Cardiopulmonary Exercise Testing Differentiates Disease Progression in Monozygotic Twins With Idiopathic Pulmonary Fibrosis

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a common type of interstitial lung disease (ILD) that causes scarring of the lungs and makes it difficult to breathe. Lung damage caused by progressive scarring worsens over time and cannot be reversed, eventually leading to pulmonary failure and death. The latest estimates suggest IPF accounts for 1% of all deaths in the United Kingdom (1).

Patients with IPF typically undergo basic resting lung function testing where measurements such as forced vital capacity (FVC) and the lung diffusing capacity for carbon monoxide (DL_{CO}) are routinely interpreted alongside radiological assessments for evaluating clinical status and mortality risk (2). However, it has also been well established in several other patient conditions associated with chronic cardiac and/or pulmonary diseases that evaluating cardiorespiratory function associated with cardiopulmonary exercise testing (CPET) can generate strong clinical information and prognostic indicators, including peak exercise oxygen uptake (Vo_{2peak}) (3,4). Evaluating patients for both lung function at rest and cardiorespiratory function associated with CPET typically strengthens the clinical interpretability of both sets of measurements (5–7).

In this case study we describe how we used serial CPET to characterize exercise cardiopulmonary function and how this information can be used to identify differences in disease progression between adult monozygotic twins with IPF, who otherwise exhibited similar genetics, baseline resting lung function, and environmental exposures over the course of their disease history.

CASE PRESENTATION

We report on a pair of female monozygotic twins who were 67 years of age at the time of testing described in this study. One twin (Twin A) was diagnosed with IPF in October 2012, and the other (Twin B) in March 2018. Past smoking histories were 1.45 and 7.35 pack-years for Twin A and Twin B, respectively. Twin A briefly underwent hormone replacement therapy, whereas Twin B maintained hormone replacement therapy for approximately 8 years (48–56 years of age). Twin A took pirfenidone for the pharmacologic management of IPF, whereas Twin B did not take any antifibrotic medications.

Both twins were enrolled in an existing study to examine the feasibility of CPET among individuals diagnosed with a range of ILDs, including IPF (5). Prospective CPET data reported in this study represent responses from 3 serial CPETs conducted over a 6-month timeframe (0, 3, 6 months). At the time of study enrolment, and throughout the 6 months, both twins exhibited comparable levels of physical (in)activity according to responses provided for the General Practice Physical Activity Questionnaire (8), and equivalent Gender-Age-Physiology (IPF GAP) scores (9).

All CPET studies were performed on an electronically braked upright cycle ergometer (Lode Excalibur; Lode,

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Groningen, Netherlands) using methods previously described (5,10). Serial resting lung function measurements (e.g., FVC and DL_{CO}) were retrospectively obtained from medical records, and only those results that were closest to each CPET date are reported herein. Relative Vo_{2peak}, FVC, and DL_{CO} responses were evaluated using percentage achieved of predicted values (11–13).

Other study measurements and assessments included body composition (BodPod; COSMED, Rome, Italy), blood analyses (neutrophil/lymphocyte [N/L] ratio) (14,15), and quality of life (Kings Brief ILD Questionnaire [K-BILD]) (16).

Over the study period, Twin A exhibited consistent FVC and DL_{CO} levels, whereas Vo_{2peak} fluctuated (Figure 1). By contrast, Twin B exhibited relatively consistent DL_{CO} and Vo_{2peak} levels over time, whereas FVC initially declined between tests 1 and 2 before stabilizing from test 2 to 3 (Figure 1).

Body composition remained relatively unchanged over the study period for both twins. Alternatively, N/L ratio and K-BILD responses over the study period were highly variable for Twin A, but generally unchanged for Twin B.

Within person CPET responses illustrate Twin A exhibited trends for improved peak power output, heart rate reserve (HRR) and breathing reserve ($V_E \cdot MVV^{-1}$) over the study period (Table 1). However, the interpretation of these trends should also consider peak power output, rating of perceived effort, and perceived dyspnea responses during the initial CPET indicated submaximal effort, which was consistent with an inability to identify the gas exchange threshold. The combination of low Vo_{2peak} and low oxygen saturation (Spo_2) observed during the final CPET did however suggest the presence of progressively worsening arterial oxygenation secondary to a pulmonary oxygen transport limitation during exercise.

In contrast to CPET trends observed for Twin A, Twin B demonstrated subtle improvements in peak power output and V_E/MVV, less variable HRR and Spo_2 levels, and more consistent exercise effort across the 3 CPETs. When coupled with the observation that Vo_{2peak} and gas exchange threshold

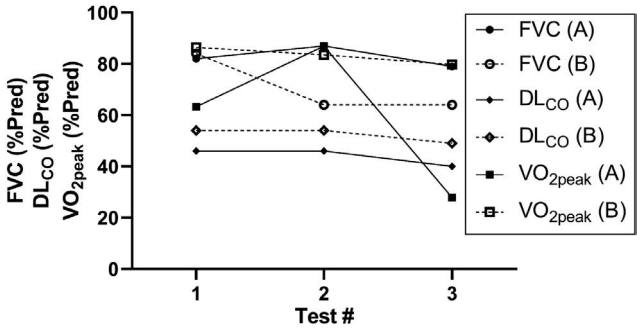

FIGURE 1. Changes in pulmonary function and aerobic fitness over observation period. Resting lung function test measurements that were retrospectively aligned with prospective cardiopulmonary exercise tests conducted at 0, 3, and 6 months respectively. FVC = forced vital capacity; DL_{CO} = lung diffusion capacity for carbon monoxide; Vo_{2peak} = peak exercise oxygen uptake.

were both low and generally unchanged over the study period, these collective responses are consistent with musculoskeletal limitations associated with deconditioning playing an influential role in determining the exercise capacity of Twin B for each of the 3 CPETs.

DISCUSSION

We report for the first time observations from serial CPET studies conducted prospectively over matched periods of time in a pair of monozygotic twins with IPF. We illustrate cardiopulmonary exercise physiology differed between twins even though these individuals exhibited the same genetic profile, pulmonary disease, and environmental and behavioral exposures. Incorporating CPET that is scheduled at regular time intervals as part of routine clinical evaluation and management of IPF can yield information that cannot be gathered via traditional lung function testing but can be used to assist in clinical decision making.

We highlight how conducting CPET and evaluating markers such as Vo_{2peak} can provide unique information that can potentially share associations with nonpulmonary outcomes such as N/L ratio and quality of life, but without correlating with traditional FVC and DL_{CO} measurements typically used to inform clinical decisions in IPF. The use of serial CPET illustrated in this study aids in improving the ability to identify possible actionable non-IPF specific contributing causes of exercise intolerance in long-standing IPF, which otherwise could not have been characterized by relying on resting lung function measurements alone.

The prognostic use of CPET assessed markers of integrative cardiopulmonary function such as Vo_{2peak} have been studied and reviewed to a limited extent in ILD (3). This case study adds to this body of knowledge by illustrating that the clinically relevant information generated from CPET can be further strengthened when routine serial testing occurs over time. Without the unique information gained from serial CPET it is possible that it would have been determined that Twin A exhibited a stable level of disease based on nominal changes observed for pulmonary function over time, whereas disease severity may have been determined to be worsened in Twin B based on declining FVC. Instead, this case study underscores how integrating information gained from CPET into the interpretation of standard clinical tests resulted in identifying a possible need for alternative approaches to clinical management strategies, such as incorporating into care plans prescribed aerobic-based exercise training. We report observations in this case study that are consistent with the suggestion that spirometry-based measurements demonstrate weak independent correlations with radiographic outcomes in ILD (17), and resting lung function measurements do not provide strong information about cardiopulmonary exercise physiological function.

Previous studies have characterized the genetic basis of specific exercise performance phenotypes (18), indicating that a series of genes can strongly affect key fitness parameters such as Vo_{2peak}. Therefore, it is somewhat unexpected that serial CPET data we report in this study does not support

TABLE 1. Clinical and exercise outcomes for both twins at each time point for the observation period.

	Twin A			Twin B		
	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
Clinical Factors						
%FFM	57.5	57.1	58.4	55.4	55.3	55.3
N/L Ratio	3.40	7.43	5.00	1.58	1.26	1.34
K-BILD	60.2	66.2	54.8	52.9	51.6	50.4
Exercise Responses						
PPO, %Pred	48.1	77.2	75.6	58.4	55.6	63.8
HRR, %	20.0	−1.0	−8.0	−4.0	1.0	3.0
$V_E \cdot MVV^{-1}$, %	43.79	50.01	27.07	70.39	51.21	54.24
GET, $\%Vo_{2peak}$	n/a	58.6	86.1	40.3	54.6	40.7
RPE	7	13	15	17	15	15
RPD	1	5	5	5	4	5
Nadir Spo_2	88	85	81	88	85	90

%FFM = fat free mass as a percentage of total body mass; GET = gas exchange threshold; HRR = heart rate reserve; K-BILD = King's Brief Interstitial Lung Disease Questionnaire; N/L Ratio = neutrophil/lymphocyte ratio; PPO = peak power output; RPE = rating of perceived exertion (Borg, 6-20); RPD = rating of perceived dyspnoea (modified Borg, 0-10); Spo_2 = peripheral oxygen saturation; $V_E \cdot MVV^{-1}$ = minute ventilation/maximal voluntary ventilation (breathing reserve); Vo_{2peak} = peak exercise oxygen uptake

the suggestion that genotype-phenotype interactions largely explained the cardiopulmonary exercise response profiles of monozygotic twins with IPF. Other influential factors responsible for the unique cardiopulmonary exercise physiological function demonstrated by each twin in this study could for example, relate to other evidence observed in monozygotic twins suggesting possible genetic associations with exercise training participation (19) and behaviors and attitudes surrounding exercise (20). However, a limitation of this study is that we did not assess attitudes toward exercise training and physical activity participation as part of this research, and therefore it is unclear to what extent such factors influenced our observations.

Exercise outcomes in twins with respiratory disease have to the best of our knowledge been described once before in those diagnosed with alpha-1 antitrypsin deficiency (α1-ATD), where it had been suggested that habitual physical activity yields beneficial effects on exercise tolerance. Physical activity that is performed even at a light intensity (e.g., golf, 2–3 times weekly) is suggested to represent enough of a stimulus to induce improvements, or at least offset declines, in fitness (21). To what extent general physical activity patterns affect cardiorespiratory fitness in IPF is incompletely understood. The twins studied herein self-reported a comparable history of physical activity participation, which may be limited in interpretive value since no accompanying objective physical activity assessment occurred to confirm the physical activity levels of each twin.

In summary, this case illustrates that genetic factors alone are not able to explain the IPF clinical phenotype and cardiopulmonary response to CPET. Monozygotic twins with IPF might also demonstrate disease trajectories over time that do not mirror one another on the basis of serial changes in traditional lung function measurements. The inclusion of CPET conducted on regularly scheduled intervals can provide unique information about the clinical status of patients with IPF to potentially strengthen the interpretability of other standard clinical assessments used for clinical management and the evaluation of future hospitalization and mortality risk.

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