Rate of pulmonary function decline in South African children with cystic fibrosis

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Background. Pulmonary function tests (PFTs) objectively measure the extent and progression of cystic fibrosis (CF) lung disease. The rate of lung function decline in developing countries has not previously been studied.

Aim. To investigate the average annual rates of pulmonary function decline in South African children with CF from 1999 to 2006.

Methodology: The medical records and best PFT over 3-monthly intervals of children attending the CF clinic at Red Cross War Memorial Children's Hospital, Cape Town, were retrospectively reviewed and analysed using the mixed model regression method.

Results. A total of 1 139 PFT were recorded on 79 patients, with a median (interquartile range) of 14 (6 - 21) PFTs per patient. The mean (standard error) forced expiratory volume in 1 second (FEV_1) at age 6 years was estimated at 73.83 (3.34) per cent predicted with an FEV_1 decline of 0.23 (0.43)% per annum. FEV_1 at age 6 was affected by age at CF diagnosis, genotype, and year of birth. Rate of FEV_1 decline was significantly affected by *Pseudomonas aeruginosa* colonisation and genotype.

Conclusions. Although FEV_1 at age 6 years was low compared with developed countries, the annual rate of FEV_1 decline in South African children with CF was minimal, setting the scene for improved survival in this population.

Pulmonary disease is the main predictor of morbidity and mortality associated with cystic fibrosis (CF).[1] The pattern of lung function decline has been reported to be predictable in developed countries,[2] with an annual rate of decline in the forced expiratory volume in 1 second (FEV_1) of less than 2% predicted for children born after 1980.[3] The rate of decline in these countries is determined by a number of different factors.[4] Children with CF living in developing country settings such as South Africa have a number of additional exposures that could impact on pulmonary function, including biomass fuel exposure,[5] an increased prevalence of respiratory infections (including pulmonary tuberculosis) in the community,[5,6] and poorer access to health care[7] than children in developed settings.

Pulmonary function tests (PFTs), particularly measurement of FEV_1, are a practical, objective way of monitoring the severity and progression of CF lung disease.[1,8] FEV_1 has been shown to be strongly associated with mortality,[9,10] while forced expiratory flow during 25 - 75% of the forced vital capacity (FEF_{25-75}) is a sensitive index of small-airway function and is affected first in CF lung disease.[9,11]

CF is a serious, progressive disease present in all the South African population groups,[12,13] with a current median survival in the Western Cape region of South Africa of 20.5 years.[14] The progression of lung disease is poorly studied in this and other developing populations. We have recently observed a significant population improvement in the pulmonary function of children with CF living in the Western Cape province of South Africa over the 8-year period 1999 - 2006.[15] This improvement occurred without demographic or other clinical changes in the population, but coincided with a number of changes to medical care and service delivery for patients with CF. Before this report,[15] only one cross-sectional study on CF lung function in South Africa had been published.[8] There have been no longitudinal studies of lung function changes over time in the South African CF population.

In a longitudinal study conducted in the developed world at a time when life expectancy for CF was about where it is in South Africa now,[14] the average annual decline in FEV_1 for patients who died between 15 and 19 years of age was approximately 5%, while patients surviving into their 20s had declines in FEV_1 of about 2%.[9] On the basis of our mortality

data, we therefore hypothesised that the average rate of FEV_1 decline in our population would be between 2% and 5% per annum.

This study aimed to investigate the average annual rates of pulmonary function decline in children with CF living in the Western Cape province of South Africa.

Materials and method

Approval for this study was obtained from the University of Cape Town's Human Research Ethics Committee. A retrospective review of PFTs and the clinical records of children over 5 years of age attending a single multidisciplinary CF clinic from January 1999 to December 2006 was performed. The study site was the CF clinic at Red Cross War Memorial Children's Hospital (RCCH), Cape Town, the only CF centre in the Western Cape region. This study period was chosen because from 1999 every child older than 5 years has had lung function testing at each clinic visit. Visits occur at monthly, 2-monthly or 3-monthly intervals as indicated. Tests were performed in a standardised manner by the same operator (BM) using the same spirometry equipment (MicroLoop Spirometer; Micro Medical Ltd, UK). PFT data were downloaded using Spida software (version 3.2) and stored in an MS Office Access database. The spirometry equipment was calibrated and serviced annually. Individual, disposable bacterial filters were used for each patient, and the equipment was decontaminated between subjects to prevent cross-infection.

For inclusion in the study, a patient had to have had at least three PFTs on separate occasions. Standing height was measured at each clinic visit using a stadiometer. PFTs were performed using the forced expiratory technique, after maximal inspiration. The best PFT value (based on FEV_1) of three reproducible efforts (without bronchodilator administration) were recorded for each patient, using American Thoracic Society (ATS) criteria.[16] FEV_1, forced vital capacity (FVC) and FEF_{25-75} were recorded. 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.[17] For each patient, the best PFT (based on FEV_1) within 3-monthly periods were recorded. Each patient therefore had a maximum of four PFTs included per year.

Clinical data recorded included gender, age, CF genotype, ethnicity (according to the previously accepted ethnic classification of white, mixed ancestry, Asian or black), pancreatic function, and colonisation with *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Patients were considered to be colonised if the same bacterium had been isolated in at least three sputum specimens taken on different occasions (not during an acute exacerbation) before pulmonary function testing.

Statistical analysis

Descriptive data were analysed using the STATISTICA data analysis software system (version 7, StatSoft Inc., 2004). Data were tested for normality and non-parametric data were reported as median (interquartile range, IQR). Chi-square tests (or Yates's corrected chi-square where values in cells were <10) were used to test for an association between categorical variables.

Mixed model regression analyses were performed as described by Corey *et al.*[9] using the statistical package R (version 2.6.0), in order to evaluate the average rate of decline of FEV_1, FVC and FEF_{25-75} (response variables) in children with CF living in the Western Cape, and to evaluate the effect of age at diagnosis, year of birth, gender, ethnicity, CF genotype, and chronic infection with *P. aeruginosa* and *S. aureus* (fixed effect regressor variables) on the rate of pulmonary function decline. Random effects were included for both the intercept (age at 6 years) and the slope (age at observation). Separate models were fitted for each of the PFT outcome variables. The effects for each covariate were estimated individually and modelled with an interaction between the fixed effect of the particular covariate and the age (time) variable. Modelling the interaction allowed the estimates for different groups to be compared and tested. A significance level of 5% was chosen.

Results

From January 1999 to December 2006, 147 patients were managed at the RCCH CF clinic. Seventy-nine (56% male) of these patients performed 1 811 PFTs, 1 139 of which met the inclusion criteria (Fig. 1). The median (interquartile range, IQR) age at the first PFT performed during the study period was 7.98 (6.22 - 11.54) years and the number of PFTs per subject was 14 (6 - 21). Seventy-six patients (96%) had pancreatic insufficiency, and no patient was infected with *Burkholderia cepacia*. Other patient characteristics are set out in Table I. Nine patients (11%) died during the study period (4 male, 5 female); the median (IQR) age at death was 16.8 (8.7 - 19.6) years. The 9 patients who died had a mean (standard error, SE) of 10.4 (2.3) PFTs recorded over 12.7 (3.3) quarters.

The mixed model equations for the regression lines of FEV_1, FVC and FEF_{25-75}, with no covariates other than age and intercept at age 6 years (the age at which patients started having PFT recorded), are presented in Table II. There was minimal annual decline in FEV_1 over the 8 years studied, with no significant difference in slope from the horizontal. FEF_{25-75} declined at a faster rate and FVC increased on average per year.

Table I presents the mixed model equations for FEV_1 with the following covariates: age at diagnosis, gender, ethnicity, CF genotype, and chronic infection status with either *S. aureus* or *P. aeruginosa*. Only the results for FEV_1 are shown; the differences between patient subgroups were similar for models of FEF_{25-75} and FVC, although the FEF_{25-75} slopes of decline were steeper and FVC much less steep than FEV_1.

The average FEV_1 in the second birth cohort (1986 - 1990) (Table I) was skewed by 3 patients with very severe lung disease, 2 of

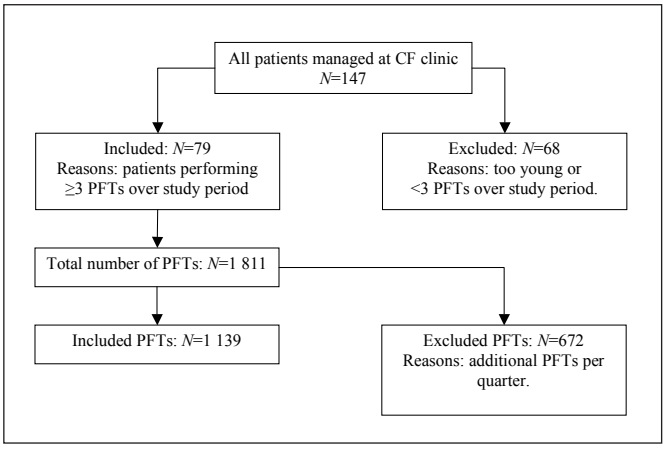

Fig. 1. Study inclusion and exclusion criteria (CF = cystic fibrosis; PFT = pulmonary function tests).

TABLE I. MEAN RATE OF CHANGE IN FEV_1 (% PREDICTED) FOR AGE AT DIAGNOSIS, GENDER, ETHNICITY, CF GENOTYPE AND CHRONIC INFECTION STATUS (INTERCEPT AT AGE 6 YEARS)

		Test of difference from first subgroup (*p*)	
Subgroup	**Mixed model equation***	**Intercept**	**Slope**
Age at diagnosis			
≤1 year (*N*=24, 30.4%)	77.05 (5.67)–0.20 (0.76)	-	-
1 - 5 years (*N*=43, 54.4%)	78.8 (7.14)–0.98 (0.96)	0.81	0.41
>5 years (*N*=12, 13.9%)	53.18 (9.95)+2.06 (1.26)	0.02	0.07
Year of birth			
1980 - 1985 (*N*=14, 17.7%)	66.32 (10.55)–1.17 (1.16)	-	-
1986 - 1990 (*N*=18, 22.8%)	44.21 (11.93)+2.26 (1.39)	0.07	0.01
1991 - 1995 (*N*=30, 38%)	79.81 (11.24)–0.14 (1.31)	0.23	0.43
≥1996 (*N*=17, 21.5%)	93.69 (11.83)–1.32 (1.80)	0.02	0.93
Gender			
Female (*N*=35, 44%)	74.08 (5.21)–0.24 (0.66)	-	-
Male (*N*=44, 56%)	73.65 (6.82) – 0.23 (0.88)	0.95	0.99
Ethnicity			
Mixed ancestry (*N*=33, 41.8%)	73.91 (5.42)–0.50 (0.69)	-	-
White (*N*=43, 87.8%)	73.73 (7.08)–0.12 (0.91)	0.98	0.68
Black African (*N*= 2, 2.5%)	Insufficient sample		
Asian (*N*=1, 1.3%)			
CF genotype			
ΔF508 homozygous (*N*=34, 43%)	81.88 (4.74)–1.34 (0.64)	-	-
ΔF508 heterozygous (*N*=23, 29%)	60.54 (7.74)+1.43 (0.98)	0.007	0.005
Two non-ΔF508 mutations (*N*=21, 26.6%)	77.22 (8.62)–0.51 (1.18)	0.59	0.48
Not genotyped (*N*=1, 1.3%)	Insufficient sample		
P. aeruginosa infection			
Not colonised (*N*=26, 33%)	70.17 (5.80)+0.29 (0.74)	-	-
Colonised (*N*=53, 67%)†	75.17 (7.15)–0.82 (0.90)	0.49	0.046
S. aureus infection			
Not colonised (*N*=26, 33%)	77.91 (5.83)+0.29 (0.81)	-	-
Colonised (*N*=53, 67%)†	71.37 (7.20)–0.42 (0.97)	0.37	0.46

*Mixed model equation is expressed as $Y_{age}=Y_6$ (mean (SE))–*k* (mean (SE)) (age–6), where Y_6 is the estimated FEV_1 value at age 6 years and slope *k* is the annual FEV_1 decline. For each covariate, one subgroup was arbitrarily chosen as a reference group with which the other subgroups were compared.

†Colonisation occurring at any stage before or during study period.

TABLE II. OVERALL AVERAGE RATE OF DECLINE IN PULMONARY FUNCTION TESTS (INTERCEPT AT AGE 6 YEARS)

Pulmonary function tests (% predicted)	Mixed models equation*	Difference of slope from zero (*p*)
FEV_1	73.83 (3.34)–0.23 (0.43)	0.59
FVC	67.54 (3.28)+0.87 (0.38)	0.02
FEF_{25-75}	70.56 (3.93)–1.90 (0.58)	0.001

*Mixed model equation is expressed as $Y_{age}=Y_6$ (mean (SE))–*k* (mean (SE))×(age–6), where Y_6 is the estimated value of PFT at age 6 years and slope *k* is the annual decline of PFT.

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

whom never had an FEV_1 >30% and all of whom died during the study period. When these subjects were excluded from the sub-analysis, no significant differences in intercept or slope were found compared with the first birth cohort.

Discussion

We had hypothesised that FEV_1 in South African children with CF would decline on average by as much as 5% per year on the basis of studies performed in developed countries in the late 1990s.[9] It is therefore very encouraging that the results of our relatively short-term longitudinal study suggest an average rate of decline in FEV_1 of less than 1% per year. These values are similar to those of Xu *et al*.,[3] who found that patients born between 1985 and 1990 had an average rate of decline in FEV_1 of 0.8%.

The low rate of PFT decline could have been influenced by a cohort effect if the PFTs of sicker patients who died had not been included. However, only 9 patients died during the study period, all of whom had PFTs recorded. The average of 10 recorded PFTs per subject who died should have provided sufficient data to avoid positively skewing the overall results.

Although lung disease was fairly stable in our general population, it was already fairly advanced by the age of 6 years, with PFT about 10% lower than described by Xu *et al*.[3] Although the annual rate of decline of FEF_{25-75} of approximately 2% was much less than the 7% decline in FEF_{25-75} reported by Corey *et al*. a decade ago,[9] this does reflect early and progressive peripheral airways disease.[18] Recent studies of PFT decline have focussed on FEV_1, and changes in FEF_{25-75} are not reported.[2,3,19] It is accepted that the critical events that establish or contribute to the severity of CF lung disease may occur at a very young age, before standard lung function testing is started.[18] We therefore need to establish better methods of early detection, monitoring and management of these events in our population in order to preserve lung function better in infancy and early childhood,[20,21] with the aim of prolonging survival of CF patients in developing countries.

Median survival of patients with CF in the USA in 2005 was 36.5 years,[22] whereas in our population the median survival over 33 years ending in 2008 was only 20.5 years.[14] The duration and quality of life depend heavily on the rate of decline in pulmonary function.[23] Considering our low rate of FEV_1 decline in children with CF over the past 8 years, it is hoped that the lifespan of these children will be much longer and more productive than previously expected. We suspect that the short life expectancy despite slow PFT decline is related to the large number of early childhood deaths in our population.[14]

In our study, patients diagnosed over the age of 5 years had a significantly lower FEV_1 at intercept (averaging <55%, consistent with moderately severe lung disease[24]) than those diagnosed earlier (averaging >75%, consistent with mild lung disease[24]). A study of the impact of early versus late CF diagnosis on pulmonary function, in which late diagnosis was defined as diagnosis between 6 weeks and 3 years, showed a twofold increase in the risk of having moderate to severe pulmonary disease (FEV_1 <70%) at ages 6 - 10, compared with patients diagnosed under 6 weeks of age.[20] Although our intercept values were significantly lower in patients diagnosed over the age of 5 years, the direction of the FEV_1 slope was subsequently positive when compared with those diagnosed under 1 year (approaching significance at p=0.07). This suggests that lack of management in early childhood had a deleterious effect on early lung function, which subsequently improved after implementation of appropriate therapy. The age of CF diagnosis has not changed over the past decade,[15] so this is unlikely to have affected the results.

Patients born after 1995 had a significantly higher baseline FEV_1 at 6 years of age than those born before 1985. In these younger patients the average FEV_1 at intercept was approximately 94%, in line with recent reports from developed countries.[25] Considering that the age of diagnosis of CF has remained fairly constant over the past 8 years, the improved baseline FEV_1 in younger patients may reflect better early management of patients with CF.

Although previous studies have shown that female patients had a steeper decline in FEV_1 than males,[9,26] possibly owing to different degrees of physical activity,[27] we could not show any difference in intercept or FEV_1 slope between males and females. This lack of difference has also been reported in recent studies of FEV_1 decline.[2,19,28]

Ethnic group was recorded as a proxy for socio-economic status, as in South Africa people of mixed ancestry and black Africans tend to live in worse socio-economic environments, with less access to health care, than white people.[29] Overall mortality has been shown to be worse in the CF mixed ancestry population.[29] It is encouraging that we could show no difference in baseline PFT or in pulmonary function decline between white patients and those of mixed ancestry, suggesting that circumstances have become less prejudicial to poorer patients.

Patients who were ΔF508 heterozygous had significantly lower baseline lung function at age 6 years than ΔF508 homozygous patients; however, the rate of decline was significantly higher in the latter group of patients – a finding also reported by Corey *et al*.[9] A relationship between CFTR genotype and severity of lung disease has been reported previously.[19] Heterozygous status may predict more severe early lung disease in our CF population, which may then become more stable than in ΔF508 homozygous patients, but the exact relationship remains unclear. This difference cannot be attributed to differences in age at CF diagnosis; nor can it be attributed to ethnic differences, as there were almost equal numbers of white patients and those of mixed ancestry in the ΔF508 heterozygous group. The majority of ΔF508 homozygous patients were white, but as indicated above ethnicity is unlikely to account for the increased rate of decline of lung function in this group of patients. Further studies are needed to evaluate whether a specific non-ΔF508 mutation is related to the severity and progression of CF lung disease in South Africa.

Chronic *P. aeruginosa* infection was related to a steeper decline in FEV_1, as has been reported previously,[19,26] while as expected chronic *S. aureus* infection did not affect the rate of pulmonary function decline.[30]

This study was limited by the small sample size, although this was comparable to that described by Que *et al*.[2] in patients born after 1980. Despite the small patient numbers, the number of observations per patient (median 14) was higher than the 8 measurements per patient reported by Konstan *et al*.[26] The relatively short time period studied limited the investigation of the relationship between decline in lung function and mortality. A longer-term study is needed to ascertain whether there is an FEV_1 threshold that predicts mortality in our population. This was a single-centre study, the results of which may not be applicable to other CF populations in South Africa or other developing countries. The study was also limited in scope, as we did not include nutritional status and there were

too few pancreatic-sufficient patients for meaningful analysis. Finer subgroup analysis (including pancreatic sufficiency and other ethnic groupings) requires a much larger patient cohort from different centres in South Africa. It should be noted, however, that nutritional parameters did not change over the study period and this is therefore unlikely to have influenced the results.[15] Further studies are warranted to determine the impact of azithromycin, now routinely used in chronic *P. aeruginosa* infection, on PFT.

Since there have been no other longitudinal studies for comparison, we can only surmise that improvements in patient care and the understanding of CF in South Africa over the past decade have resulted in the surprisingly low rate of lung function decline reported here. These results suggest that the outlook for South Africans with CF is improving,[31] and emphasise the importance of continual monitoring and audit in multidisciplinary centres of care.

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Conflicts of interest: None to declare.

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