable pattern of progression.[5] The rate of progression of lung disease may be affected by factors intrinsic or extrinsic to the individual.[6] Lung function measurements have been used as an outcome measure in patients with CF[7] as there is a strong association between lung function and mortality.[8,9]

High-resolution computed tomography (HRCT) has been proposed as an option for assessing and monitoring CF-related lung disease.[10] However, HRCT is very expensive and not available at many centers of medical care within South Africa. Considering the expense and the potential for harm in terms

1. School of Child and Adolescent Health, University of Cape Town (UCT), Cape Town, WC, South Africa.
2. School of Child and Adolescent Health, UCT, Cape Town, WC, South Africa. Red Cross War Memorial Children's Hospital (RCCH), Cape Town, WC, South Africa.

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of repeated high radiation doses, combined with a lack of proven therapeutic benefit,[11] HRCT is not currently considered an appropriate routine investigation within a resource-constrained environment. Pulmonary function testing (PFT), conversely, is an objective, practical way of measuring the extent and progression of lung disease,[4,12] is largely risk-free, and is widely available even in resource-constrained settings. Forced expiratory volume in 1 second (FEV_1) has been shown to reflect the progression of lung disease in CF accurately, and to predict mortality.[8,9] Forced expiratory flow during 25-75% of forced vital capacity (FVC) (FEF_{25-75}) is a sensitive index of small airway function and is affected first in CF lung disease.[8,13]

The state of CF lung disease in South Africa has not been well studied. In the last 10 years a single cross-sectional study of 42 CF patients at Red Cross War Memorial Children's Hospital (RCCH) analyzed pulmonary function.[12] Children with moderate or severe lung disease were older than those with mild disease (reflecting the expected decline in pulmonary function with age[8,13]). As has been reported elsewhere, colonization with *Pseudomonas aeruginosa* was associated with increased severity of lung disease.[14]

In the subsequent 9 years since Zar et al.'s report[12] there have been changes in medical care and service delivery within the RCCH CF Clinic. These include new antibiotic regimens, more aggressive nutritional care, a greater range of physiotherapy techniques, routine seasonal influenza vaccinations, and multidisciplinary care. It is not known whether these changes have been translated into objective improvements in lung function. This study aimed to assess the change in lung function in a CF population between the beginning of 1999 and the end of 2006.

Methods

A retrospective review of PFT and the clinical records of children over 5 years of age attending the RCCH CF Clinic, situated in the Western Cape Province of South Africa, from January 1999 to December 2006 was performed. This period was chosen as, since 1999, every child older than 5 years has undergone lung function testing at each clinic visit. PFT were performed in a standardized manner by the same operator (BM) using the same spirometry equipment (MicroLoop Spirometer; Micro Medical Ltd, UK). These data were downloaded using Spida software (version 3.2) and stored in an MS Office Access Database. PFT were performed using the forced expiratory technique, after maximal inspiration. The best PFT value (based on FEV_1) of three reproducible efforts were recorded for each patient, using American Thoracic Society (ATS) criteria.[15]

Data extracted from the clinical records included gender, age, CF genotype, ethnicity (according to the previously accepted racial classifications of white, mixed ancestry, Asian or black), pancreatic function, and colonization with *Staphylococcus aureus* or *P. aeruginosa*. Patients were considered to be colonized if the same bacterium had been isolated in three sputum specimens taken on different occasions prior to PFT.

The following baseline PFT parameters were used for analysis: FEV_1, FVC and FEF_{25-75}. Standing height was measured at each clinic visit, using a stadiometer. The spirometer automatically calculated the PFT percentages predicted for age, gender and height according to European Community for Coal and Steel (ECCS)/European Respiratory Society (ERS) predictive equations.[16]

For each patient, the best PFT (based on FEV_1) over 3-monthly intervals were recorded. Thus, each patient had a maximum of four PFT included per year. For inclusion in the study, a patient must have performed at least three PFT on separate occasions. Severity of lung disease was classified according to FEV_1 values, as mild ($FEV_1 \geq 70\%$ predicted); moderate (FEV_1 60-69% predicted); moderately severe (FEV_1 50-59% predicted); severe (FEV_1 35-49% predicted); or very severe ($FEV_1 < 35\%$ predicted).[16] Ethics approval was obtained from the institutional Human Research Ethics Committee (Rec/Ref: 413/2007).

Analysis

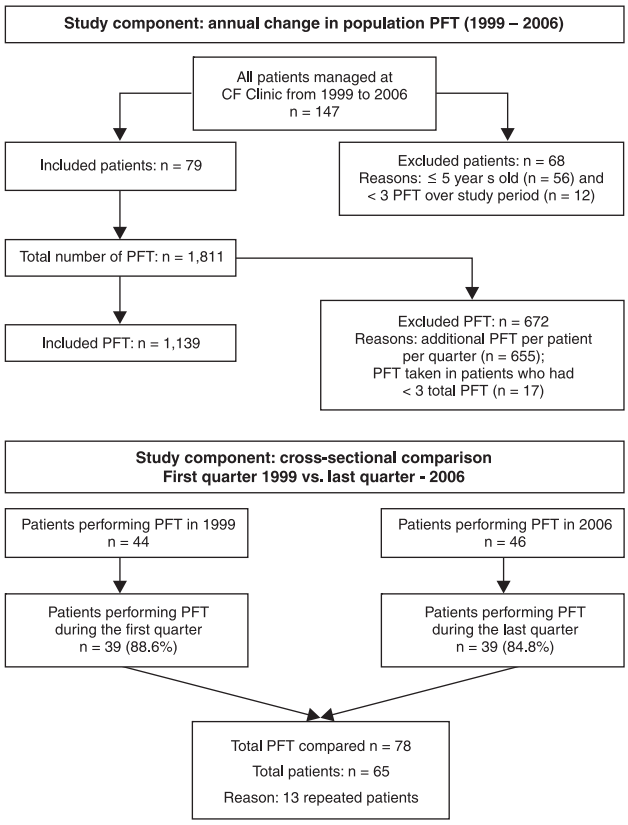
Statistical analysis was performed using Statistica data analysis software system (version 7, StatSoft, Inc. 2004). Data were tested for normality using Shapiro-Wilk's W test.

For the first part of the study, the best spirometry results of all patients performed during the first quarter of each year from 1999 to 2006, as well as the last quarter of 2006 were plotted and compared using the Kruskal-Wallis analysis of variance (ANOVA) and test of medians (a nonparametric test for multiple independent samples).

The second component of the study was a cross-sectional comparison between the best spirometry results of all patients undergoing PFT during the first quarter of 1999 and those tested during the last quarter of 2006. PFT recorded during the two quarters were compared using Mann-Whitney U tests (non-parametric equivalent of the *t* test for independent samples) for continuous data, and chi-square tests (or Yates corrected chi-square where values in cells were < 10) for categorical data. Results of patients who repeated PFT during both measurement periods were analyzed using the Wilcoxon matched pairs test.

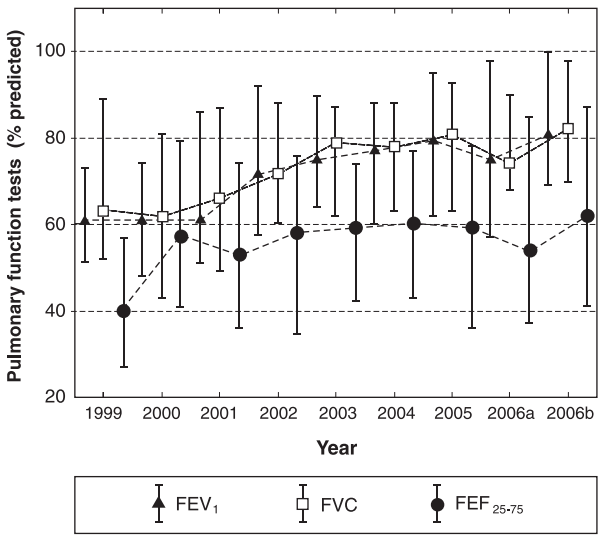
Results

A general study flowchart is presented in Figure 1. From January 1999 to December 2006, a total of 147 pediatric patients of all ages were managed at the RCCH CF Clinic. Seventy-nine (44, 56% male) of these patients performed 1,811 PFT; 1,139 of which met the inclusion criteria (Figure 1).



CF = cystic fibrosis; PFT = pulmonary function tests.

Figure 1 - Study flowchart



FEF_{25-75} = forced expiratory flow during 25-75% of the forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

Figure 2 - Change in population pulmonary function over 8 years (points represent the median, vertical bars the interquartile range)

Seventy-six patients (96%) were pancreatic insufficient. Thirty-four patients (43%) were ΔF508 homozygous; 23 (29%) were ΔF508 heterozygous; 21 (26.6%) had two non-ΔF508 CF mutations; and one patient was not genotyped. Fifty-three patients (67%) were colonized or became colonized with *S. aureus* during the study period; and an equal number of patients were colonized or became colonized with *P. aeruginosa*. No patients were colonized by *Burkholderia cepacia*. Nine patients (11%) died during the study period; median (IQR) age of death was 16.8 (8.7-19.6) years. Figure 2 shows the significant changes in population FEV_1 and FVC ($p < 0.001$), and a trend towards significance in FEF_{25-75} ($p = 0.09$), over the 8-year period.

During the first quarter of 1999 and the last quarter of 2006, 78 PFT were performed on 65 patients, 82% of the total number (n = 79) of patients performing PFT over the 8-year period. Forty-four children performed PFT during the 1999 calendar year; 39 (88.6%) of whom were measured during the first quarter. Similarly, 46 patients performed PFT during 2006 with 39 (84.8%) children being measured during the last quarter of the year (Figure 1).

There were significant improvements in PFT from 1999 to 2006; with a proportional increase in the number of children with mild lung disease (Table 1). Children were similar with regard to demographic variables between 1999 and 2006. Thirteen patients (six male) repeated PFT at both measurement periods. PFT for these patients did not change significantly over the 8-year time period (Table 2). In the first quarter of 1999, patients had earlier isolation of *P. aeruginosa* than *S. aureus* ($p = 0.03$), but in the last quarter of 2006 there was no difference between age at isolation of the two organisms ($p = 0.3$) (Table 1).

Discussion

Lung volumes, particularly FEV_1, have been shown to be reliable outcome measures in studies of CF.[7-9] This study did not investigate the progression of lung disease in South African patients with CF; instead it investigated the change in lung function of a South African CF population over an 8-year period. We have shown a 20% improvement in the population's median pulmonary function scores from 1999 to 2006. The number of patients with mild lung disease also increased significantly, with a proportional decrease in those with moderately severe lung disease. The reduction in the numbers of patients with severe and very severe lung disease was not significant.

It has not yet been possible to show that the survival of this population has been increasing over recent decades. In a study of 3 decades of follow-up in this region, median survival for CF was 19.8 years in 2003.[17] Comparison of two halves of the study period could not show any improvement

Table 1 - Comparative patient data

	First quarter 1999 (n = 39)	Last quarter 2006 (n = 39)	p
Age (years)	10.8 (7.4-13.9)	11.7 (8.6-14.8)	0.1
Age at diagnosis (years)	1.0 (0.0-4.0)	1.0 (0.0-3.0)	0.4
Gender (M:F)	19:20	21:18	0.7
Pancreatic sufficient, n (%)	2 (5.1)	1 (2.6)	1.0
Genotype, n (%)	38 (97)	39 (100)	
ΔF508 homozygous	15 (39.5)	20 (51.3)	0.3
ΔF508 heterozygous	15 (39.5)	8 (20.5)	0.1
Two non-ΔF508 CF mutations	7 (18.4)	11(28.2)	0.5
Gene not determined	1 (2.6)	0	1.0
Ethnic group, n (%)			
White	20 (51.3)	22 (56.4)	0.6
Mixed ancestry	18 (46.2)	15 (38.5)	0.6
Black African	1 (2.6)	2 (5.1)	1.0
Bacterial colonization			
S. aureus colonized, n (%)	29 (74.4)	24 (61.5)	0.2
Age at first *S. aureus* isolation (months)	74 (36-128)	36 (6-85.5)	0.02
P. aeruginosa colonized, n (%)	26 (66.7)	27 (69.2)	0.8
Age at first *P. aeruginosa* isolation (months)	29 (4-83)	28 (5-50)	0.5
Nutritional parameters			
Expected weight for height (%)	99 (93-100)	94 (89-104)	0.4
Body mass index (kg/m^2)	16.1 (14.8-17.3)	15.7 (14.7-18.6)	0.4
Pulmonary treatment, n (%)			
Inhaled gentamicin or colistin	11 (28.2)	18 (46.2)	0.1
Oral azithromycin	1 (2.6)	15 (38.5)	0.0003
Nebulized hypertonic saline	0	3 (7.7)	0.2
Nebulized DNase	2 (5.1)	0	0.5
Pulmonary function tests (% predicted)			
FEV_1	61 (51-73)	81 (69-100)	0.004
FVC	63 (52-89)	82 (70-98)	0.007
FEF_{25-75}	40 (27-57)	62 (41-87)	0.01
Severity of lung disease, n (%)			
Mild	12 (30.8)	29 (74.4)	0.0001
Moderate	8 (20.5)	3 (7.7)	0.2
Moderately severe	10 (25.6)	2 (5.1)	0.03
Severe	6 (15.4)	3 (7.7)	0.5
Very severe	3 (7.7)	2 (5.1)	0.1

CF = cystic fibrosis; F = feminine; FEF_{25-75} = forced expiratory flow during 25-75% of the forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; M = masculine.
Data are presented as median (interquartile range) unless otherwise stated.

Table 2 - Selected data of patients tested during both comparative quarters (n = 13)

	First quarter 1999	Last quarter 2006	p
Age (years)	7.9 (6.4-10.2)	15.7 (14.2-17.9)	
Weight for height (%)	99 (94-100)	93.5 (86.5-104)	0.1
Body mass index (kg/m^2)	15.2 (14.2-16.4)	17.6 (15.7-20.7)	0.004
FEV_1 (% predicted)	65 (57-102)	73 (54-84)	0.4
FVC (% predicted)	67 (59-98)	72 (57-78)	0.5
FEF_{25-75} (% predicted)	42 (31-83)	55 (38-74)	1.0

FEF_{25-75} = forced expiratory flow during 25-75% of the forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity. Data are median (interquartile range).

in outcome for younger subjects with CF[17] but the improvements in population FEV_1 reported here make it likely that outcomes are going to improve.[18]

The reasons for the observed improvements in population lung function cannot be determined on the basis of this study, but are likely to be multifactorial and may relate to a number of changes in the management of CF patients delivered by a multidisciplinary team,[7,18,19] as described in the introduction. Although there were similar numbers of patients receiving chronic suppressive therapy for *P. aeruginosa,* the increased use of oral azithromycin for *P. aeruginosa* colonized patients may have contributed to improved lung function, as has been reported previously.[20] Patients in 2006 had earlier isolation of *S. aureus,* therefore the improved PFT in this later patient group may be partly related to earlier recognition and treatment of *S. aureus* infection.

A large majority of patients were pancreatic insufficient, with an almost inevitable impact on nutritional status and growth – factors associated with pulmonary status and outcome in CF.[21-23] Between 1986 and 1996, mean weight for age increased significantly in children with CF in South Africa, approaching normal levels by the end of that decade.[24] It was suggested that this improved growth set the scene for improved prognosis for people with CF in this country. Although we could not identify a change in nutritional status based on expected weight for height or body mass index over the eight years of our review (Table 1), the improvements in nutritional status reported previously[24] could be contributing to the improvement in pulmonary function seen in this population. It is noteworthy that the body mass index of patients who performed PFT in both 1999 and 2006 did increase significantly over the 8-year time period (Table 2).

The study design has several limitations. Not all patients with CF were included in the samples, however the study population represented 82% of all patients performing PFT over this period and patient characteristics were also similar to that of the general CF population over 5 years of age. Although the data were retrospectively analyzed, PFT were prospectively collected using the same technique, equipment and operator, minimizing potential variations in PFT results.[25] To minimize selection bias we included all patients who performed three or more PFT during the study period. This clinic does not cohort or select patient groups for specific clinics visits. Patient groups of the two compared quarters were well matched for a number of variables, and the annual population changes in PFT (which include different groups of patients) reflect the same changes seen in the cross-sectional comparison. PFT for patients who were tested during both 1999 and 2006 were not different between the two quarters so are unlikely to have biased the results. The fact that this group of 13 patients did not show a significant drop in PFT over this time is also encouraging; although average rates of PFT change cannot be extrapolated from this very small sample. Both the first quarter of 1999 and the last quarter of 2006 occurred in summer so seasonal changes in lung infection prevalence and etiology are unlikely to have accounted

for any differences. These sampling periods were chosen in order to obtain data over 8 complete years.

Ethnic groups are a proxy to socioeconomic status in South Africa as black people and those with mixed ancestry tend to live in worse socioeconomic environments, often with less access to healthcare, than white people.[26] Previously, this led to ethnic differences in prognosis for children with CF in South Africa.[27] In the present study, ethnic group did not affect lung function, which may indicate that circumstances have become less prejudicial to poorer patients.

Although it has been shown that *P. aeruginosa* colonization is associated with lower PFT,[23] this was not apparent from our data. The reasons for this are not clear. Although *S. aureus* is often the first pathogen to infect the respiratory tract of children with CF,[28] we found that in the first cohort, patients were older at the first *S. aureus* isolation than for *P. aeruginosa*. The reasons for this may relate to the fact that sputum specimens were not obtained routinely at clinic visits before the late 1990's. Since then regular specimens have been obtained from an early age.

We have demonstrated significant improvements in the lung function of a Western Cape CF population in recent years. Considering that pulmonary function is an accepted proxy for patient outcome,[7] these results are very encouraging and reinforce the need to maintain and further develop multidisciplinary centers of care for South Africans with CF.[19]

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Correspondence:
Brenda Morrow
UCT School of Child and Adolescent Health
5th Floor - Institute of Child Health Building
Red Cross War Memorial Children's Hospital
Klipfontein Road, Rondebosch, 7700
Cape Town, WC - South Africa
Tel.: +27 (21) 658.5074
Fax: +27 (21) 689.1287
E-mail: brenda.morrow@uct.ac.za