8.1* What name(s) did the doctor use to describe the child's chest problem? (record)
8.2* Where did the child go for treatment for this chest problem? (private doctor, day hospital, Red Cross Hospital, other hospital or clinic, other (specify))

9*. Is the child *currently* on any treatment for any of the following: wheezing/whistling in the chest, tight chest, night cough or asthma?
9.1* If *yes* what treatment? (tablets, syrup, inhaler, nebuliser (oxygen), injection, other (specify))

10.* Do you know of anything you can do *inside the child's bedroom* to prevent allergy or breathing problems? (record)

11.* Do you know of anything your child can avoid *eating or drinking* so as to prevent allergy or breathing problems? (record)

12.* Has the child ever been asked by a doctor or nurse to blow into a peak flow meter? (show picture of meter)

13.* Has the child ever had asthma?
13.1* Does s/he still have asthma?

* Interview (2nd) questionnaire only.

LUNG FUNCTION IN SOUTH AFRICAN CHILDREN WITH CYSTIC FIBROSIS

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Objective. To determine the pattern of lung function in stable cystic fibrosis (CF) patients and to investigate the relationship of abnormal lung function to demographic variables, CF genotype and pulmonary colonisation with *Pseudomonas aeruginosa* (PA).

Design. A descriptive study done at the CF clinic at Red Cross War Memorial Children's Hospital in Cape Town.

Methods. Data were recorded and pulmonary function testing (PFT) was performed in 42 CF patients.

Results. 29 patients (69%) had mild disease, while 11 (26%) and 2 (5%) had moderate and severe disease respectively. Twenty-four patients (57%) demonstrated lower airway obstruction (LAO). Patients with moderate or severe disease were significantly older than those with mild disease (13.3 (3.7) years (mean (SD)) compared with 11.1 (3.0) years ($t = 2.1$; $P = 0.04$)). PA colonisation status differed significantly with the pattern of lung function ($\chi^2 = 6.6$; $P = 0.04$) and severity of lung disease ($\chi^2 = 12.6$; $P = 0.002$). Nine (35%) of the 26 patients tested before and after bronchodilator therapy showed a positive response.

Conclusion. The majority of patients had mildly impaired or normal lung function, with LAO predominating. A minority of patients were bronchodilator-responsive. PA colonisation may be associated with the development of abnormal lung function and more severe pulmonary disease.

S Afr Med J 1998; 88: 994-997.

Cystic fibrosis (CF) is one of the most common serious inherited disorders among South Africa's white and coloured populations[1] and may be more common than formerly realised in the black population.[2] Clinical manifestations include pancreatic insufficiency, hepatic dysfunction, infertility and pulmonary disease. Of these, pulmonary disease, characterised by endobronchial bacterial infection and neutrophil-dominated

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inflammation, is the major cause of morbidity and mortality. *Staphylococcus aureus* and *Haemophilus influenzae* are the initial respiratory pathogens, while *Pseudomonas aeruginosa* (PA) predominates later.[3]

The extent, progression and reversibility of pulmonary disease may be assessed reliably using pulmonary function testing (PFT). PFT may also be used to predict prognosis. The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) are significant predictors of survival in CF patients.[4]

South African patients with CF have a less favourable prognosis than their European or North American counterparts, with a median survival of 18 years.[5] Although many deaths occur in infancy, more rapidly progressive lung disease may partly account for these differences. However there are a paucity of data on lung function in South African CF patients, with a single descriptive study published.[6] We report on the pattern and reversibility of lung function in stable CF patients. We investigated the relationship of lung function to demographic variables, CF genotype and pulmonary colonisation with PA.

METHODS

Patients older than 5 years attending the CF clinic at Red Cross War Memorial Children's Hospital in Cape Town were consecutively entered into the study. Patients were excluded if they could not reliably perform PFT or if they had had a pulmonary exacerbation within the preceding month. Patients currently attending the clinic received treatment as outlined in Table I.

Data recorded included age, sex, CF genotype, pancreatic function and sputum culture results. PA colonisation was defined as three positive sputum cultures within the preceding year. PFT was performed by the same technician with spirometry (Vitalograph Spirometer, Vitalograph Ltd, England)

Table I. Current treatment for pulmonary disease in CF patients at Red Cross War Memorial Children's Hospital

Indication	Therapy	Comment
General maintenance of optimal clinical condition	Pancreatic enzyme replacement therapy	For pancreatic-insufficient patients
	Nutritional support	Emphasis on adequate diet and nutritional supplements
Improvement of mucociliary clearance	Chest physiotherapy	May prevent development of pulmonary complications and airway obstruction
Prevention of *S. aureus* colonisation	Flucloxacillin twice a day	Use of prophylaxis is controversial
First isolate of PA	Antibiotics effective against PA for 2 weeks	Aggressive long-term anti-*Pseudomonas* therapy to delay onset of infection used by Danish CF centre
Pulmonary exacerbation	Antibiotics for 2 weeks	Antibiotics given orally or intravenously depending on severity of exacerbation
	Chest physiotherapy	
	Inhaled bronchodilators if responsive bacteria	Use antibiotics effective against colonising bacteria
		Two antibiotics should be used for PA
Chronic PA infection	Aminoglycoside inhalations	May reduce clinical symptoms and improve lung function
		Routine use of 3-monthly intravenous antibiotics used by Danish CF centre
Airway inflammation	Ibuprofen daily	Most effective in young patients
		High doses necessary for efficacy; regular monitoring of plasma levels required
Asthma	Inhaled bronchodilators for relief of acute attacks	Increased incidence of airway hyperreactivity in CF patients, but variable response to bronchodilators
	Inhaled anti-inflammatory agents for prophylaxis of moderate or severe asthma	
Prophylaxis for influenza virus	Annual influenza vaccine	
Other therapies not routinely available		
Reduction in sputum viscosity	rhDNase	Most useful for patients with obstructive lung disease, purulent airway secretions and endobronchial bacterial infection
		Usefulness limited by cost
		Improves lung function but response variable
Improvement of mucociliary clearance	Inhaled hypertonic (6%) saline	Reported to improve lung function but further studies needed to confirm this

using the forced expiratory manoeuvre. FVC and FEV_1 were measured, and forced expiratory flow at 25 - 75% of the FVC (FEF_{25-75}) was calculated. All values were expressed as a percentage of predicted normal values.[7]

Lung function was considered normal when the lung volumes and the expiratory flow rates were within predicted normal limits and proportional to each other. A restrictive pattern was defined as FVC less than or equal to 85% of the predicted normal value, with a proportionate decrease in the expiratory flow rates. Lower airway obstruction (LAO) was defined as a FEV_1 or FEF_{25-75} below 2 standard deviations (SD) from the predicted normal value and disproportionately decreased relative to FVC (FEV_1/FVC < 70% or FEF_{25-75} (% predicted)/FVC (% predicted) ≤ 0.8. Pulmonary disease was further classified as mild (FVC ≥ 70% of the predicted value), moderate (FVC 40 - 69% of the predicted value) and severe (FVC < 40% of the predicted value).

The effect of a brochodilator was assessed by measuring the change in PFT 20 minutes after inhalation of 200 µg fenoterol via dry powder device (Berotec inhalets; Boehringer Ingelheim). A positive response was defined as an increase from baseline in any of the following indices: FVC of 10%, FEV_1 of 15% or FEF_{25-75} of 20%.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS). One-way ANOVA was used to compare groups with different patterns (obstructive, restrictive, or normal) and severity (mild, moderate, severe) of lung function in terms of age and lung indices (FVC, FEV_1 FEF_{25-75}). The chi-square test was used to determine whether the pattern and severity of lung function differed according to gender (male, female), CF genotype (ΔF508 homozygous, ΔF508 heterozygous with another CF mutation or two non-ΔF508 CF mutations) and PA colonisation status.

Results

The 42 patients (22 male) who participated in this study represent 65% of CF patients attending our clinic and 86% of those eligible for the study. Three eligible patients did not participate as they were unable to perform PFT, while 4 did not visit the clinic during the study period. The mean age was 11.8 years (range 5.9 — 18.8 years). Forty (95%) of the patients were pancreatic-insufficient. Seventeen (41%) of the patients were ΔF508 homozygous, 18 (43%) were ΔF508 heterozygous with another CF mutation, 5 (12%) had two non-ΔF508 CF mutations, and 2 were not genotyped. Sixteen patients (38%) were colonised with PA.

Twenty-four patients (57%) demonstrated LAO, 3 (7%) had a restrictive pattern and 15 (36%) had normal lung function. Table II presents the indices of lung function in these groups, which did not differ significantly in terms of age or gender. When the severity of lung function was classified by FVC, 29 patients (69%) had mild disease while 11 (26%) and 2 (5%) had moderate and severe disease respectively. Patients with moderate or severe disease were significantly older than those with mild disease (13.3 (3.7) years compared with 11.1 (3.0) years (t = 2.1; P = 0.04).

Table II. Patterns of lung function in patients with CF (% predicted) (mean (SD))

	Obstructive (N = 24)	Restrictive (N = 3)	Normal (N =15)
FVC	70.3 (18.6)	71.3 (15.0)	93.2 (5.6)
FEV_1	59.1 (21.1)	69.3 (13.3)	94.7 (5.3)
FEF_{25-75}	38.2 (21.2)	69.7 (13.3)	94.6 (7.1)

Pattern of lung function did not differ significantly according to gender or CF genotype. PA colonisation status differed significantly with the pattern of lung function (χ^2 = 6.6; P = 0.04) and severity of lung disease (χ^2 = 12.6; P = 0.002). Of the 16 patients colonised with PA, 2 (13%) had normal function; 13 (81%) and 1 (6%) had obstructive and restrictive patterns respectively. In contrast, of the 26 patients not colonised with PA, 13 (50%) had normal lung function. The majority (77%) of patients with moderate or severe lung disease were colonised with PA, whereas 79% of patients with mild disease were not.

Nine (35%) of the 26 patients tested before and after bronchodilator administration showed a positive response. Thirty per cent of patients with LAO demonstrated reversibility. There was no relationship between the severity of lung disease and bronchodilator response, and no patient experienced a decline in lung function following bronchodilator administration.

Discussion

This study indicates that the majority of our CF patients have mild lung disease, with the most common abnormality being LAO. This may reflect a relatively young patient population as pulmonary disease initially produces airway obstruction. With progression of infection and inflammation, fibrosis and restrictive lung disease occur.[8] Another possibility is that we selected relatively healthy patients. The sample included patients older than 5 years of age; it is therefore possible that patients who are more ill and who die younger would not have participated in the study. However currently very few of our patients die during early childhood. In addition the sample comprised the majority (86%) of patients older than 5 years enrolled as patients at the CF clinic. Consistent with previous reports, we did not find a relationship between genotype and the pattern or severity of lung function.[9] Older patients had more severe lung disease, reflecting the reported yearly decline in pulmonary function.[10]

Airway obstruction was indicated mainly by a decrease in FEF_{25-75}, indicating that the site of obstruction is the peripheral

airways. FEF_{25-75} is a sensitive indicator of small-airways disease, deteriorating before changes in FEV_1 or FVC become apparent.[8] Only a small number of patients demonstrated reversibility of LAO with bronchodilators. The poor response that we found may be multifactorial. Airway obstruction in CF is caused by thickened secretions, endobronchial infection and inflammation and bronchial hyperreactivity to various stimuli.[11] Of these, bronchial hyperreactivity may respond to bronchodilator therapy. Other studies have reported that between 0% and 95% of patients respond to bronchodilators.[12,13] Differences in patient population, in the definition of response and in the method of administration of bronchodilator may also explain our low response rate. We used a low dose (200 µg) of β_2-agonist via a dry powder device, while others have used higher doses via nebuliser or metered dose inhaler. However we chose to evaluate bronchodilator response with the device most frequently prescribed for patients. Patients may also demonstrate variable responses to bronchodilators with repeated PFT; thus longitudinal testing results in higher numbers of responders.[14] Chronic bronchodilator therapy should therefore be based on results of repeated tests.

In most CF centres PA is the predominant respiratory pathogen in patients by the end of the first decade of life.[15] The majority of patients acquire PA during their lifetime and rarely, if ever, eradicate it from their lungs.[16] Thirty-eight per cent of our patients were colonised with this organism compared with more than 50% of similarly aged North American children with CF.[17] Differences in environmental exposure to *Pseudomonas*, in antibiotic usage or in methods of obtaining and culturing sputum specimens may account for some of these differences. Despite our lower colonisation rates there was a significant association between infection with PA and abnormal lung function. Chronic pulmonary colonisation with PA has been associated with pulmonary deterioration and a poorer prognosis.[15,18] Hoiby[15,19] has suggested that PA colonisation leads to rapid clinical deterioration; others, however, have reported a more gradual and variable process.[20] Our data are consistent with a causal relationship between PA colonisation and the development of abnormal lung function and more severe pulmonary disease.

Although South African CF patients have been reported to have a worse prognosis than their American or European counterparts,[5] this study indicates that PA infection and more severe lung disease do not explain the differences in mortality. Other factors such as delay in CF diagnosis, worse nutritional status, poorer socio-economic conditions and access to health care may impact on survival. Another possibility is that young patients who are severely ill may die before 5 years of age and so would not form part of the group of patients we studied. Furthermore, advances in our understanding of CF and newer and more effective therapies may have resulted in improved prognosis compared with that which has been reported.

We thank Ms Felicity Leisegang, Department of Chemical Pathology, Red Cross Children's Hospital, for performing CF genotyping.

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Accepted 4 Apr 1998.