Title: Cardiorespiratory requirements of the 6-min walk test in older patients with left ventricular systolic dysfunction and no major structural heart disease

Running title: Cardiorespiratory requirements of the 6-min walk test in older chronic heart failure

ABSTRACT:

The six-minute walk test (6-MWT) is widely used to assess functional status in patients with chronic heart failure (CHF). The aims of the present study were: (1) to compare metabolic gas exchange during the 6-MWT in older patients with left ventricular systolic dysfunction (LVSD) and in breathless patients with no major structural heart disease (MSHD); (2) to determine the exercise intensity of the 6-MWT relative to peak oxygen uptake; (3) to establish the accuracy and reproducibility of the Metamax 3B ergospirometer during an incremental workload. Twenty four older patients with LVSD (19 male; age 76 ± 5 years; BMI 27 ± 4), and 18 patients with no MSHD (12 male; age 75 ± 8 years; BMI 27 ± 4) attended on consecutive days at the same time. Patients completed a 6-MWT with metabolic gas exchange measurements using the Metamax 3B portable ergospirometer, and an incremental cycle ergometry test using both the Metamax 3B and Oxycon Pro metabolic cart. Patients returned and performed a second 6-MWT and an incremental treadmill test, metabolic gas exchange was measured with the Metamax 3B. In patients with LVSD, the 6-MWT was performed at a higher fraction of maximal exercise capacity (P=0.02).The 6-MWT was performed below the anaerobic threshold in patients with LVSD (83%) and in patients with no MSHD (61%). The Metamax 3B showed satisfactory to high accuracy at 10W and 20W in patients with LVSD (r =0.77-0.97, P<0.05), and no MSHD (r =0.76-0.94, P<0.05). Metabolic gas exchange variables measured during the 6-MWT showed satisfactory to high day-to-day reproducibility in patients with LVSD (ICC=0.75-0.98), but a higher variability was evident in participants with no MSHD (ICC=0.62-0.97). The Metamax 3B portable ergospirometer is an accurate and reproducible device during submaximal, fixed rate exercise in older patients with LVSD and no MSHD. In elderly patients with LVSD and no MSHD, the 6-MWT should not be considered a maximal test of exercise capacity but rather a test of submaximal exercise performance. Our study demonstrates that the 6-MWT takes place at a higher proportion of peak oxygen uptake in patients with LVSD compared to those with no MSHD, and may be one reason why fatigue is a more prominent symptom in these patients.

Keywords: Anaerobic threshold, heart failure, accuracy, reproducibility.

INTRODUCTION:

Left ventricular systolic dysfunction (LVSD) is a common and serious complication of myocardial infarction that leads to greatly increased risk of sudden death and heart failure (HF) [6]. Left ventricular systolic dysfunction and heart failure are not synonymous [18]. Some patients will suffer major left ventricular damage and yet be asymptomatic. Left ventricular systolic dysfunction can be measured fairly objectively but signs and symptoms of HF are subjective and the threshold for diagnosis will vary widely among clinicians. The six-minute walk test (6-MWT) is widely used to assess functional status in patients with LVSD and HF, and is reproducible and sensitive to changes in quality of life [13, 20, 26]. It is a self-paced test, and exercise intensity mimics activities of daily living [4, 29]. However, some reports indicate that its performance may require an exercise intensity above the anaerobic threshold in patients with HF, in contrast to healthy participants [7, 8]. Recently, we showed [14] that clinical predictors of poor 6-MWT performance were similar in patients with LVSD and in patients referred with symptoms of breathlessness, but diagnosed with no major structural heart disease (MSHD). No previous studies have compared metabolic gas exchange measurements during the 6-MWT in these two groups of patients.

Automated metabolic gas analysers provide a broader range of data than traditional Douglas bag methods, and these systems can be used as a 'gold standard' criterion in validation studies [12, 19]. The Oxycon Pro stationary metabolic cart (Viasys, PA, USA) has been previously validated against the Douglas bag system for metabolic measurements of oxygen uptake collected in low to high exercise intensity domains [5, 9, 28]. However, a difficulty in assessing the oxygen cost of the 6-MWT is the need for a valid and reliable portable automated metabolic gas analyser. In patients with HF, the majority of previous studies have used the Cosmed portable breath-by-breath system (Cosmed, Rome, Italy) to collect metabolic gas exchange measurements [7, 8, 10, 17, 29]. The Cortex Metamax I and II portable ergospirometers have been validated during low and moderate intensity exercise in healthy, younger volunteers with results not differing substantially from Douglas bag methods [19, 22] and stationary metabolic carts [23, 24]. Only one previous investigation has shown that data from the Cortex Metamax I device is reproducible in young, healthy participants [12], but the Metamax 3B model has yet to be validated during exercise with incremental workload in older patients with LVSD or in patients with signs of breathlessness but without MSHD. The aims of the present study were: (1) to compare metabolic gas exchange during the 6-MWT in elderly patients with LVSD and in breathless patients with no MSHD; (2) to determine the exercise intensity of the 6-MWT relative to peak oxygen uptake; (3) to establish the accuracy and reproducibility of the Metamax 3B ergospirometer during incremental exercise in these patient groups.

METHODS:

The Hull and East Riding ethics committee approved the study, and all patients provided written informed consent for participation. Patients were recruited from the local community heart failure clinic. Eighty three percent of patients had heart failure of ischaemic aetiology, and all had suffered from the condition for at least 6 months before the study. Patients were studied when they were clinically stable, without any changes in medication during the previous three months. Heart failure was defined in accordance with National Institute for Clinical Excellence Guidelines [25] and the European Society of Cardiology [27]. Left ventricular function was determined from 2D-echocardiography or magnetic resonance imaging. Echocardiography was carried out by one of three trained operators. Left ventricular function was assessed by visual estimation on a scale of normal, mild, moderate, and severe impairment, and was assessed by a second operator blind to the assessment of the first; where there was disagreement on the severity of LV dysfunction, the echocardiogram was reviewed jointly with the third operator and a consensus reached. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's formula from measurements of end-diastolic and end-systolic volumes on apical 2D views, following the guidelines of Schiller and colleagues [30], and LVSD was diagnosed if LVEF was ≤ 40%. When the echocardiogram was of low quality, patients underwent a cardiac magnetic resonance (CMR) scan to determine left ventricular volume and function.

Patients with co-morbidities including chronic obstructive pulmonary disease (COPD) (FEV1 >70% predicted), osteoarthritis, diabetes mellitus, and hypertension were included in the study. Severe renal impairment was diagnosed as estimated GFR <30 $mL \cdot min \cdot 1.73m^2$. There was a history of tobacco use in 83% of patients, although only 6% were current tobacco users. Patients were excluded if they were unable to walk without assistance from another person (not including mobility aids). For comparative purposes, an age-matched control group of participants with no MSHD was included. These participants were referred to the clinic with symptoms of breathlessness, but were not diagnosed with heart failure following investigation; the same inclusion/exclusion criteria applied. All participants were invited to attend on consecutive days at the same time; on Day 1, patients performed a 6-MWT and a submaximal, fixed rate exercise test on a cycle ergometer. On Day 2, patients performed a second 6-MWT, and a symptom-limited graded exercise test to volitional exhaustion on a treadmill.

Day 1

Patients underwent clinical history and physical examination, together with ECG, and echocardiogram. The 6-MWT was conducted following a standardised protocol [1, 11]. A 15 m flat, obstacle-free corridor, with chairs placed at either end was used. Patients were instructed to walk as far as possible, turning 180º every 15 m in the allotted time of six minutes. The Metamax 3B portable ergospirometer (Cortex, Leipzig, Germany) was used to measure metabolic gas exchange. The device requires the patient to wear a tightly fitting facemask to collect exhaled air. A turbine is connected to the facemask to measure respiratory flow. The power source and expired gas analysers are worn in a harness fitted to the chest. The oxygen and carbon dioxide analyser use an electro-chemical cell and infrared absorpimetry system. The radio transmission range is 1000m and data are continuously transmitted to the receiver. The total weight of the device is 330g. Before patient assessment, the device was calibrated against gases of known concentration and volume.

During the 6-MWT, patients were able to rest, if needed, and time remaining was called every second minute [3]. Patients walked unaccompanied so as not to influence walking speed. After six minutes, patients were instructed to stop and total distance covered was calculated to the nearest metre. Standardised verbal encouragement was given to patients after 2 min and 4 min. A rest period of between 30-45 min was administered between the end of the 6-MWT and the start of the cycle ergometer test.

After an initial familiarisation test, participants performed an unloaded warm-up stage on a cycle ergometer for 3 min (Rehcor, Cardiokinetics, Salford, UK). Participants performed three continuous 5-min stages at 10W, 20W and 30W. The duration of these stages was chosen to elicit steady state exercise responses. In randomised order, participants had metabolic gas exchange measured with either the Metamax 3B or Oxycon Pro metabolic cart (VIASYS, PA, USA) for 4 min. The devices were changed after 4 minutes. Initially, the incumbent device was paused, and the mouthpiece connected to the facemask was detached and replaced with the mouthpiece from the second ergospirometer. The exchange took less than 10 seconds, and the final minute of activity was measured immediately following the change of mouthpieces and activation of the new analyser. For comparative purposes, oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), and the respiratory exchange ratio (RER) were averaged over the final 30s of each workload i.e. 3 min 30 sec until 4 min of exercise (1st analyser), and 4 min 30 sec until 5 min of exercise (2nd analyser).

Day 2

The following day, participants returned and repeated the 6-MWT following the same protocol. After a 1 hour rest period, participants then underwent a symptom-limited, treadmill-based maximal exercise test to volitional exhaustion using the Bruce protocol modified by the addition of a Stage 0 with 1.0 mph and 5% gradient. Metabolic gas exchange measurements were made by the Metamax 3B portable ergospirometer. Peak oxygen uptake (p$\dot{V}O_2$), peak carbon dioxide production (p$\dot{V}CO_2$), and peak minute ventilation (p$\dot{V}E$) were measured during the final 30s of the test. Anaerobic threshold (AT) was calculated by the V-slope method [2], and was assessed by a second operator blind to the assessment of the first; where there was disagreement, the AT was reviewed jointly by a third operator and a consensus reached.

Statistical Analysis

Data were analysed using SPSS statistical software for Windows version 11.5 (SPSS Inc, Chicago, Illinois, USA). To assess reproducibility, intraclass correlation coefficients (ICC) with 95% confidence intervals (CIs) were calculated. An ICC of ≥0.75 has been recommended as displaying satisfactory agreement when studying groups of patients, so we used this threshold in our study [13]. Before assessing the accuracy of the ergospirometer, we ran a Kolmogorov-Smirov test which showed that the normality assumption had been violated; consequently, we used the Spearman's correlation coefficient. Paired samples *t*-tests were used to identify group differences; this test statistic was selected as data were normally distributed. Data are presented as mean ± SD, all tests were two-sided, and $P<0.05$ was taken as being statistically significant.

RESULTS:

Twenty four patients with LVSD (19 male; 76 ± 5 years; BMI 27 ± 4; LVEF 36 ± 5%), and 18 participants with no MSHD (12 male; 75 ± 8 years; BMI 27 ± 4; LVEF 58 ± 14%) took part in the study (Table 1). No 6-MWT was prematurely stopped, and only one patient stopped to rest. Five patients in the LVSD group and 3 in the no MSHD group failed to attempt 30W during the fixed rate cycle ergometer test due to breathlessness or leg fatigue. Twenty two percent of echocardiograms were classified as low quality, and in these cases, CMR scans were performed to determine left ventricular volume and function.

Metabolic gas exchange during the 6-MWT

Peak oxygen uptake and anaerobic threshold values were obtained from the incremental treadmill test. Patients with no MSHD had a higher peak oxygen uptake (*P*=0.04) and AT (*P*=0.02) than patients with LVSD (Table 2). Conversely, patients with LVSD have a higher VE/VCO_2 slope (*P*=0.001). Oxygen uptake requirements for the 6-MWT were not different between groups, which shows that $\dot{V}O_2$/metre was lower in controls. Oxygen consumption increased during the 6-MWT in both groups (*P*<0.05) (Figure 1). The AT was higher than mean $\dot{V}O_2$ values during the 6-MWT (*P*<0.05) (Figure 2). In all patients with LVSD, the 6-MWT was performed at a higher proportion of maximal exercise capacity compared with controls (*P*=0.02). The AT in relation to p$\dot{V}O_2$ was significantly higher in patients with LVSD (89 ± 8% v 79 ± 5%, *P*=0.04), and $\dot{V}O_2$ during the 6-MWT as a proportion of the AT was higher in patients with LVSD (83 ± 16% v 61 ± 17%, *P*=0.001). Patients with no MSHD walked significantly further (*P*=0.03) than those with LVSD (Table 3).

Accuracy and reproducibility of the Metamax 3B ergospirometer

Data from the Metamax 3B was accurate (*r* =0.87-0.97, *P*<0.05) and reproducible (ICC=0.78-0.98) at 10W and 20W in patients with LVSD, and in patients without MSHD (*r* =0.76-0.94, *P*<0.05; ICC=0.76-0.98) (Figure 3). At 30W, we did not measure accuracy and reproducibility due to drop-out in both groups.

Day-to-day reproducibility of the 6-MWT

The 6-MWT showed high day-to-day reproducibility in patients with LVSD (ICC=0.98), and those with no MSHD (ICC=0.97). Reproducibility of metabolic gas exchange variables was ICC=0.75-0.98 in patients with LVSD, while in participants without MSHD reproducibility was ICC=0.62-0.97 (Table 3).

DISCUSSION:

Metabolic gas exchange during the 6-MWT

The current study shows that patients with LVSD and no MSHD perform the 6-MWT below the AT; and thus, the 6-MWT is a submaximal test. Patients with LVSD performed the 6-MWT at a higher relative exercise intensity (83% of AT), than those with no MSHD (61% of AT). The mean respiratory exchange ratio was <1.00 during the 6-MWT in both patient groups, also indicating a submaximal test. Five previous studies have examined the relative exercise intensity of the 6-MWT in a similar cohort of patients [7, 8, 10, 17, 29]. Only one of these studies [27] reported that the 6-MWT was a submaximal test in patients with HF. Gayda and colleagues [10] recruited 25 patients with coronary artery disease following a cardiac event, mean age 60 ± 10 years. Patients with a LVEF of >35% were included, with 15 of 25 patients having an LVEF >65%. Patients performed the maximal exercise test on a cycle ergometer, and then performed a 6-MWT using the Cosmed K2 portable ergospirometer. Gayda et al [10] reported that oxygen uptake during the 6-MWT was higher, although not significantly than the AT. It was not clear from the study why patients were asked to perform the maximal exercise test on a cycle ergometer, which does not mimic the movement pattern of the 6-MWT. Secondly, patients did not perform the maximal exercise test with the same ergospirometer, which is likely to have implications for the validity and reproducibility of the data.

Kervio and co-workers [17] recruited 12 patients with HF (9 male, mean age 64 ± 6 years, LVEF = 30 ± 8%) treated with conventional medication. 12 patients with HF (10 male, 66 ± 6 years, LVEF 24 ± 9%) receiving conventional drug therapy plus cardiac pacing were also included. Patients were excluded if they were limited because of co-morbidities including angina, neurological impairments, and orthopaedic limitations (arthritis, claudication). All patients were aged between 55-75 years and categorised in NYHA functional classes II and III, performed a symptom-limited treadmill test using the Cosmed K4 portable ergospirometer and two 6-MWTs (corridor length =18m) using the same device. During the 6-MWT, patients were provided with verbal encouragement every 30 seconds. Oxygen uptake values during the 6-MWT were significantly higher than the AT ($P<0.01$), and consequently the authors reported that the 6-MWT was a near maximal test (90% of peak oxygen uptake). These data conflict with findings in the current study. These differences probably reflect different clinical, demographic and methodological characteristics between the two studies. The current study recruited older patients, inclusion criteria were less restrictive, 6-MWT corridor length was shorter, and verbal encouragement was less frequent. Elderly patients with LVSD and no MSHD perform the 6-MWT below the AT following our protocol and using a corridor length of 15m. These data should not be extrapolated to other populations, or to research groups using a more aggressive 6-MWT coaching approach. Our approach is justified in an elderly, chronic disease population and follows the established guidelines of the American Thoracic Society [1].

We found that there was a gradual increase in oxygen uptake during the 6-MWT. These data suggest that the metabolic demands of the 6-MWT increase as the test duration continues, a finding that has been shown previously in patients with coronary artery disease [10]. However, our data show that even in the final minute of the 6-MWT, the oxygen uptake metabolic demands remain below the AT.

Day-to-day reproducibility of the 6-MWT

The distance walked during the 6-MWT showed high day-to-day reproducibility in patients with LVSD (ICC=0.98), and those with no MSHD (ICC=0.97). Metabolic gas exchange variables were highly reproducibility in patients with LVSD (ICC=0.75-0.98), but a greater degree of variability was seen in participants with no MSHD (ICC=0.62-0.97). Kervio and colleagues [15] showed similar reproducibility data for patients with HF who performed two 6-MWT's on the same day (am and pm). They reported an ICC=0.98-0.99 for 6-MWT distance, and an ICC=0.97-0.99 for mean oxygen uptake during the 6-MWT, in patients with HF under optimal drug therapy and optimal drug therapy plus cardiac pacing. Our study shows that the 6-MWT produces higher day-to-day reproducibility for metabolic gas exchange variables in patients with LVSD than in patients with no MSHD. It is difficult to speculate on explanations for this observation. We have previously shown that the reproducibility of the 6-MWT over 12 months is satisfactory (ICC = 0.80, 95% CI=0.69-0.87) in 74 patients with HF showing no change in symptoms [9]. There is a small decline in reproducibility over 12 months in patients with HF.

Accuracy and reproducibility of the Metamax 3B ergospirometer

In patients with HF, the Cosmed system (Cosmed, Rome, Italy) has been previously used to collect metabolic gas exchange data [7, 8, 10, 17, 29]. Data collected from the portable Metamax I and II systems have shown a strong correlation with data collected from Douglas bags [19, 22] and stationary metabolic carts [23, 24] in healthy, younger adults during low to high intensity incremental exercise. The Metamax 3B model had yet to be validated during exercise with incremental workload in older patients with LVSD or in patients with symptoms of breathlessness but without MSHD. We compared the Metamax 3B portable device against the Oxycon stationary metabolic cart, which has been previously validated against Douglas bag systems [5, 9, 28] and recommended as a 'gold standard' criterion measure [12, 21]. Stationary Oxycon systems have been used previously in HF trials [e.g. 14, 16].

We found satisfactory accuracy and reproducibility in the Metamax 3B in older patients with and without LVSD. Accuracy and reproducibility was not calculated at 30W due to patient drop-out as a result of breathlessness and leg pain. Many of these patients had a peak oxygen uptake of <14 $mL \cdot kg^{-1} \cdot min^{-1}$, and 30W of exercise was an excessively high relative intensity. To identify whether an upward drift in oxygen uptake due to the 'slow component' occurred during the transition phases of the submaximal cycle ergometry test we found that the mean oxygen uptake value was 5.8 $mL \cdot kg^{-1} \cdot min^{-1}$ after 4 min, and 5.9 $mL \cdot kg^{-1} \cdot min^{-1}$ after 5 min at 10W. At 20W, mean oxygen uptake value was 6.9 $mL \cdot kg^{-}$

$^{1}\cdot min^{-1}$ after 4 min, and 6.9 $mL\cdot kg^{-1}\cdot min^{-1}$ after 5 min in patients with LVSD. The same trend was noted in patients with no MSHD suggesting that an upward drift in oxygen uptake due to the 'slow component' was not a factor in the current study.

Studies reporting accuracy and reproducibility data for portable Cortex Metamax systems are scarce, we could only find one study [23], which showed that the Metamax I is highly reproducible (ICC=0.98) during fixed rate, ramped cycle ergometry exercise in healthy, young men. Our findings show that the Metamax 3B portable ergospirometer can be used confidently to perform metabolic gas exchange measurements in patients with LVSD and no MSHD at submaximal workloads (10-20W).

CONCLUSION

The Metamax 3B portable ergospirometer is accurate and reproducible device during submaximal, fixed rate exercise in elderly patients with LVSD and no MSHD. The 6-MWT shows very good day-to-day reproducibility in these patients. However, data should not be extrapolated to other populations, or to groups using a more aggressive 6-MWT coaching approach. In elderly patients with LVSD and no MSHD, the 6-MWT should not be considered a maximal test of exercise capacity but rather a test of submaximal exercise performance. Our study demonstrates that the 6-MWT takes place at a higher proportion of peak oxygen uptake in patients with LVSD compared to those with no MSHD, and may be one reason why fatigue is a more prominent symptom in these patients.

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List of Figures and Tables

Table 1. Baseline clinical characteristics of the sample

Table 2. Maximal exercise test performance in patients with LVSD and no MSHD

Table 3. Day-to-day variability and metabolic gas exchange during the 6-MWT in patients with LVSD and no MSHD

Figure 1. Minute-by-minute changes in mean oxygen uptake values during the 6-MWT in patients with LVSD and no MSHD (mean ± SD)

LVSD: left ventricular systolic dysfunction; No MSHD: no major structural heart disease

Figure 2. Oxygen uptake during the 6-MWT, oxygen uptake at the anaerobic threshold during the 6-MWT, and peak oxygen uptake in patients with LVSD and no MSHD (mean ± SD)

LVSD: left ventricular systolic dysfunction; No MSHD: no major structural heart disease; 6-MWT: 6-minute walk test

Figure 3. Mean oxygen uptake values: Comparison of the portable Metamax 3B ergospirometer and Oxycon Pro metabolic cart in patients with LVSD and no MSHD (mean ± SD)

LVSD: left ventricular systolic dysfunction; No MSHD: no major structural heart disease