DOI: 10.1111/j.1365-2362.2011.02626.x

ORIGINAL ARTICLE

Cardiopulmonary assessment in primary ciliary dyskinesia

Giuliana Valerio[*], Francesco Giallauria[†], Silvia Montella[‡], Nicola Vaino[*], Carlo Vigorito[†], Virginia Mirra[‡] and Francesca Santamaria[‡]

[*]Dipartimento di Studi delle Istituzioni e dei Sistemi Territoriali, Università degli Studi di Napoli ''Parthenope'' , [†]Dipartimento di Medicina Clinica, Scienze Cardiovascolari ed Immunologiche, Area Funzionale di Riabilitazione Cardiologica, [‡]Dipartimento di Pediatria, Università degli Studi di Napoli ''Federico II'', Naples, Italy

ABSTRACT

Background Primary ciliary dyskinesia (PCD) is a rare, usually autosomal recessive disorder of ciliary dysfunction associated with lung involvement, which has a great impact on health. There is limited information concerning the aerobic fitness of children and adolescents with PCD. The aim of this study was to assess cardiopulmonary functional capacity and its relationship with pulmonary function and physical activity (PA) levels in patients with PCD.

Design Ten patients with PCD (age 13·2 ± 2·8 years) underwent spirometry and cardiopulmonary exercise testing. PA was investigated through a questionnaire. Eight age- and body mass index-matched healthy children were enrolled as controls. Main variables were forced expiratory volume at 1 s, peak oxygen uptake (VO_{2peak}) and time spent in PA.

Results Forty per cent of patients with PCD had impaired lung function as expressed by FEV_1 < 85% predicted. Only patients with impaired lung function exhibited reduced VO_{2peak} (18·1 ± 7·9 mL/kg/min). Time spent in total daily PA was slightly lower in patients than controls, with no difference between patients with normal or reduced lung function. In multiple regression models, male gender (β = 0·518, P = 0·018), age (β = 0·752, P = 0·035) and time spent in vigorous PA (β = 0·353, P = 0·049) were independent predictors of aerobic fitness.

Conclusions Assessment of resting pulmonary function and cardiopulmonary functional capacity could contribute to the evaluation of pulmonary impairment in PCD. Given the benefit of physical exercise on airway clearance and on general health and quality of life, patients with PCD should be encouraged to adopt an active lifestyle.

Keywords Cardiopulmonary exercise test, chronic lung diseases, peak oxygen uptake, physical activity, primary ciliary dyskinesia, pulmonary function.

Eur J Clin Invest 2012; 42 (6): 617–622

Introduction

In the last decades, a relevant interest has been directed to the assessment of aerobic fitness in chronic lung diseases, as it may be a marker for less severe illness and a valuable tool for predicting prognosis [1]. Peak oxygen uptake (VO_{2peak}) during maximal cardiopulmonary exercise testing is considered the 'gold standard' measure of aerobic fitness [2]. While most studies were performed in asthma or cystic fibrosis (CF), there is very limited information concerning the aerobic fitness of children and adolescents with primary ciliary dyskinesia (PCD, MIM #242650). PCD is a rare (1 : 15 000–30 000 live births) and usually autosomal recessive disease, associated with *situs viscerum inversus* (Kartagener syndrome) in nearly half the cases [3]. Impaired mucociliary clearance because of defective motility of cilia is the hallmark of the condition [4]. Early major clinical events are recurrent lower and upper airway infections that can favour the development of chronic lung disease [4,5]. Although less severe than CF, PCD has a progressively greater impact on health in the second half of life, producing significant morbidity and restriction of life style [6].

There is strong evidence indicating that cardiopulmonary fitness is associated with reduced cardiovascular risk factors, higher bone mineral density and positive general effects on depression, anxiety, mood status and self-esteem in children [7,8]. To date, data on cardiopulmonary functional capacity

evaluation are lacking in patients with PCD. Therefore, this study aims at evaluating cardiopulmonary functional capacity and its relationship with pulmonary function tests and physical activity (PA) levels in a group of children and adolescents with PCD.

Patients and methods

Patients

The study was performed between June 2007 and December 2008. At this time, 24 children with PCD (17 men; age, 7·6 ± 5·5 years; range, 0·1 ± 19 years) were followed at the Department of Pediatrics, Federico II University of Naples, Italy. Fourteen of them were excluded from the study, as they were unable to perform spirometry and/or maximal cardiopulmonary exercise testing for their young age (3·5 ± 3·8 years). Therefore, the study sample included 10 subjects (seven men; age, 13·2 ± 2·8 years).

Primary ciliary dyskinesia was suspected on the basis of clinical features and/or *situs viscerum inversus* [5]. Diagnosis was confirmed by light microscopy and electron microscopic ultrastructural analysis of cilia on a nasal brush specimen. Light microscopy revealed dysmotility or immotility in all cases. Clinical characteristics and electron microscopy data of the study population are summarized in Table 1. In all patients, ongoing treatment consisted of the following: daily airway clearance therapy, which included chest physiotherapy and nebulized saline prior to chest physiotherapy, and aggressive treatment of upper and lower airway infections with antibiotic therapy. None of them were on treatment with inhaled bronchodilators or corticosteroids. Exclusion criteria were acute upper and/or lower airway infections and any concurrent medical illness at the time of the study.

Table 1 Clinical and electron microscopy data of patients with PCD

Clinical data	Patients
Men/Women	7/3
Situsvisceruminversus	8
Age at PCD diagnosis (years)	7·0 ± 5·3
Ultrastructural defects of cilia*	
Inner and/or outer dynein arms absence	6
Outer doublets disarranged	1
Few outer and inner dynein arms	2
Short inner dynein arms	1
Microtubule translocation 9 + 0	0
Basal body abnormality	1
Outer doublets extra tubules	0
Ciliary aplasia	0

*As patients can have more than one ultrastructural abnormality, totals can exceed 100%.
PCD, primary ciliary dyskinesia.

Height and weight were measured with the subjects wearing only light clothes and no shoes. The body mass index (BMI) was calculated (weight/height^2) and then transformed into BMI standard deviation scores (BMI-SDS) according to the Italian standards [9].

We also recruited eight age-, sex- and BMI-matched healthy nonatopic subjects (seven male; mean age, 13·7 ± 3·1 years) who had a normal spirometry.

Methods

Lung function assessment. Prior to cardiopulmonary exercise, pulmonary function was determined according to standard spirometry techniques [10]. Forced vital capacity (FVC), forced expiratory volume at 1 s (FEV_1) (expressed as % of predicted) and FEV_1/FCV (expressed as %) were obtained. FEV_1 > 85% predicted was regarded as normal.

Physical activity assessment. To obtain information about the levels of PA, a modified version of the long International Physical Activity Questionnaire (IPAQ) for adolescents [11] and translated into Italian according to the IPAQ committee guidelines (http://www.ipaq.ki.se/cultural.htm) was administered to patients with PCD and controls. The questionnaire focuses on four domains: (i) school-related PA, including activity during physical education classes and breaks; (ii) transportation; (iii) housework and (iv) leisure time. IPAQ was administered as interview directly to the patients if age was > 15 years or alternatively to their parents or legal guardians if age was below 15 years. For each of the four domains, the number of days per week and the number of PA periods per day (> 10 min of walking, moderate activity or vigorous activity) were recorded. Outcome measures were average minutes per day of walking, moderate or vigorous activities; the sum of these variables was computed to obtain minutes per day of total PA.

Cardiopulmonary exercise test. Both patients and controls underwent an incremental cardiopulmonary exercise test on a bicycle ergometer (Ergoline Ergometrics 800; Bitz, Germany). Before each test, oxygen and carbon dioxide analysers and a flow mass sensor were calibrated by the use of available precision gas mixtures and a 3-L syringe, respectively. All equipments were calibrated according to the instructions of the manufacturer before testing. To stabilize gas measurements,

patients were asked to remain still on the ergometer for at least 3 min before starting exercise. After a 1-min warm-up period at 0 W workload, a ramp protocol of 15 W/min was started and continued until exhaustion. The pedalling was kept constant at 55–65 revolutions per minute. All patients were verbally encouraged to exercise to exhaustion, as assessed using a cut-off > 1·01 for the respiratory exchange ratio at peak exercise. After maximal exercise has been reached, a cooling-down phase consisted of 5 min of pedalling at a slow rate (< 40 revolutions/min) at a work rate of 0 W. A 12-lead electrocardiogram was monitored continuously during the test, and cuff blood pressure was manually recorded every 2 min.

Respiratory gas exchange measurements were obtained breath by breath with the use of a computerized metabolic cart (Vmax 29C; Sensormedics, Yorba Linda, CA, USA). Peak oxygen consumption (VO_{2peak}) was recorded as the mean value of VO_2 during the last 20 s of the test and was expressed in millilitres per kilogram per minute. At the end of the cardiopulmonary exercise test, patients were asked to identify the primary reason for stopping. Medical treatment administered the day of exercise testing was recorded. VO_{2peak} was measured and compared with maximal predicted VO_2 by use of a sex-, age-, height- and weight-adjusted and protocol-specific formula outlined by Wassermann *et al*. [12,13]. The ventilation (VE) vs. VCO_2 relationship was measured by plotting minute VE against carbon dioxide production (VCO_2) obtained every 10 s of exercise (VE/VCO_2 slope): both VE and VCO_2 were measured in litres per minute. The VE/VCO_2 slope was calculated as a linear regression function, excluding the nonlinear part of the relationship after the onset of acidotic drive to VE as previously described [14,15].

The ethics review board of the Medical School, Federico II University, approved the study, and informed, written consent was obtained from the parent/legal guardian of each child and from adult patients themselves. Reporting of the study conforms to the STROBE statement for observational studies and the EQUATOR guidelines for health research [16].

Statistical analysis

Results are expressed as mean ± standard deviation unless otherwise specified. The outcome variables were normally distributed, and therefore the independent samples *t*-test or the ANOVA test with Bonferroni *post hoc* analyses were used for comparisons. Multiple linear regression analysis was performed to determine the determinants of VO_{2peak}. The dependent variable was VO_{2peak}, while the independent variables were gender, age, BMI-SDS, FEV_1% and time spent in total or vigorous PA. *P*-value < 0·05 was considered significant. All statistical analyses were carried out using the Statistical Package of Social Sciences (SPSS, Chicago, IL, USA) for Windows software program release 15·0.

Results

All patients performed the cardiopulmonary exercise testing without complications and were able to complete the protocol to volitional exhaustion. No electrocardiography abnormalities were noted during exercise testing. Neither the patients with PCD nor the control group had oxygen desaturation during exercise.

Spirometry was obtained by all patients with PCD. FVC was 95·5 ± 11·8% predicted, FEV_1 was 87·5 ± 9·6% predicted and the FEV_1/FCV was 77·1 ± 6·1%. FEV_1 was normal (i.e. > 85% predicted) in six patients with PCD (60% of the total). Compared with controls, patients with PCD had significantly lower VO_{2peak} ($P < 0·04$) and significantly higher VE/VCO_2 slope ($P = 0·005$) (Table 2). Further analyses were separately performed in patients with normal (FEV_1 94·1 ± 5·4% predicted) or reduced lung function (FEV_1 77·7 ± 3·6% predicted) and compared with controls (Table 2). VO_{2peak} in PCD patients with reduced lung function was significantly lower than controls, while no difference was found when patients with preserved lung function and controls were compared (Table 2). No difference was found among groups with regard to age or BMI-SDS.

Results of the IPAQ questionnaire showed that the time spent in total daily PA was slightly lower in patients with PCD than controls ($P = 0·07$), but did not differ between PCD patients with normal or reduced lung function. When data about vigorous PA were analysed, vigorous PA was reported by six of eight (75%) controls (mean time 34·3 ± 25·9 min/day) and only by two of six (33·3%) PCD patients with normal lung function (mean time 25·0 ± 25·2 min/day). Among patients with PCD and reduced lung function, none reported vigorous PA.

As shown in Table 3, after adjusting for age, gender, BMI and FEV_1% predicted, the time spent in vigorous PA was significantly associated to VO_{2peak} levels in patients with PCD ($P = 0·049$).

Discussion

The present study showed that children and adolescents with PCD had a significantly reduced VO_{2peak} and increased VE/VCO_2 slope compared with age- and BMI-matched healthy controls. When cardiopulmonary findings were stratified according to lung function, only PCD patients with impaired lung function exhibited impaired cardiopulmonary functional capacity.

Cardiopulmonary exercise testing is frequently used as a tool for evaluating chronic condition in children [13,17]. It is well known that exercise capacity, as determined by direct measurement of VO_{2peak}, exerts a major long-term influence on prognosis after myocardial infarction, cardiovascular revascularization and ischaemic heart disease, playing a valuable role in risk stratification and counselling [18,19]. To the best of our knowledge, this is the first study exploring cardiopulmonary

Table 2 Demographic, clinical and cardiopulmonary parameters of the study population

		Patients with PCD		
	Controls	**Whole group**	**Preserved lung function**	**Reduced lung function**
Gender (M/F)	7/1	7/3	5/1	2/2
Age (years)	13·7 ± 3·1	13·2 ± 2·8	13·3 ± 2·4	13·0 ± 3·7
BMI (kg/m^2)	22·0 ± 2·5	21·1 ± 3·05	22·6 ± 3·1	18·9 ± 0·8
BMI-SDS	0·51 ± 0·71	0·24 ± 0·91	0·60 ± 1·0	−0·31 ± 0·42
HR peak (b/pm)	173 ± 17	165·9 ± 15	172 ± 7	157 ± 21
VO_{2peak}* (mL/kg/min)	29·19 ± 6·84	22·0 ± 6·61	24·62 ± 4·52	18·07 ± 7·92
VE/VCO_2 slope†	26·68 ± 3·17	31·15 ± 2·61	30·58 ± 2·75	31·99 ± 2·49†
O_2 pulse (mL/beat)	10·19 ± 3·11	9·88 ± 8·74	7·55 ± 1·73	13·37 ± 14·04
Total PA (min/day)	95·71 ± 55·98	58·86 ± 21·24	63·21 ± 25·02	52·32 ± 14·67

*Patients with PCD (whole group) vs. controls ($P < 0·04$) and reduced lung function vs. controls ($P = 0·038$).
†Patients with PCD (whole group) vs. controls ($P = 0·005$) and reduced lung function vs. controls ($P = 0·028$).
BMI-SDS, BMI standard deviation scores; PA, physical activity; PCD, primary ciliary dyskinesia; VE, ventilation.

functional capacity as expressed by VO_{2peak} and VE/VE/VCO_2 slope in patients with PCD. The lack of data regarding cardiopulmonary functional capacity evaluation in patients with PCD is attributable to the fact that PCD is a rare disease. Several evidences from cross-sectional studies exploring cardiopulmonary functional capacity in children with CF [20–25] essentially conclude that lower FEV_1 and reduced weight for height or lean body mass correlate with lower peak oxygen uptake and that peak VO_2 could predict earlier mortality [1,26].

Several authors reported that higher VO_{2peak} was significantly correlated with survival and that neither FEV_1 improved the relationship in a multivariate model nor VO_{2peak} was better than FEV_1 in predicting likelihood of survival over 5 years [27,28]. More recently, a longitudinal study in patients with CF found that VO_{2peak} fell during the study period of 7–8 years in 70% of the patients, with a mean annual decline of 2·1 mL/min/kg [27]. Interestingly, the initial VO_{2peak} was not predictive of mortality, but in that series, the rate of the decline and the final VO_{2peak} were significant predictors. The study also demonstrated a dramatic increase in mortality among patients with $VO_{2peak} < 32$ mL/min/kg, whereas none of the subjects with $VO_{2peak} > 45$ mL/min/kg died. Finally, the baseline and the last values of FEV_1, and the rate of its decline over time were all significant predictors of mortality [27].

During cardiopulmonary exercise testing, a close linear relation exists between VCO_2 and VE. This relationship appears more linear and less variable than that between oxygen consumption and minute VE [12]. The slope of the regression line between the carbon dioxide output and the minute VE (VE/VCO_2 slope) is, thus, used to describe the ventilatory response to exercise [12]. So far, much interest has been directed towards the excessive exercise ventilatory response found in patients with chronic heart failure that is characterized by a steeper VE/VCO_2 slope [28]. The steeper slope is associated with reduced cardiac output during exercise, increased pulmonary artery and capillary wedge pressures, increased dead space/tidal volume ratio and augmented chemoreceptor sensitivity.

Table 3 Multiple regression analyses

Dependent variable VO_2 peak	**B**	**SE**	**β**	***P***
Model 1				
Independent variables				
Gender (0 = female, 1 = male)	7·945	1·800	0·581	0·012
Age	1·501	0·567	0·633	0·057
BMI-SDS	1·936	1·689	0·270	0·316
FEV_1%	−0·003	0·125	−0·004	0·983
Total PA	0·105	0·039	0·337	0·054
Model 2				
Independent variables				
Gender (0 = female, 1 = male)	7·090	1·824	0·518	0·018
Age	1·783	0·571	0·752	0·035
BMI-SDS	2·642	1·674	0·368	0·190
FEV_1%	−0·022	0·124	−0·031	0·869
Vigorous PA	0·173	0·062	0·353	0·049

BMI-SDS, BMI standard deviation scores; PA, physical activity.

As our patients with PCD did not show any symptoms or signs of cardiac disease, the higher VE/VCO_2 slope we observed might be predominantly because of the altered control of VE [29]. However, the mechanisms causing an increased ventilatory response to exercise in patients with PCD may be multifactorial [30].

Exercise capacity is limited by the degree of severity of pulmonary disease and also by poor nutritional status [24]. A longitudinal study performed in CF documented that VO_{2peak} was correlated with FEV_1 during childhood and that both FEV_1 and patients' age influenced VO_{2peak} [31]. Nevertheless, lung function may be early reduced or impaired in patients with PCD [32]. In our study, FEV_1 was < 85% of predicted in 40% of the patients with PCD. However, none of them showed severely reduced lung function nor was malnourished, as shown by the normal range of BMI. Nevertheless, the time spent in total PA did not significantly differ between patients with different degree of pulmonary function impairment. Interestingly, none of the PCD patients with reduced lung function performed any kind of vigorous PA. We found that the time spent in vigorous PA was an independent predictor of aerobic fitness, along with male gender and age. Physiologically, small gender differences in aerobic capacity are already evident prior to puberty, increase significantly at puberty and persist throughout adolescence into adulthood [33]. The progressive increase in oxygen consumption with age, which has been shown particularly in men, can be explained not only by physical developmental factors during puberty but also by differing levels of PA [34]. Our results confirm that, as it occurs in healthy children [35], vigorous PA can be an important determinant of cardiopulmonary function capacity also in PCD children with mild-to-moderate pulmonary disease. It is feasible that patients with more severe disease have less PA because their chronic disease makes them reluctant to be active. Unfortunately, the cross-sectional design of our study does not allow inferring any causal relationship between reduced VO_{2peak} and PA levels.

Subjects with chronic lung disease have been shown to benefit from exercise training, mainly because it results in improvements of aerobic fitness, cardiopulmonary efficiency and mucociliary clearance, and reduces the subjective sensation of dyspnoea [36]. Increased levels of habitual PA have been also shown to slow the lung function decline [37] and to reduce mortality [27]. The clinical course of PCD resembles CF, although the severity of lung involvement appears generally much less in PCD [30]. Also, the prognosis of PCD has been reported as good, at least on the basis of spirometry [38,39]. However, a recent study showed that pulmonary function consistently deteriorated in one-third of 74 patients with PCD, although it remained stable over time in more than 50% of them [40]. Therefore, prompting patients to increase daily PA could significantly affect the severity of PCD pulmonary disease and improve patients' quality of life. Interestingly, it was previously demonstrated that exercise is a more potent stimulus for bronchodilation than inhaled β_2-agonists in children and adolescents with PCD and obstructive pulmonary disease [41].

Notwithstanding the major drawback because of the small sample size, we believe that our study may provide valuable information on the aerobic fitness of children and adolescents with PCD and its relationship with lung function. Physical training at recommended levels may increase exercise tolerance in patients with PCD, while the use of different cardiopulmonary parameters in the evaluation of exercise tests may give more insight into the mechanisms of reduced exercise tolerance. Cardiopulmonary exercise testing findings may help parents, teachers and coaches to realize that PA is feasible also in subjects with PCD. Patients with PCD should be encouraged to adopt an active lifestyle, given the benefit of physical exercise not only on airway clearance but also on general health and quality of life [42]. Finally, we believe that the combination of resting pulmonary function measurements and of cardiopulmonary functional capacity might be remarkably helpful for pulmonary assessment in PCD as well as for the prescription of tailored exercise programmes, to make PA safe for these patients.

Acknowledgements

The Authors thank Prof Luis A. Moreno Aznar, University of Zaragoza, for kindly providing us the IPAQ version for Adolescents on behalf of the Healthy Lifestyle by Nutrition in Adolescence (HELENA) Study.

Address

Dipartimento di Studi delle Istituzioni e dei Sistemi Territoriali, Università degli Studi di Napoli ''Parthenope'', Naples, Italy (G. Valerio, N. Vaino); Dipartimento di Medicina Clinica, Scienze Cardiovascolari ed Immunologiche, Area Funzionale di Riabilitazione Cardiologica, Università degli Studi di Napoli ''Federico II'', Naples, Italy (F. Giallauria, C. Vigorito); Dipartimento di Pediatria, Università degli Studi di Napoli ''Federico II'', Naples, Italy (S. Montella, V. Mirra, F. Santamaria).
Correspondence to: Francesca Santamaria, MD, Dipartimento di Pediatria, Università degli Studi di Napoli ''Federico II'', Via Pansini 5, 80131 Naples, Italy. Tel.: +39 081 7463495; fax: +39 081 7463116; e-mail: santamar@unina.it

Received 20 June 2011; accepted 1 November 2011

References

1 Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992;**327**:1785–8.

2 Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD. Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. *Med Sci Sports Exerc* 2007;**39**:103–7. Erratum in: Med Sci Sports Exerc 2007;**39**:574.
3 Afzelius BA. Cilia-related diseases. *J Pathol* 2004;**204**:470–7.
4 Schidlow DV. Primary ciliary dyskinesia (the immotile cilia syndrome). *Ann Allergy* 1994;**73**:457–68.
5 Bush A, Chodhari R, Collins N, Copeland F, Hall P, Harcourt J *et al.* Primary ciliary dyskinesia: current state of the art. *Arch Dis Child* 2007;**92**:1136–40.
6 McManus IC, Mitchison HM, Chung EM, Stubbings GF, Martin N. Primary ciliary dyskinesia (Siewert's/Kartagener's syndrome): respiratory symptoms and psycho-social impact. *BMC Pulm Med* 2003;**3**:4.
7 Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. *Int J Obes (Lond)* 2008;**32**:1–11.
8 Tanha T, Wollmer P, Thorsson O, Karlsson MK, Lindén C, Andersen LB *et al.* Lack of physical activity in young children is related to higher composite risk factor score for cardiovascular disease. *Acta Paediatr* 2011;**100**:717–21.
9 Cacciari E, Milani S, Balsamo A, Dammacco F, De Luca F, Chiarelli F *et al.* Italian cross-sectional growth charts for height, weight and BMI (6–20 y). *Eur J Clin Nutr* 2002;**56**:171–80.
10 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A *et al.* Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38.
11 Hagstromer M, Bergman P, De Bourdeaudhuij I, Ortega FB, Ruiz JR, Manios Y *et al.* Concurrent validity of a modified version of the International Physical Activity Questionnaire (IPAQ-A) in European adolescents: the HELENA Study. *In J Obes (Lond)* 2008;**32**:S42–8.
12 Wasserman K, Hansen JE, Sue DY, Whipp BJ. *Principles of Exercise Testing and Interpretation*. Philadelphia: Lea & Febiger; 1987.
13 Ten Harkel AD, Takken T, Van Osch-Gevers M, Helbing WA. Normal values for cardiopulmonary exercise testing in children. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:48–54.
14 Giallauria F, Lucci R, De Lorenzo A, D'Agostino M, Del Forno D, Vigorito C. Favourable effects of exercise training on N-terminal pro-Brain Natriuretic Peptide plasma levels in elderly patients after acute myocardial infarction. *Age Ageing* 2006;**35**:601–7.
15 Giallauria F, Cirillo P, Lucci R, Pacileo M, De Lorenzo A, D'Agostino M *et al.* Left ventricular remodeling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-Brain Natriuretic Peptide. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:113–8.
16 Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *Eur J Clin Invest* 2010;**40**:35–53.
17 Takken T, Blank AC, Hulzebos EJ, Van Brussel M, Groen WG, Helders PJ. Cardiopulmonary exercise testing in congenital heart disease: equipment and test protocols. *Neth Heart J* 2009;**17**:339–44.
18 Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P *et al.* Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002;**106**:666–71.
19 Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P *et al.* Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol* 2003;**42**:2139–43.
20 Godfrey S, Mearns M. Pulmonary function and response to exercise in cystic fibrosis. *Arch Dis Child* 1971;**46**:144–51.
21 Cerny FJ, Pullano TP, Cropp GJ. Cardiorespiratory adaptations to exercise in cystic fibrosis. *Am Rev Respir Dis* 1982;**126**:217–20.
22 Cropp GJ, Pullano TP, Cerny FJ, Nathanson IT. Exercise tolerance and cardiorespiratory adjustments at peak work capacity in cystic fibrosis. *Am Rev Respir Dis* 1982;**126**:211–6.
23 Marcotte JE, Canny GJ, Grisdale RK, Desmond K, Corey M, Zinman R *et al.* Effects of nutritional status on exercise performance in advanced cystic fibrosis. *Chest* 1986;**90**:375–9.
24 Marcotte JE, Grisdale RK, Levison H, Coates AL, Canny GJ. Multiple factors limit exercise capacity in cystic fibrosis. *Pediatr Pulmonol* 1986;**2**:274–81.
25 Lands LC, Heigenhauser GJ, Jones NL. Analysis of factors limiting maximal exercise performance in cystic fibrosis. *Clin Sci* 1992;**83**:391–7.
26 Moorcroft AJ, Dodd ME, Webb AK. Exercise testing and prognosis in adult cystic fibrosis. *Thorax* 1997;**52**:291–3.
27 Pianosi P, Leblanc J, Almudevar A. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax* 2005;**60**:50–4.
28 Clark AL, Poole-Wilson PA, Coats AJS. The relationship between ventilation and carbon dioxide production in patients with chronic heart failure. *J Am Coll Cardiol* 1992;**20**:1326–32.
29 Green K, Buchvald FF, Marthin JK, Hanel B, Gustafsson PM, Nielsen KG. Ventilation inhomogeneity in children with primary ciliary dyskinesia. *Thorax* 2011; Sep 26; doi:10.1136/thoraxjnl-2011-200726 [Epub ahead of print].
30 Santamaria F. Structural and functional lung disease in primary ciliary dyskinesia. *Chest* 2008;**134**:351–7.
31 Pianosi P, LeBlanc J, Almudevar A. Relationship between FEV1 and peak oxygen uptake in children with cystic fibrosis. *Pediatr Pulmonol* 2005;**40**:324–9.
32 Brown DE, Pittman JE, Leigh MW, Fordham L, Davis SD. Early lung disease in young children with primary ciliary dyskinesia. *Pediatr Pulmonol* 2008;**43**:514–6.
33 Rowland T, Goff G, Margel L, Ferrone L. Influence of cardiac functional capacity on gender differences in maximal oxygen uptake in children. *Chest* 2000;**117**:629–35.
34 Krahenbuhl GS, Skinner JS, Kohrt WM. Developmental aspects of maximal aerobic power in children. *Exerc Sport Sci Rev* 1985;**13**:503–38.
35 Dencker M, Thorsson O, Karlsson MK, Lindén C, Svensson J, Wollmer P *et al.* Daily physical activity and its relation to aerobic fitness in children aged 8–11 years. *Eur J Appl Physiol* 2006;**96**:587–92.
36 Wilkes DL, Schneiderman JE, Nguyen T, Heale L, Moola F, Ratjen F *et al.* Exercise and physical activity in children with cystic fibrosis. *Paediatr Respir Rev* 2009;**10**:105–9.
37 Williams CA, Benden C, Stevens D, Radtke T. Exercise training in children and adolescents with cystic fibrosis: theory into practice. *Int J Pediatr*. 2010; pii 670640. doi:10.1155/2010/670640 [Epub 2010] Sep 19.
38 Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M *et al.* Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med* 2004;**169**:459–67.
39 Ellerman A, Bisgaard H. Longitudinal study of lung function in a cohort of primary ciliary dyskinesia. *Eur Respir J* 1997;**10**:2376–9.
40 Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung function in patients with primary ciliary dyskinesia: a cross-sectional and 3-decade longitudinal study. *Am J Respir Crit Care Med* 2010;**181**:1262–8.
41 Phillips GE, Thomas S, Heather S, Bush A. Airway response of children with primary ciliary dyskinesia to exercise and β_2-agonist challenge. *Eur Respir J* 1998;**11**:1389–91.
42 Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G *et al.* Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. *Eur Respir J* 2009;**34**:1264–76.

