ORIGINAL ARTICLE

Does carbon dioxide retention during exercise predict a more rapid decline in FEV_1 in cystic fibrosis?

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Background: Carbon dioxide (CO_2) retention during exercise is uncommon in mild to moderate lung disease in cystic fibrosis (CF). The ability to deal with increased CO_2 is dependent on the degree of airflow limitation and inherent CO_2 sensitivity. CO_2 retention (CO_2R) can be defined as a rise in $P_{ET}CO_2$ tension of $\geqslant$5 mm Hg with exercise together with a failure to reduce $P_{ET}CO_2$ 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 FEV_1 at baseline for the two groups was similar; the CO_2R group (n = 15) was 62% and the non-CO_2 retention group (CO_2NR) was 64% (n = 43). The decline in FEV_1 after 12 months was −3.2% (SD 1.1) in the CO_2R group and −2.3% (SD 0.9) in the CO_2NR group. The decline after 24 months was −6.3% (SD 1.3) and −1.8% (SD 1.1) respectively. After 36 months, the decline in FEV_1 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 CO_2R group and 6.7% (SD 1.8) in the CO_2NR group. Using the primary outcome measure as a decline in FEV_1 of >9%, final multivariate analysis showed that the relative risks for this model were (95% CIs in parentheses): $\Delta P_{ET}CO_2$ 11.61 (3.41 to 24.12), peak $\dot{V}O_2$ 1.23 (1.10 to 1.43), and initial FEV_1 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.

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.[1–3] Forced expiratory volume in one second (FEV_1) has been shown to be closely linked to mortality.[4] Other factors that play a major role in the decline of lung function are infections due to *Pseudomonas aeruginosa* and *Burkholderia cepacia*,[5] nutritional status,[6] and gender.[1] 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,[7 8] and patients with high levels of aerobic fitness showed a three times greater likelihood of survival than patients with lower levels of fitness.[7]

Carbon dioxide retention during exercise is uncommon in mild to moderate CF lung disease. The ability to deal with increased carbon dioxide is dependent on the degree of airflow obstruction and the inherent sensitivity to carbon dioxide. Patients with an FEV_1 less than 60% are more likely to retain CO_2.[9] We sought to ascertain if carbon dioxide retention during exercise is associated with a greater rate of decline in FEV_1. We hypothesised that CO_2 retention during exercise could be a measure that predicts children who are at higher risk of decline in FEV_1. This is because CO_2 retention is a marker of mechanical impairment, increased dead space, ventilation perfusion abnormalities, and the patient's response to CO_2 stimulus may not be detectable on routine pulmonary function testing.

METHODS

Subjects

As part of the annual evaluation of children with CF, an aerobic exercise test and pulmonary function tests are performed. This was a retrospective analysis of exercise and pulmonary function data in children with CF. The inclusion criteria for this study were children with CF who had a minimum of three consecutive years of exercise test data. The recruitment period for this study was 1996 to 2000. This ensured that there was a minimum of three consecutive years of follow up. The exercise test data were excluded from analysis if the children had an acute pulmonary exacerbation as defined by an acute >10% decrease in FEV_1, increased productive cough, and/or pyrexia at the time of the exercise test. Children who had *Burkholderia cepacia* or proven cystic fibrosis related diabetes were excluded from the study.

Pulmonary function tests

FVC, FEV_1, and MVV (Gould Sentry System 50, Gould Inc. Dayton, Ohio) were measured annually according to standard spirometric techniques.[10] Pulmonary function values were

Abbreviations: CO_2, carbon dioxide; CO_2R, CO_2 retention; CO_2NR, CO_2 non-retention; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MVV, maximal voluntary ventilation; $PaCO_2$, arterial partial pressure CO_2; $P_{ET}CO_2$, end-tidal CO_2 partial pressure; SD, standard deviation; $\dot{V}_E$, minute ventilation, $\dot{V}CO_2$, CO_2 production; $\dot{V}O_2$, oxygen consumption

Table 1 Baseline demographics and exercise parameters carbon dioxide retainers (CO_2R) versus non-retainers (CO_2NR)

	CO_2R (n = 15)	CO_2NR (n = 43)
Age (years)	13.9 (1.7)	13.6 (1.8)
Male:female ratio	6:9	16:27
Body mass index (kg/m^2)	21.2 (0.7)	21.9 (0.8)
PS:PI ratio	0:15	1:42
Baseline peak $\dot{V}O_2$ (ml/kg/min)	36.8 (3.1)	37.3 (3.4)
Baseline FEV_1 (% predicted)	62 (4)	65 (4)
RQ (at peak exercise)	1.17 (0.1)	1.15 (0.1)
% increase in tidal volume	45.7 (2.2)	95.4 (2.8)

PS, pancreatic sufficiency; PI, pancreatic insufficiency; FEV_1, forced expiratory volume in 1 second; RQ, respiratory quotient.

expressed as a percent of predicted value based on standards previously developed in this laboratory.[11] MVV was assessed by the sprint method.[12]

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.[13] Heart rate (lead II, ECG), inspired $\dot{V}_E$ (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. $\dot{V}O_2$, and $\dot{V}CO_2$ were calculated using the nitrogen balance technique.[14] 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 PCO_2 ($P_{ET}CO_2$, 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 $P_{ET}CO_2$ were recorded.

Data analysis

The children were divided into those who retained CO_2 during progressive exercise test (CO_2R group) and those who did not (CO_2NR group). CO_2 retention was arbitrarily defined as a rise of ⩾5 mm Hg $P_{ET}CO_2$ from the first work rate until the peak work rate and a failure to reduce $P_{ET}CO_2$ after the peak work rate 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 FEV_1 as the primary continuous variable over time. Statistical significance was assigned when $p < 0.05$. Univariate logistic regression analysis was performed on the following variables: gender, age, minute ventilation at peak exercise, BMI, $\Delta P_{ET}CO_2$ as a continuous variable, peak $\dot{V}O_2$, pulse oximetry, and initial FEV_1. $\Delta P_{ET}CO_2$ was [(change in $P_{ET}CO_2$ to peak exercise) + (change in $P_{ET}CO_2$ from peak to termination of exercise)]. Using the presented definition of CO_2 retention, the parameter $\Delta P_{ET}CO_2$ would be expected to be ⩾2 mm Hg in this study in the CO_2R group.

Univariate predictors of moderate statistical significance ($p < 0.25$) were included in the multivariate logistic regression model. Decline in FEV_1 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.[11] 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).

Table 2 Univariate analysis for decline in FEV_1 over 36 months >9%

Parameter	Relative risk	p value	95% CI for risk ratio
Age (years)	1.00	0.78	0.98 to 1.08
Female	1.23	0.41	0.37 to 1.78
BMI (kg/m^2)	0.96	0.61	0.43 to 1.14
$\dot{V}O_2$ peak (ml/kg/min)	0.78	0.16	0.51 to 0.92
$\dot{V}_E$ peak (l/min)	0.85	0.28	0.66 to 0.96
FEV_1 at start (%)	0.92	0.18	0.81 to 1.05
ΔP_{ET} CO_2*(mm Hg)	5.81	0.0005	4.20 to 7.18

BMI, body mass index; $\dot{V}O_2$,oxygen consumption; $\dot{V}_E$, minute ventilation; $\Delta P_{ET}CO_2$, [(change in $P_{ET}CO_2$ to peak exercise) + (change in $P_{ET}CO_2$ from peak to termination of exercise)].
*:ΔP_{ET} CO_2 ⩾2 mm Hg in CO_2R and ΔP_{ET} CO_2 <2 mm Hg in CO_2NR.

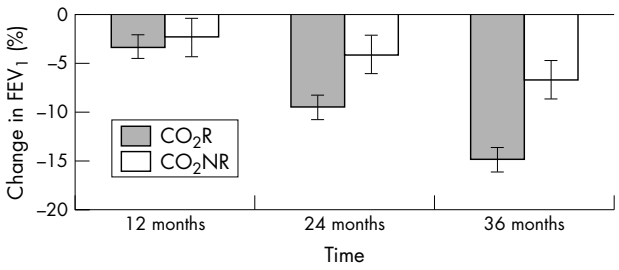

Figure 1 Cumulative decline in FEV_1 over time in carbon dioxide retainers (CO_2R) and non-retainers (CO_2NR). Error bars depict SD.

RESULTS

The demographic details at baseline are presented in table 1. The mean age at entry of the subjects in the CO_2R group was 13.9 years (SD 1.7) and in the CO_2NR 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 FEV_1 values at baseline for the two groups were similar (CO_2R 62% (range 41–68%) and CO_2NR 65% (range 44–69%)).

At entry in to the study, the mean change in $P_{ET}CO_2$ from rest to peak was 6.62 mm Hg (SD 1.13) in the CO_2R group and 2.27 mm Hg (SD 1.17) in the CO_2NR group. With exercise, the CO_2R and CO_2NR group reduced their P_{ET} CO_2 by 2.12 mm Hg (SD 0.80) and 3.70 mm Hg (SD 0.70) respectively. The mean $P_{ET}CO_2$ at rest in the CO_2R and CO_2NR groups were 38.7 mm Hg (1.6) and 37.6 mm Hg (2.1) respectively ($p > 0.05$). In addition, the CO_2R and CO_2NR groups increased their tidal volume by 45.7% (SD 2.2) and 95.4% (SD 2.8) ($p < 0.05$) respectively. There was no evidence of desaturation using pulse oximetry in any of the children tested. $\dot{V}_E$ at peak exercise was significantly less in the CO_2R group: 61 l/min (SD 7) versus 78 l/min (SD 9) in the CO_2NR group ($p < 0.05$).

Table 3 Multivariate analysis for decline in FEV_1 over 36 months >9%

Parameter	Relative risk	p value	95% CI for RR
ΔP_{ET} CO_2 (mm Hg)	11.61	0.004	3.41 to 24.12
$\dot{V}O_2$ peak (ml/kg/min)	1.23	0.001	1.10 to 1.43
FEV_1 %	1.14	0.005	1.02 to 1.28

What is already known on this topic

- Carbon dioxide retention during exercise is uncommon in mild to moderate CF lung disease
- Previous researchers have shown that the ability to deal with increased carbon dioxide is related to factors such as the degree of airflow obstruction and the inherent sensitivity to carbon dioxide
- However, using the current definitions of carbon dioxide retention, the *prognostic* value of carbon dioxide retention in children with CF has not been evaluated

What this study adds

- Carbon dioxide (CO_2) retention was defined as a rise of $\geqslant$5 mm Hg end tidal CO_2 from the first work rate until the peak work rate and a failure to reduce end tidal CO_2 after the peak work rate by 3 mm Hg by the termination of the exercise
- This study shows that 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

The decline in FEV_1 after 1 year was −3.2% (SD 1.1) in the CO_2R group and −2.3% (SD 0.9) ($p > 0.05$) in the CO_2NR group. The decline in FEV_1 in year 2 was −6.3% (SD 1.3) in the CO_2R group and −1.8% (SD 1.1) in the CO_2NR 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_2R and CO_2NR groups respectively ($p < 0.05$). Overall, the FEV_1% predicted declined by −14.8% (SD 2.1) in the CO_2R group and −6.7% (SD 1.8) in the CO_2NR 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 $\dot{V}O_2$ 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 $PaCO_2$.[15] In healthy children carbon dioxide levels rarely increase during exercise and actually fall slightly in vigorous exercise.[16] Using the definitions for carbon dioxide retention presented earlier, $\Delta P_{ET}CO_2$ would be $\geqslant$2 mm Hg for CO_2R and <2 mm Hg for CO_2NR. This study shows that for every 1 mm Hg $\Delta P_{ET}CO_2$ [$\Delta P_{ET}CO_2$ = (change in $P_{ET}CO_2$ to peak exercise) + (change in $P_{ET}CO_2$ from peak to termination of exercise)], 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.[9] They also noted a significant correlation between desaturation and CO_2 retention at peak work capacity and postulated that $\dot{V}_E$ 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,[17] who suggested that this may be one of the more sensitive indicators of pulmonary dysfunction in cystic fibrosis. Coates and colleagues[18] 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 $\dot{V}_E$ at peak exercise was significantly less in our CO_2R group. This is secondary to the significantly smaller change in tidal volume in this group compared to the CO_2NR group throughout the exercise test. Compared to healthy subjects, children with severe lung disease have been shown to have an increased $\dot{V}_E$ per unit work rate.[19] The reason that some of our cohort who had similar pulmonary function profiles retained CO_2 may be due to their poorer $\dot{V}_E$ response, and/or a higher degree of ventilation/perfusion mismatch in these children.

Nixon *et al* reported that patients with a $P_{ET}CO_2$ >41 mm Hg at peak exercise were more than twice as likely to die within seven years as patients with a $P_{ET}CO_2$ $\leqslant$36 mm Hg.[7] 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.[20] Therefore, the different handling techniques of a CO_2 stimulus may be one cause of exertional hypercapnia.

The CO_2R group showed an increasingly significant decline in FEV_1 over three years. Though the CO_2R group had a slightly lower FEV_1 profile (62.3%, range 41–68%) compared to the CO_2NR 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_2R group. By the third year there was a decline of −5.3% (SD 1.2) and −2.5% (SD 1.1) in the CO_2R and CO_2NR groups respectively. The average decline in FEV_1 per annum was −4.9% in the CO_2R group compared with −2.3% in the CO_2NR group. This estimate for the CO_2NR group is similar to that reported from Toronto for a combined sample of children and adults with CF.[11 21]

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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