Cystic fibrosis (CF) is a multisystem condition with the greatest morbidity and mortality arising from the pulmonary component of the disease. Though the overall survival of the condition has improved markedly over the past two decades, the natural history of the disease continues to be characterised by a steady decline in lung function. Pulmonary function testing provides a more objective assessment of the progress of pulmonary disease in CF than do clinical scoring systems. Forceful expiratory volume in one second (FEV₁) has been shown to be closely linked to mortality. Other factors that play a major role in the decline of lung function are infections due to Pseudomonas aeruginosa and Burkholderia cepacia, nutritional status, and gender. In view of this, markers to identify children who may be at a higher risk of a more rapid decline than others are continually being sought. Identification of such markers may allow earlier intervention with more aggressive therapy and alert clinicians to their more at-risk population. Previous studies have evaluated the prognostic value of exercise testing in patients with cystic fibrosis, and patients with high levels of aerobic fitness showed a three times greater likelihood of survival than patients with lower levels of fitness.

Carbon dioxide retention during exercise is uncommon in mild to moderate lung disease in cystic fibrosis (CF). The ability to deal with increased CO₂ is dependent on the degree of airflow limitation and inherent CO₂ sensitivity. CO₂ retention (CO₂R) can be defined as a rise in P₄₀ tension of ≥5 mm Hg with exercise together with a failure to reduce Pₑ₂CO₂ tension after peak work by at least 3 mm Hg by the termination of exercise. The inability to defend carbon dioxide during exercise is associated with a more rapid decline in lung function.

**Background:** Carbon dioxide (CO₂) retention during exercise is uncommon in mild to moderate lung disease in cystic fibrosis (CF). The ability to deal with increased CO₂ is dependent on the degree of airflow limitation and inherent CO₂ sensitivity. CO₂ retention (CO₂R) can be defined as a rise in P₄₀ tension of ≥5 mm Hg with exercise together with a failure to reduce Pₑ₂CO₂ tension after peak work by at least 3 mm Hg by the termination of exercise.

**Aim:** To ascertain if carbon dioxide retention during exercise is associated with more rapid decline in lung function.

**Methods:** Annual spirometric and exercise data from 58 children aged 11–15 years, with moderate CF lung disease between 1996 and 2002 were analysed.

**Results:** The mean FEV₁ at baseline for the two groups was similar; the CO₂R group (n = 15) was 62% and the non-CO₂R group (CO₂NR) was 64% (n = 43). The decline in FEV₁ after 12 months was −3.2% (SD 1.1) in the CO₂R group and −2.3% (SD 0.9) in the CO₂NR group. The decline after 24 months was −3.8% (SD 1.0) in the CO₂R group and −3.2% (SD 1.1) in the CO₂NR group. After 36 months, the decline in FEV₁ was −5.3% (SD 1.2) and −2.6% (SD 1.1) respectively. The overall decline in lung function was 14.8% (SD 2.1) in the CO₂R group and 6.7% (SD 1.8) in the CO₂NR group. Using the primary outcome measure as a decline in FEV₁ of >9%, final multivariate analysis showed that the relative risks for this model were (95% CIs in parentheses): ΔPETCO₂ 16.11 (3.41 to 24.12), peak VO₂ 1.23 (1.10 to 1.43), and initial FEV₁ 1.14 (1.02 to 1.28).

**Conclusion:** Results show that the inability to defend carbon dioxide during exercise is associated with a more rapid decline in lung function.
expressed as a percent of predicted value based on standards previously developed in this laboratory. MVV was assessed by the sprint method.

**Exercise testing**

Patients performed an annual maximal incremental cycling test on an electrically braked cycle ergometer (Rodby Electronik AB, Enhorna, Sweden). One minute work increments were chosen according to sex, height, and physical activity level. Heart rate (lead II, ECG), inspired V̇E (Parkinson–Cowan dry gas meter, Manchester, UK), mixed expired oxygen (Applied Electrochemistry oxygen analyser, Sunnyvale CA), carbon dioxide (P.K.Morgan 901–MK2, Chatham, UK), and respiratory rate (thermister) were monitored continuously on an eight channel recorder. V̇O₂ and VCO₂ were calculated using the nitrogen balance technique. The test was considered complete when the patient reached exhaustion, based on an inability to maintain a continuous pedalling speed of 60 revolutions per minute. At the 15 second mark of each work rate, the end-tidal PCO₂ (PETCO₂, mm Hg) was calculated by measuring the expired carbon dioxide at the mouthpiece at the end of tidal breathing. The peak and end of exercise PETCO₂ were recorded.

**Data analysis**

The children were divided into those who retained CO₂ during progressive exercise test (CO₂R group) and those who did not (CO₂NR group). CO₂ retention was arbitrarily defined as a rise of ≥5 mm Hg PETCO₂ from the first work rate until the peak work rate and a failure to reduce PETCO₂ by 3 mm Hg by the termination of the exercise.

The Shapiro Wilk statistic was used to assess if the data followed a normal distribution. One way ANOVA with repeated measures was used to detect the changes in FEV₁ followed a normal distribution. One way ANOVA with PETCO₂ as a continuous variable, peak V̇O₂, pulse oximetry, and initial FEV₁. \( \Delta P_{ETCO₂} \) was \( [(\text{change in } P_{ETCO₂} \text{ to peak exercise}) \div (\text{change in } P_{ETCO₂} \text{ from peak to termination of exercise})] \). Using the presented definition of CO₂ retention, the parameter \( \Delta P_{ETCO₂} \) would be expected to be ≥2 mm Hg in this study in the CO₂R group.

Univariate predictors of moderate statistical significance \( (p < 0.25) \) were included in the multivariate logistic regression model. Decline in FEV₁ over 36 months was the primary outcome, with a decline of greater than 9% over the three years deemed to be clinically significant. A value of 9% over three years was chosen as this is the approximate rate of decline in typical subjects with CF. Computations were made with the SAS statistical program (version 6.12, SAS Institute, Cary, NC). Results were expressed as relative risks with their 95% confidence intervals (CI).

### RESULTS

The demographic details at baseline are presented in table 1. The mean age at entry of the subjects in the CO₂R group was 13.9 years (SD 1.7) and in the CO₂NR group was 13.6 years (SD 1.8). This difference was not statistically significant. The body mass index was similar in both groups. The mean FEV₁ values at baseline for the two groups were similar (CO₂R 62% [range 41–68%] and CO₂NR 65% [range 44–69%]).

At entry in to the study, the mean change in PETCO₂ from rest to peak was 6.62 mm Hg (SD 1.13) in the CO₂R group and 2.27 mm Hg (SD 1.17) in the CO₂NR group. With exercise, the CO₂R and CO₂NR group reduced their PETCO₂ by 2.12 mm Hg (SD 0.80) and 3.70 mm Hg (SD 0.70) respectively. The mean PETCO₂ at rest in the CO₂R and CO₂NR groups were 38.7 mm Hg (1.6) and 37.6 mm Hg (2.1) respectively \( (p > 0.05) \). In addition, the CO₂R and CO₂NR groups increased their tidal volume by 45.7% (SD 2.2) and 94.5% (SD 2.8) \( (p < 0.05) \) respectively. There was no evidence of desaturation using pulse oximetry in any of the children tested. V̇E at peak exercise was significantly less in the CO₂R group; 61 l/min (SD 7) versus 78 l/min (SD 9) in the CO₂NR group \( (p < 0.05) \).
The decline in FEV$_1$ after 1 year was $-3.2\%$ (SD 1.1) in the CO$_2$R group and $-2.3\%$ (SD 0.9) ($p > 0.05$) in the CO$_2$NR group. The decline in FEV$_1$ in year 2 was $-6.3\%$ (SD 1.3) in the CO$_2$R group and $-1.8\%$ (SD 1.1) in the CO$_2$NR group ($p < 0.05$). In year 3, the decline was $-5.3\%$ (SD 1.2) and $-2.5\%$ (SD 1.1) in FEV$_1$ in the CO$_2$R and CO$_2$NR groups respectively ($p < 0.05$). Overall, the FEV$_1$% predicted declined by $-14.8\%$ (SD 2.1) in the CO$_2$R group and $-6.7\%$ (SD 1.8) in the CO$_2$NR group over three years ($p < 0.01$). The decline in FEV$_1$ is presented graphically in fig 1.

Univariate analyses are presented in table 2. Parameters of moderate statistical significance ($p < 0.25$) were included in the multivariate analysis. The primary outcome measure was the relative risk of a decline in FEV$_1$ of $>9\%$. The final multivariate analysis results are presented in table 3. The relative risks for the final model were (95% CIs in parentheses): $\Delta$P$_{ET}$CO$_2$ 11.61 (3.41 to 24.12), peak VO$_2$ 1.23 (1.10 to 1.43), initial FEV$_1$ 1.14 (1.02 to 1.28). We computed $\Delta$P$_{ET}$CO$_2$ as [(change in P$_{ET}$CO$_2$ to peak exercise) + (change in P$_{ET}$CO$_2$ from peak to termination of exercise)].

**DISCUSSION**

This study suggests that children with CF with a similar degree of pulmonary disease as measured by FEV$_1$, if found to have CO$_2$ retention on exercise testing will have a greater decline in FEV$_1$ over a three year period compared to their counterparts who do not retain CO$_2$. In addition to FEV$_1$ and peak aerobic capacity, we have now shown that the presence of CO$_2$ retention during exercise can be an additional prognostic marker of disease progress in cystic fibrosis.

Although PaCO$_2$ values cannot be predicted accurately from $P_{ET}$CO$_2$ values in an individual person, particularly in patients with lung disease or with disorders affecting ventilation/perfusion relationships, measurement of $P_{ET}$CO$_2$ is often valuable for following trends in PaCO$_2$. In healthy children carbon dioxide levels rarely increase during exercise and actually fall slightly in vigorous exercise. Using the definitions for carbon dioxide retention presented earlier, $\Delta$P$_{ET}$CO$_2$ would be $\geq 2$ mm Hg for CO$_2$R and $< 2$ mm Hg for CO$_2$NR. This study shows that for every 1 mm Hg $\Delta$P$_{ET}$CO$_2$ there was an almost 12-fold increase in the risk of the child dropping their FEV$_1$ by 9\% or more over the next three years. The association of CO$_2$ retention during exercise and poor pulmonary function has been previously reported by Cropp and colleagues. They also noted a significant correlation between desaturation and CO$_2$ retention at peak work capacity and postulated that $V_E$ was not sufficient to maintain alveolar ventilation. This in combination with excessive dead space ventilation resulted in alveolar hypoventilation. Excessive dead space ventilation in patients with CF was also noted by Godfrey and Mearns, who suggested that this may be one of the more sensitive indicators of pulmonary dysfunction in cystic fibrosis. Coates and colleagues showed that the failure to increase tidal volume appropriately, rather than a large physiologic dead space, led to alveolar hypoventilation with consequent exertional hypercapnia.

The $V_E$ at peak exercise was significantly less in our CO$_2$R group. This is secondary to the significantly smaller change in tidal volume in this group compared to the CO$_2$NR group throughout the exercise test. Compared to healthy subjects, children with severe lung disease have been shown to have an increased $V_E$ per unit work rate. The reason that some of our cohort who had similar pulmonary function profiles retained CO$_2$ may be due to their poorer $V_E$ response, and/or a higher degree of ventilation/perfusion mismatch in these children.

Nixon et al reported that patients with a $P_{ET}$CO$_2$ of 41 mm Hg at peak exercise were more than twice as likely to die within seven years as patients with a $P_{ET}$CO$_2$ of 36 mm Hg. Coates et al have shown that the ventilatory response to a CO$_2$ stimulus in children with CF is the combined result of the degree of chronic airflow obstruction and an inherent sensitivity to the CO$_2$ drive to breathe. Therefore, the different handling techniques of a CO$_2$ stimulus may be one cause of exertional hypercapnia.

The CO$_2$R group showed an increasingly significant decline in FEV$_1$ over three years. Though the CO$_2$R group had a slightly lower FEV$_1$ profile (62.3\%, range 41–68\%) compared to the CO$_2$NR group (64.7\%, range 44–69\%) at the commencement of the study, the difference was not great enough to explain the more rapid decline in the CO$_2$R group. By the third year there was a decline of $-5.3\%$ (SD 1.2) and $-2.5\%$ (SD 1.1) in the CO$_2$R and CO$_2$NR groups respectively. The average decline in FEV$_1$ per annum was $-4.9\%$ in the CO$_2$R group compared with $-2.3\%$ in the CO$_2$NR group. This estimate for the CO$_2$NR group is similar to that reported from Toronto for a combined sample of children and adults with CF.

In summary, children with CF who were found to have CO$_2$ retention on exercise testing showed a faster rate of decline in FEV$_1$ when compared to those who did not retain CO$_2$. This additional information may be used to identify those children who may require more intensive therapy to prevent this increased rate in pulmonary decline.

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