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SHORT REPORT

Airway response of children with primary ciliary dyskinesia to exercise and β_2-agonist challenge

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Airway response of children with primary ciliary dyskinesia to exercise and β_2-agonist challenge. G.E. Phillips, S. Thomas, S. Heather, A. Bush. ©ERS Journals Ltd 1998.

ABSTRACT: In primary ciliary dyskinesia (PCD), chest physiotherapy for airway clearance is essential. Exercise and inhaled β_2-agonists can produce bronchodilation thereby augmenting physiotherapy. However, both can also cause bronchoconstriction, and the effects of these stimuli in PCD are not known.

In a preliminary study, the mean coefficients of variation for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR) in children with PCD were determined. They were 5.4%, 4.4% and 8.4%, respectively. Twelve children with PCD and 12 normal children performed pulmonary functions under resting conditions; during and after a validated treadmill exercise test; and before and 15 min after 200 µg of inhaled salbutamol.

At baseline, FEV_1, FVC, forced mid-expiratory flow ($FEF_{25–75\%}$) and PEFR were significantly reduced in the PCD group compared with the control group. Exercise produced a significant increase in PEFR in the PCD group. There was no significant difference between the groups in response to salbutamol. Within the PCD group, exercise produced a significantly greater increase in PEFR than β_2-agonist therapy.

In conclusion, in children with primary ciliary dyskinesia there is evidence of obstructive pulmonary disease. In these children, exercise is a more potent stimulus for bronchodilation than by inhaled β_2-agonists. Enhancement of airway clearance may best be achieved by encouraging patients to exercise before physiotherapy rather than by inhaling β_2-agonists, but the effects of each should be assessed for each individual before instigating treatment.

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Primary ciliary dyskinesia (PCD), formerly referred to as immotile cilia syndrome, is an autosomal recessive disorder, characterized by chronic upper and lower respiratory tract infection, and in 50% cases, mirror image organ arrangement or situs inversus [1]. Untreated, chronic lower respiratory tract infection leads to bronchiectasis, and previous studies have described abnormalities of pulmonary function compatible with airways obstruction [2–4]. Airflow limitation in children with PCD has not specifically been examined nor intrasubject variability formally assessed. It is known that suppurative lung disease can increase the coefficient of variation of spirometry, for example in cystic fibrosis, the variability of forced expiratory volume in one second (FEV_1) may be up to 15% within an individual [5]. Where respiratory disease is characterized by an obstructive airways pattern, a spontaneous variability in the degree of obstruction may be demonstrated [6]. Inflammatory lung disease affects the response to exercise; asthmatics characteristically bronchoconstrict [7], whereas patients with cystic fibrosis may bronchodilate [8, 9]. Conversely, patients with cystic fibrosis may bronchoconstrict when β_2-agonists are inhaled [10]. The eff-ects of these stimuli in PCD have not been characterized. These changes are of more than theoretical importance. The mainstay of treatment for PCD involves chest physiotherapy to enhance clearance of bronchial secretions. It would clearly be advantageous to ensure maximal bronchodilation prior to physiotherapy.

The purpose of this study was thus to ascertain if children with PCD had evidence of reversible airway obstruction and if so, how bronchodilation could best be achieved to augment airway clearance with physiotherapy.

Methods

Subjects

We studied 12 children with PCD (males n=7; median age 11 yrs; range 7–15 yrs) and 12 normal children acted as controls (males n=6; median age 11 yrs; range 8–14 yrs). The diagnosis of PCD [11] was based on a compatible clinical picture, reduced or absent ciliary beat frequency and abnormal appearances on electron microscopy of cilia in the absence of local infection (outer dynein arm defect n=3; inner dynein arm defect n=2; outer and inner arm detects n=2; dynein arms absent n=4; inner arm and radial spoke defect n=1). Normal children recruited for the study were siblings, friends or family friends of the children with PCD with no history of chronic or recent acute respiratory problems, used no medication, and had a normal physical examination and spirometry. Siblings of patients with PCD are automatically screened for the disease

as clinical routine. The study was approved by the Royal Brompton Hospital Ethics committee, and written informed consent was given by all subjects and their parents.

Procedures

Intrasubject variability of spirometry in children with PCD was determined. Ten children (eight of whom went forward to complete the airway responses study) performed ten successive flow volume loops using a Compact Vitalograph spirometer (Vitalograph, Buckingham UK). The mean coefficients of variation were: FEV_1=5.4%, forced vital capacity (FVC)=4.4% and peak expiratory flow rate (PEFR)=8.4%. Thus, for the purpose of this study, we considered the criteria for a significant change in these measurements to be 11%, 9% and 17%, respectively.

The children recruited for the study attended the Pulmonary Function Unit at the Royal Brompton Hospital as outpatients. They had abstained from β_2-agonists for at least 4 h prior to participating and from vigorous exercise or a heavy meal for 2 h. The study procedures were explained, and the children familiarized with all the equipment. Baseline pulmonary function was recorded as the best of three flow volume loops, using the Compact Vitalograph. Before each study period, the spirometer underwent a volume calibration using a 1 L syringe. Next, a treadmill exercise test was performed in an air-conditioned laboratory according to standardized protocol [12]. The treadmill was inclined at 15%, and the speed adjusted to produce a heart rate of 65–85% of the subjects predicted maximum (210 - (0.65 or 0.85 × age in years)) [13]. Heart rate was monitored continuously by surface electrocardiography, and arterial oxygen saturation by pulse oximetry (Ohmeda Biox 3700, Ohmeda, Boulder, CO, USA). Peak flow measurements were made with a Wright Peak Flow meter (Ferraris, London, UK) immediately prior to exercise, and every two minutes during the exercise period. Subjects exercised for 8 min. On completion of exercise, further peak flow measurements were made every minute for 5 min, every 5 min for the next 20 min, with the final measurements being made at 1 h. The exercise tests were supervised by a single observer, blind to the peak flow measurements. Finally, when the children had returned spontaneously to their baseline lung function, bronchodilator response was assessed by giving 200 μg salbutamol *via* a metered-dose inhaler and spacer device under supervision. PEFR and the best of three flow volume loops were recorded before and 15 min after administration of the bronchodilator.

Analysis

The percentage rise in PEFR and percentage fall in PEFR with exercise were calculated for each subject in accordance with standard practice [12]. The Mann-Whitney test was used to compare pulmonary function between the two groups (alternative hypothesis two-sided). To compare the rise in PEFR with exercise to that occurring in response to β_2-agonist therapy, a paired t-test was used (two-sided alternative hypothesis). For all analyses the result was considered statistically significant if $p<0.05$.

To determine a clinically significant bronchodilator response, the percentage change in FEV_1 was calculated. In accordance with the coefficient of variation study, a significant response was recorded if the change was >11%.

For baseline assessment of pulmonary function, predicted values from COTES [14] and POLGAR and PROMADHAT [15] were used.

Results

The control children had normal lung function with the exception of three where forced mid-expiratory flow ($FEF_{25–75\%}$) was only 60% of the predicted value [15]. Baseline pulmonary function for the PCD subjects is given in table 1. The children with PCD had significantly reduced mean FEV_1 ($p<0.002$), FVC ($p<0.03$), $FEF_{25–75\%}$ ($p<0.01$) and PEFR ($p<0.002$) compared with the control children. Table 2 shows the changes in PEFR in response to exercise for the children with PCD. Five of twelve children with PCD had a significant rise in PEFR (>17%) on exercise. A further five had equivocal rises (>10%). Of the PCD subjects who demonstrated a rise in PEFR, PEFR remained elevated 30 min after cessation of exercise. An hour after exercise, 6 subjects still had a PEFR greater

Table 2. – Pulmonary ciliary dyskinesia (PCD) subjects - changes in peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1) in response to exercise and to β_2-agonist salbutamol

PCD subject	% Rise in PEFR with exercise	% Fall in PEFR with exercise	% Change in FEV_1 with β-agonist
1	10	6	-5.6
2	17*	2	-10.7
3	23*	0	0
4	20*	0	-1.1
5	23*	0	5.6
6	-2	26*	12.9*
7	7	15*	8.2
8	16	2	12.6*
9	34*	31*	24*
10	13	3	1.8
11	12	2	4.3
12	11	5	2.1

*: significant clinical responses (see text for explanation).

Table 1. – Baseline measurements of pulmonary function in the children with primary ciliary dyskinesia (PCD)

	PCD subjects											
	1	2	3	4	5	6	7	8	9	10	11	12
FEV_1 %	74	85	72	63	92	75	85	85	48	68	61	65
FVC %	92	103	74	78	106	90	120	113	66	86	89	74
$FEF_{25–75\%}$ %	68	59	71	45	70	60	46	48	25	44	34	56
PEFR %	90	87	84	82	84	77	107	93	57	88	80	84

Values are presented as percentage of predicted for age, height and sex [14, 15]. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $FEF_{25–75\%}$: forced mid-expiratory flow; PEFR: peak expiratory flow rate.

than their baseline value. Two children showed unequivocal bronchoconstriction to exercise (including one of the five who also bronchodilated) and one showed a borderline bronchoconstriction. One normal subject had a rise in PEFR of >20% on exercise, and one had a fall in PEFR of 29% despite having no symptoms. Ten of twelve children with PCD had a better bronchodilator response to exercise than β_2-agonists, $p<0.002$. Only three children with PCD bronchodilated with salbutamol (table 2). No fall in arterial oxygen saturation was demonstrated at any time during the study.

Discussion

The main new finding of this study is that children with PCD may exhibit bronchodilatation to exercise. Their response was greater to exercise than to β_2-agonists, and indeed one subject with PCD actually bronchoconstricted with salbutamol. This pattern of variable airflow obstruction is more akin to that which may be seen in cystic fibrosis rather than asthma [8, 9].

Pulmonary function in children with PCD is characterized by a mild to moderate obstructive pattern. Possible pathological changes accounting for this include, airway smooth muscle hypertrophy and fibrosis, intraluminal secretions and altered lung mechanics secondary to repeated infection. Clearance of airway secretions is likely to be facilitated by bronchodilatation, and the aim of this study was to determine whether β_2-agonists or exercise would better achieve this. In most cases, exercise was a more potent bronchodilator than β_2-agonists. Indeed, the latter may rarely cause bronchoconstriction. There were some individual variations in airway response but in this small group, it was not possible to predict airway responsiveness from baseline lung function. The duration of the bronchodilation response resulting from exercise was at least 30 min and chest physiotherapy would usually be carried out within this time.

Evidence-based practice encourages the use of exercise in the management of many respiratory diseases for a number of reasons including: enhanced clearance of bronchial secretions [16], improvements in pulmonary function and cardiorespiratory fitness [17], and a reduction in the sensation of breathlessness [18]. It would appear from the results of this study that exercise can and should be promoted in the management of PCD. A subsidiary aim of this study was to assess the safety of exercise in PCD. Although no patient desaturated in this study, it is possible, however, that more severely affected patients might require oxygen supplementation during exercise.

In conclusion, this paper describes airway obstruction in children with primary ciliary dyskinesia and reports for the first time the intrasubject variation that can be anticipated in spirometry in these children. We conclude that, in children with primary ciliary dyskinesia (PCD), exercise appears to be a more powerful bronchodilator stimulus than β_2-agonists. However, because there is unpredictable individual variation in response we recommend a physiological assessment before any treatment regimen based on exercise or β_2-agonist therapy is implemented.

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