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Effect of increased inspired oxygen on exercise performance in patients with heart failure and normal ejection fraction

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ABSTRACT

Introduction: We investigated whether increased concentrations of inspired oxygen (Fio_2) affects exercise tolerance in patients with heart failure and normal ejection fraction (HeFNEF).
Methods: 46 patients (mean age 75 years (63% male) and median NTproBNP 1432 (interquartile range: 543–2378 ng/l)) with HeFNEF (defined as signs or symptoms of heart failure requiring treatment with diuretics, with a left ventricular ejection fraction of >45% by echocardiography and amino terminal pro brain natriuretic peptide (NTproBNP) >220 ng/l) completed three maximal incremental exercise tests with different Fio_2 (21%, 28% and 40%) in random order. Fio_2 was controlled by investigator but blinded to patients. The primary outcome was exercise time (ET).
Results: Increasing Fio_2 significantly increased exercise time (522 ± 180 seconds for 21% to 543 ± 176 seconds, and 542 ± 177 seconds, for 28% and 40%, respectively, $P = 0.04$) with no difference in peak workload (57 ± 25 W, 58 ± 25 W and 57 ± 25 W, for 21%, 28% and 40%, respectively, $P = 0.50$). There was an increase in oxygen saturation but no change in peak heart rate with increasing Fio_2. Compared to patients with LVEF ≥50%, patients with LVEF between 45 and 49% had a significantly greater exercise time and peak workload. There was a correlation between the difference in exercise time between Fio_2 21% and 40% and age; but not with BMI, haemoglobin, creatinine or NTproBNP.
Conclusion: Increasing Fio_2 during exertion leads to a small increase in exercise time in patients with HeFNEF.

1. Introduction

Epidemiological studies suggest that heart failure with normal ejection fraction (HeFNEF) accounts for almost 50% of patients with heart failure (HF), and its prevalence is increasing [1–3]. Compared to patients with heart failure and reduced ejection fraction (HeFREF), those with HeFNEF are usually older and have more comorbidities [4], which plays a significant role in the development and/or worsening of HF symptoms and substantially contributes to the adverse prognosis of patients with HeFNEF. HeFNEF is a heterogeneous clinical syndrome which can be difficult to diagnose and treat [4].

Clinical trials have failed to demonstrate that any pharmacological treatment improves outcomes for patients with HeFNEF [5–10]. However, another important aim of treatment is to alleviate symptoms and to improve wellbeing [11]. The clinical hallmark of HeFNEF is exertional breathlessness, at least partially due to an abnormal increase in left atrial pressure during exercise [4]. Reduction in delivery of oxygen to the periphery and myocardium might contribute to, and aggravate, breathlessness and fatigue [4]. Small trials suggest that increasing inspired oxygen concentration during exercise might prolong exercise time and improve symptoms in patients with HeFREF or pulmonary hypertension [12–14], but the effect on patients with HeFNEF is unknown.

We aimed to assess the effects of increasing inspired oxygen fraction (Fio_2) on exercise capacity in patients with HeFNEF.

2. Methods

This was a single centre, randomised, single-blinded, cross-over trial in patients with HeFNEF. The research conforms to the Helsinki declaration. Ethics approval was granted by an external research ethics committee. The trial was registered on the ClinicalTrials.gov website (Identifier: NCT02949531). All patients gave written informed consent.

Ambulatory patients older than 50 years of age attending a community heart failure clinic were considered for the study if they had had a clinical diagnosis of heart failure with a left ventricular ejection fraction (LVEF) by echocardiography ≥45% and a plasma concentration of amino terminal pro B type natriuretic peptide (NTproBNP) >220 ng/l [15]. Patients had to be taking a diuretic. Patients unable to exercise, and those who had severe mitral or aortic valve disease, haemoglobin <100 g/l, estimated glomerular filtration rate <30 ml/min/1.73 m^2, or severe chronic obstructive pulmonary disease (FEV_1 <50% predicted) were excluded from the study.

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2.1. Exercise protocol

Patients undertook three maximal incremental exercise tests on a stationary cycle using a standardised exercise protocol. Patients cycled at 60 revolutions per minute starting from 0 watts for 4 min; subsequently, resistance increased by 10 watts/min. Patients were encouraged to exercise to their maximum capacity. At the end of the exercise test, the reason for stopping and modified Borg score were recorded.

Inspired oxygen fraction (Fio_2) was administered at different concentrations (21%, 28% and 40%) in a random sequence which was computer generated. All three oxygen concentrations were delivered via a Venturi mask. This allowed the investigator to control the oxygen concentration administered whilst the patients and the technicians conducting the test were blinded to Fio_2. During the exercise test, blood pressure, oxygen saturation, heart rate and rhythm were continuously monitored. The three exercise tests were conducted at approximately weekly intervals.

The primary endpoint was exercise time (ET; seconds). Secondary end points included: peak workload (watts), modified Borg score, peak heart rate (beats per minute), and peak arterial oxygen saturation (O_2 sat; percentage).

2.2. Statistical analysis

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± standard deviation (SD) and non-normally distributed continuous variables as median and interquartile range.

Between-group means of the primary and secondary endpoints were compared using analysis of variance (ANOVA). The method uses "least squares" to fit linear models. We used one-way ANOVA with repeated measures on dose-group. An underlying assumption of the F test is independence of observations. In a repeated measures design, this assumption is almost certainly violated (observations from the same subject are likely to be correlated). To overcome this, we used a correction factor (a number have been proposed in the literature) to the degrees-of-freedom for the F test. We chose one developed by Box which is conservative in a statistical sense (if significant by Box it will be significant by the rest) [16]. Other assumptions of ANOVA were met. Paired *t*-tests were then used to compare the primary and secondary endpoints between exercise tests.

Sub-group analyses of the primary and secondary endpoints were pre-specified and used to explore the relation between age, haemoglobin, creatinine, NTproBNP, body mass index (BMI), sex, the use of a walking aid and heart rhythm (atrial fibrillation vs sinus rhythm) and the end points. The current European Society of Cardiology guidelines on heart failure set an LVEF cut-off at 50% for diagnosing HeFNEF, so we re-analysed the results for patients above and below this LVEF cut-off [11]. Primary and secondary endpoints are shown in boxplots. All analyses were performed on SPSS (V 23.0) and Stata statistical computer packages. A statistical significance was assumed at $P < 0.05$ (two tailed).

There were no missing values for exercise time so an analysis of missing data by multiple imputations was unnecessary [17].

3. Results

Of the 50 patients enrolled, 46 patients completed the three visits, and 4 withdrew (Supplementary Fig. 1). The baseline characteristics of the 46 patients who completed the study are shown in table 1. Most patients were men, overweight and had NYHA class II symptoms. Compared to patients with LVEF ≥50%, patients with LVEF between 45 and 49% had a significantly higher NTproBNP and creatinine, and a lower haemoglobin level.

Increasing Fio_2 led to an increase in exercise time of approximately 20 s ($P = 0.04$). There was no dose response relation: exercise time was increased by the same amount during both tests with increased Fio_2 compared with 21% Fio_2 (Supplementary Table 1; Fig. 1). Increasing Fio_2 had no effect peak workload ($P = 0.50$) and modified Borg score ($P = 0.17$) (Supplementary Table 1; Fig. 1). There was no effect of increasing Fio_2 on heart rate during exercise ($P = 0.65$), although arterial oxygen saturation throughout exercise was higher with increasing Fio_2 ($P = 0.03$) (Supplementary Table 1).

Patients with LVEF ≥50% had a lower exercise time and peak workload than those with LVEF between 45 and 49%, but had a slightly greater increase in exercise time with the increase in Fio_2 from 21% to 28% (Table 2). There was no interaction between increasing Fio_2 and exercise capacity in any subgroup (Supplementary Table 2). There was a positive correlation between the difference in exercise time between Fio_2 of 21% and 40% and age, but not with BMI, haemoglobin, creatinine or NTproBNP level (Supplementary Table 3).

Table 1
Baseline characteristics for all patients who completed three visits of the study and divided according to LVEF (≥50% or between 45 and 49%). SBP: systolic blood pressure, BMI: body mass index; NYHA: New York Hear Association, IHD: ischaemic heart disease, COPD: chronic obstructive pulmonary disease, NTproBNP: amino terminal pro brain natriuretic peptide, Hb: haemoglobin, ECG: electrocardiogram, ECHO: echocardiography, LVEF: left ventricular ejection fraction, LA: left atrial; IVS: interventricular septum, FCV: forced vital capacity, FEV1: forced expiratory volume in 1 s, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, MRA: mineralocorticoid receptor antagonist. Categorical variables are expressed as number (percentage) and continuous variables are expressed as mean (standard deviation) or median (interquartile range) depending on distribution. *P values significant (<0.05) between LVEF ≥50% and 45–49%.

Baseline characteristics	All patients ($N = 46$)	LVEF >50% ($N = 29$)	LVEF 45–49% ($N = 17$)
Demographics			
Age (years)	75 (8)	76 (8)	75 (8)
Male sex (%)	29 (63)	18 (62)	11 (65)
SBP (mm Hg)	146 (23)	150 (23)	140 (23)
Heart rate (bpm)	69 (11)	70 (11)	68 (11)
BMI (kg/m^2)	31 (7)	32 (8)	31 (6)
Weight (kg)	90 (25)	91 (28)	91 (18)
NYHA function class			
I (%)	4 (9)	3 (10)	1 (6)
II (%)	37 (80)	23 (79)	14 (82)
III (%)	5 (11)	3 (10)	2 (12)
Medical history			
Hypertension (%)	28 (61)	19 (66)	9 (53)
Diabetes (%)	16 (35)	10 (35)	6 (35)
IHD (%)	20 (44)	13 (45)	7 (41)
Stroke (%)	3 (7)	3 (10)	0 (0)
Asthma/COPD (%)[a]	10 (22)	8 (28)	2 (12)
Walking aids (%)	14 (30)	9 (31)	5 (29)
Blood test			
NTproBNP (ng/l)	1432 (543–2378)	1282 (443–2244)	2184 (1372–2501)*
Hb (g/l)	12.9 (1.7)	13.5 (1.7)	12.0 (1.5)*
Creatinine (μmol/l)	102 (80–137)	98 (75–125)	125 (95–155)*
ECG and ECHO			
Sinus rhythm (%)	21 (46)	15 (52)	6 (35)
Mean LVEF (%)	54 (7)	58 (5)	47 (1)*
LA size (cm)	4.3 (0.6)	4.2 (0.6)	4.5 (0.5)
IVS (cm)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Spirometry			
FCV % predicted	70 (17)	69 (21)	71 (12)
FEV1% predicted	75 (20)	77 (23)	73 (17)
Medical therapy			
Beta blocker (%)	37 (80)	23 (79)	14 (82)
ACEi (%)	30 (65)	17 (59)	13 (77)
ARB (%)	10 (22)	7 (24)	3 (18)
Loop diuretics (%)	39 (89)	26 (90)	13 (77)
MRA (%)	23 (50)	13 (45)	10 (59)
Diuretic (%)	46 (100)	29 (100)	17 (100)
Digoxin (%)	8 (17)	8 (28)	0 (0)*
Statin (%)	34 (74)	22 (76)	12 (71)
Aspirin (%)	14 (30)	10 (35)	4 (24)
Anticoagulant (%)	28 (61)	16 (55)	12 (71)

[a] Those with severe COPD (FEV_1 <50% predicted) were excluded from the study.

4. Discussion

We have found that in patients with HeFNEF, increasing oxygen concentration during exercise leads to a small increase in exercise time but had no effect on peak work load.

There are no previous trials of supplementary oxygen during exercise in patients with HeFNEF. Trials of oxygen supplementation during exercise in patients with heart failure with reduced ejection fraction (HeFREF) have yielded mixed results. Moore and colleagues reported a dose dependent increase in exercise time from 548 ± 275 s on room air to 632 ± 288 s with FiO_2 of 50% in 12 patients with HeFREF during resistance cycling on a stationary bike to maximum capacity (workload was increased by 15 W at 2-min intervals) [12]. In contrast, Russell and

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