Impaired oxygen uptake kinetics in heart failure with preserved ejection fraction

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ABSTRACT

Objective The time needed to increase oxygen utilisation to meet metabolic demand (VO_2 kinetics) is impaired in heart failure (HF) with reduced ejection fraction and is an independent risk factor for HF mortality. It is not known if VO_2 kinetics are slowed in HF with preserved ejection fraction (HFpEF). We tested the hypothesis that VO_2 kinetics are slowed during submaximal exercise in HFpEF and that slower VO_2 kinetics are related to impaired peripheral oxygen extraction.

Methods Eighteen HFpEF patients (68 ± 7 years, 10 women) and 18 healthy controls (69 ± 6 years, 10 women) completed submaximal and peak exercise testing. Cardiac output (acetylene rebreathing, $\dot{Q}_c$), ventilatory oxygen uptake (VO_2 , Douglas bags) and arterial-venous O_2 difference ($a\text{-vO}_2$ difference) derived from $\dot{Q}_c$ and VO_2 were assessed during exercise. Breath-by-breath O_2 uptake was measured continuously throughout submaximal exercise, and VO_2 kinetics was quantified as mean response time (MRT).

Results HFpEF patients had markedly slowed VO_2 kinetics during submaximal exercise (MRT: control: 40.1 ± 14.2 , HFpEF: 65.4 ± 27.7 s; $p < 0.002$), despite no relative impairment in submaximal cardiac output ($\dot{Q}_c$: control: 8.6 ± 1.7 , HFpEF: 9.7 ± 2.2 L/min; $p = 0.79$). When stratified by MRT, HFpEF with an MRT ≥ 60 s demonstrated elevated $\dot{Q}_c$ and impaired peripheral oxygen extraction that was apparent during submaximal exercise compared with HFpEF with a MRT < 60 s (submaximal $a\text{-vO}_2$ difference: MRT < 60 s: 9.7 ± 2.1 , MRT ≥ 60 s: 7.9 ± 1.1 mL/100 mL; $p = 0.03$).

Conclusion HFpEF patients have slowed VO_2 kinetics that are related to impaired peripheral oxygen utilisation. MRT can identify HFpEF patients with peripheral limitations to submaximal exercise capacity and may be a target for therapeutic intervention.

VO_2 kinetics and exercise intolerance. However, a distinguishing feature of HFrEF is reduced cardiac output ($\dot{Q}_c$) at rest that remains depressed throughout submaximal and maximal exercise, such that oxygen uptake is partially limited by reduced bulk oxygen delivery to working skeletal muscle.^{6,7} HFrEF and HFpEF share many pathophysiological features that contribute to impaired VO_2 kinetics including reduced skeletal muscle diffusive and oxidative capacity.⁸ However, a critical difference between these HF patients is the presence of an adequate $\dot{Q}_c$ response to *submaximal* exercise in heart failure with preserved ejection fraction (HFpEF) compared with HFrEF patients^{7,9,10} despite significant central limitations during maximal exercise in HFpEF.¹¹

Similar to HFrEF, peak $\dot{Q}_c$ and impaired peripheral oxidative capacity limit peak exercise performance in HFpEF patients.^{7,9-17} While *peak* $\dot{Q}_c$ is blunted due to chronotropic incompetence and impaired stroke volume reserve during maximal exercise,¹² it is unclear to what extent HFpEF patients experience impaired haemodynamic and metabolic function during *submaximal* exercise, similar to activities of daily living. In contrast to HFrEF, HFpEF patients consistently demonstrate normal augmentation of $\dot{Q}_c$ during low-intensity submaximal exercise.^{7,9,10,18} Thus, the pathophysiology of exercise intolerance during submaximal exercise may be distinct from HFrEF patients. However, to date, no studies have investigated how the unique pathophysiology observed in HFpEF impacts VO_2 kinetics. Therefore, we tested the hypothesis that HFpEF patients would demonstrate slow VO_2 kinetics (longer MRT) compared with age matched controls and that this abnormality may be primarily related to reduced peripheral oxidative capacity.

INTRODUCTION

VO_2 kinetics reflect the speed at which oxygen delivery and utilisation rise to meet the metabolic demand of contracting skeletal muscle during the transition from rest to steady state exercise, which may be quantified as the mean response time (MRT).¹ Impaired VO_2 kinetics are a common characteristic of heart failure with reduced ejection fraction (HFrEF) that is closely associated with the severity of cardiac dysfunction.²⁻⁵ Impairments along every step of the oxygen transport and utilisation cascade have been identified in HFrEF, each contributing mechanistically to impaired

METHODS

Subject characteristics

A total of 18 patients with a hospital discharge diagnosis of CHF were enrolled in studies at the Institute for Exercise and Environmental Medicine between 2007 and 2016. Haemodynamic data from 11 HFpEF patients in this investigation have been reported previously¹⁸ and are combined with data from seven subsequent HFpEF patients whose data have not been published previously. Detailed inclusion and exclusion criteria are provided in online supplementary materials. All subjects signed an informed consent form approved by the

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Cardiopulmonary exercise testing (CPET)

Subjects completed two modified Astrand-Saltin incremental treadmill protocols to determine peak oxygen uptake (VO_2 peak) as reported previously.¹⁸ On the first occasion, maximal exercise testing was used for screening and familiarisation (day 1). At least 72 hours later, exercise testing was repeated to assess steady-state haemodynamics, VO_2 and VO_2 kinetics during submaximal exercise, followed by haemodynamics and VO_2 during maximal exercise (day 2). Resting haemodynamics and ventilatory VO_2 were measured during 3 min of quiet standing on a treadmill. Following resting measurements, a low-intensity steady-state protocol was initiated at the desired treadmill velocity, enabling a rapid transition into the steady state workload. The workload was chosen for each individual to be below ventilatory threshold ($\sim 40\%$ – 50% predicted VO_2 peak, calculated from day 1 CPET) for 6 min. After a minimum of 10 min of rest, peak exercise was assessed a second time using the same modified Astrand-Saltin incremental treadmill protocol as performed on day 1. Atrioventricular nodal blockers were withheld for 48 hours prior to avoid confounding effects of β -blockade on oxygen uptake kinetics (see online supplementary material S1). Other antihypertensive medications were continued.

Heart rate (HR) was monitored continuously via electrocardiogram (Schiller AT-10; Welch Allyn Inc, Skaneateles Falls, New York, USA), and blood pressure was measured using electrophygmomanometry (Suntech Tango+; Morrisville, North Carolina, USA). Measurements of ventilatory gas exchange were made on a breath-by-breath basis using an infrared turbine flow metre (VMM, Interface Associates; Laguna Niguel, California, USA) and mass spectrometry for rapid gas analysis via proprietary software. In addition, breath-by-breath ventilatory gas exchange was also verified at steady state by collection of expired gas in a Douglas bag for 1 min and analysed via mass spectrometry. Steady-state ventilatory volume was measured by use of a 120 L Tissot spirometer (W.E. Collins P-1700; Braintree, Massachusetts, USA). During maximal exercise, peak VO_2 was defined as the highest oxygen uptake measured from at least a 30 s Douglas bag collection. $\dot{Q}_c$ was measured using a modified acetylene rebreathing technique that is well validated, reproducible and equivalent to invasive measures of $\dot{Q}_c$ during maximal exercise.¹⁸ Arterial-venous oxygen difference ($a\text{-vO}_2$ difference) was calculated from the ratio between $\dot{Q}_c$ and oxygen uptake using the Fick equation.

VO_2 kinetics

VO_2 kinetics were measured during the transition from rest to steady-state exercise ($\sim 40\%$ – 50% VO_2 peak) as described above. Ventilatory VO_2 data were linearly interpolated to 1 s intervals, time averaged into 5 s bins and fit using first-order kinetics (see online supplementary materials S2 and S3), with the time delay set to the start of exercise and therefore inclusive of both the cardiodynamic phase I and phase II rise in VO_2 . MRT was defined as the exponential time constant τ , which represents the time needed for oxygen uptake to rise to $\sim 63\%$ of steady state VO_2 . Oxygen deficit was calculated using Simpson's method as the difference between cumulative oxygen demand and cumulative oxygen utilisation.

Statistical analysis

The sample was selected from all of the CPET tests collected as part of research studies at the Institute for Exercise and

Environmental medicine between 2007 and 2016 (18 and online supplementary materials S5 and S6) to maximise sample size. Inclusion/exclusion of all tests was determined prior to statistical analysis, and the sample represents all tests with adequate breath by breath and haemodynamic data available at IEEM for this particular analysis. The typical error of VO_2 uptake kinetics (specifically MRT) in our laboratory is 8%–13% (or 5–8 s; see online supplementary material S7). Various physiological variables are reported as descriptive variables of the experimental intervention in both groups. Primary comparisons of MRT and $a\text{-vO}_2$ difference between control and HFpEF patients was made using unpaired Student's *t*-tests. As an exploratory post hoc analysis, HFpEF patients were stratified into fast and slow kinetics based on an MRT of 60 s (MRT <60 s and MRT $\geq$ 60 s, respectively). Comparison of haemodynamics were made separately during rest, the VO_2 kinetics protocol and the graded exercise testing protocol between control, MRT <60 s and MRT $\geq$ 60 s using analysis of variance and Newman-Keuls post hoc tests, which is robust up to three comparison groups but does not adjust for multiple comparisons. Fishers' exact test was used for categorical data. Significance was set a priori at $p < 0.05$. Data for all primary comparisons are expressed in text as mean difference with 95% CIs, and all data were expressed in tabular form as mean $\pm$ SD.

RESULTS

Subject characteristics

Clinical characteristics of control subjects ($n=18$), HFpEF patients ($n=18$) and HFpEF patients stratified by MRT (MRT <60 s: $n=9$; MRT $\geq$ 60 s: $n=9$) are presented in table 1.

VO_2 kinetics and haemodynamics during submaximal exercise: HFpEF versus control

During submaximal exercise, there was no evidence of chronotropic incompetence, and the rise in $\dot{Q}_c$ was not different between HFpEF and controls ($\Delta\dot{Q}_c$: control: 4.61 ± 1.02 vs HFpEF: 4.82 ± 1.62 L/min; $p=0.65$). Submaximal $a\text{-vO}_2$ difference (mL/100 mL) was not different between HFpEF and controls (mean difference: 0.96 mL/100 mL, 95% CI -0.286 to 2.204; $p=0.18$). There were no significant differences in oxygen demand (VO_2) or the amplitude of VO_2 kinetics

Table 1 Clinical characteristics of healthy controls and patients with HFpEF

Characteristic	Control (n=18)	HFpEF (n=18)	HF MRT <60 s (n=9)	HF MRT $\geq$ 60 s (n=9)
Sex (M:F)	8:10	8:10	4:5	4:5
Age (year)	70 (7)	68 (7)	68 (7)	69 (7)
Height (cm)	167 (10)	167 (9)	167 (8)	166 (10)
Weight (kg)	75 (12)	99 (19)*	100 (15)*	98 (24)*
BMI (kg/m ²)	26 (3)	35 (6)*	36 (4)*	35 (7)*
BSA (m ²)	1.85 (0.19)	2.13 (0.26)*	2.15 (0.2)*	2.11 (0.3)*
HF pharmacotherapy, n (%)				
Diuretic		16 (89)	7 (78)	9 (100)
ACEi or ARB		11 (61)	4 (44)	7 (78)
β -blocker		11 (61)	4 (44)	7 (78)
Nitrate		4 (22)	1 (11)	3 (33)
Statin		8 (44)	3 (33)	5 (56)
Aspirin		6 (33)	1 (11)	5 (56)

Mean (SD) unless otherwise noted.

* $p < 0.05$ versus control.

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, Body surface area; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MRT, mean response time.

Figure 1 (A) Representative breath-by-breath ventilatory oxygen uptake kinetics in a HFpEF patient (blue) and a healthy control subject (black). Breath-by-breath oxygen utilisation ($\dot{V}O_2$) was measured during submaximal treadmill exercise, interpolated linearly at 1 s intervals and fitted using on-transient monoexponential curve fitting. (B) Mean response curves for controls HFpEF patients and HFpEF patients stratified by mean response time (MRT) modelled using group average amplitude ($\Delta \dot{V}O_2 = \text{steady state } \dot{V}O_2 - \text{baseline } \dot{V}O_2$) and MRT, defined as the exponential time constant of $\dot{V}O_2$ onset kinetics, which reflects the time needed for oxygen uptake to rise to ~63% of steady state $\dot{V}O_2$. HFpEF, heart failure with preserved ejection fraction.

($\Delta \dot{V}O_2$), defined as the rise in $\dot{V}O_2$ from baseline to steady state (control: 0.61 ± 0.15 vs HFpEF: 0.63 ± 0.15 L/min; $p=0.70$). However, MRT was much longer in HFpEF patients (mean difference: -25.3 s, 95% CI 10.4 to 40.2; $p=0.002$) nearly doubling the oxygen deficit (control: 0.38 ± 0.23 vs HFpEF: 0.63 ± 0.28 L; $p=0.007$) (figures 1 and 2).

Haemodynamics at peak exercise: HFpEF versus control

At peak exercise, absolute $\dot{V}O_2$ was slightly but variably lower in HFpEF compared with controls (control: 1.65 ± 0.44 vs HFpEF: 1.44 ± 0.48 L/min; $p=0.19$). Peak $\dot{V}O_2$ was consistently and significantly lower in HFpEF patients when scaled to body weight (control: 22.2 ± 4.0 vs HFpEF: 14.6 ± 3.1 mL/min/kg; $p<0.001$). There was no difference in peak Qc between groups (control: 13.4 ± 4.0 vs HFpEF: 13.9 ± 3.5 L/min; $p=0.69$) (table 4). In contrast to submaximal exercise, significant impairments in peripheral a- $\dot{V}O_2$ difference were apparent at peak exercise in HFpEF patients (mean difference: -2.41 mL/100 mL,

Figure 2 Mean response time (MRT) is slower and oxygen deficit is greater in HFpEF patients. The MRT in seconds (s) of oxygen uptake kinetics (A) and accumulated O_2 deficit (B) during submaximal treadmill exercise in HFpEF patients and age-matched healthy controls. The MRT of oxygen uptake kinetics were slower, and O_2 deficit was exaggerated in HFpEF patients compared with controls. * $P<0.01$ versus controls; $n=18$, 8M:10F for each group, respectively. HFpEF, heart failure with preserved ejection fraction.

95% CI -0.59 to -4.231 ; $p=0.01$) consistent with previous studies performed in the upright posture.^{7 10 12 19} Peak heart rate was lower in HFpEF patients compared with controls (control: 158 ± 13 vs HFpEF: 132 ± 23 bpm; $p=0.01$), and there were no significant differences between groups in blood pressure (systolic, diastolic and mean arterial pressure), peak cardiac index or peak stroke volume index.

Haemodynamics in HFpEF patients with MRT <60 s and MRT ≥ 60 s

To better understand the impact of slowed kinetics on exercise performance, HFpEF patients were stratified using an MRT of 60 s,^{2 4} creating two subgroups: HFpEF with normal MRT (MRT <60 s) and HFpEF with slowed MRT (MRT ≥ 60 s). Previous investigations have demonstrated that MRTs ≥ 60 s in HFpEF patients are predictive of reduced survival, transplant free survival and survival free of hospitalisation.⁴⁻⁶ Subject characteristics, haemodynamics at rest, submaximal and peak exercise are presented in tables 1–4. During submaximal exercise, there was no difference in baseline $\dot{V}O_2$, steady state $\dot{V}O_2$ and $\dot{V}O_2$ amplitude between the HFpEF cohorts (table 3). In HFpEF patients with MRT ≥ 60 s, peripheral oxygen extraction

Table 2 Resting haemodynamics in healthy controls and patients with HFpEF

Variable	Control (n=18)	HFpEF (n=18)	HF MRT <60 s (n=9)	HF MRT ≥60 s (n=9)
SBP (mm Hg)	132 (21)	130 (24)	120 (17)	133 (15)
DBP (mm Hg)	83 (8)	74 (12)*	73 (12)	72 (11)
MAP (mm Hg)	100 (11)	93 (14)	89 (11)	92 (10)
HR (beats/min)	76 (12)	79 (17)	80 (19)	77 (16)
Q _c (L/min)	4.0 (1.0)	4.9 (1.4)*	4.2 (1.0)	5.5 (1.5)*†
Q _c index (L/min/m ²)	2.1 (0.4)	2.3 (0.7)	2.0 (0.5)	2.6 (0.7)*†
SV (mL)	53 (18)	63 (20)	54 (20)	71 (16)*
SV index (mL/m ²)	28 (8)	30 (11)	25 (10)	34 (10)*
TPR (dyne/s/cm ⁵)	2106 (508)	1607 (325)*	1736 (334)	1477 (277)*
VO ₂ (L/min)	0.22 (0.05)	0.30 (0.11)*	0.28 (0.1)	0.32 (0.1)*
VO ₂ (mL/kg/min)	2.9 (0.5)	3.2 (1.1)	2.8 (0.5)	3.6 (1.3)
a-vO ₂ difference (mL/100 mL)	5.7 (1.7)	6.4 (2.1)	7.02 (2.4)	5.74 (1.8)

Means (SD).

*P<0.05 versus control.

†P<0.05 versus MRT <60 s.

a-vO₂, arterial-venous oxygen difference; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HF, heart failure; HR, heart rate; MAP, mean arterial pressure; Q_c, cardiac output; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; VO₂, oxygen utilisation.

was reduced during submaximal exercise compared with control and MRT <60 s (a-vO₂ difference: control: 9.8±1.8; MRT <60 s: 9.7±2.1; MRT ≥60 s: 7.9±1.1 mL/100 mL; p<0.05). These patients also required a greater Q_c for the same absolute VO₂ (Control: 8.6±1.7; MRT <60 s: 8.7±2.0; MRT ≥60 s: 10.7±2.1 L/min; p<0.05). With the exception of blood pressure (MAP: MRT <60 s: 105±14 vs MRT ≥60 s: 122±13 mm Hg), there were no other significant differences in haemodynamics at peak exercise between MRT <60 s and MRT ≥60 s.

DISCUSSION

This investigation found that patients with HFpEF have significantly slowed VO₂ kinetics during submaximal exercise

compared with age-matched sedentary controls. The impairment in VO₂ kinetics is similar in magnitude to that reported in HFrEF despite preserved Q_c during submaximal exercise. When HFpEF patients were stratified by MRT, those with an MRT ≥60 s showed an impairment in peripheral oxidative capacity earlier during submaximal exercise, similar in intensity to activities of daily living, which may result in rapid accumulation of oxygen deficit. Together, these findings suggest that oxygen transport and utilisation is severely compromised during submaximal exercise in HFpEF patients that may contribute significantly to exercise intolerance and fatigue.

VO₂ kinetics in heart failure (HF)

In HF and other clinical populations, slower kinetics extend the time required for oxygen delivery to meet metabolic demand resulting in a large 'oxygen deficit' and fatigue.²⁰ In this cohort of HFpEF patients, MRT was markedly (>50%) impaired compared with the MRT of age-matched controls resulting in greater than 50% increase in oxygen deficit (figure 2). Interestingly, the magnitude of impairment in MRT in HFpEF is similar to MRT values reported previously for HFrEF patients.^{2 4 21-23} The presence of impaired MRT despite preserved *submaximal* Q_c, a common finding in HFpEF patients,^{9 10 14 18} underscores extensive impairments in vascular and metabolic capacity in HFpEF patients. The physiological consequence of such severely slowed VO₂ kinetics is fatigue related to the rapid depletion of intramuscular high-energy phosphates. Indeed, assessment of intramuscular energetic parameters using ³¹P magnetic resonance spectroscopy during plantar flexion exercise in HFpEF and HFrEF patients revealed a greater rate of phosphocreatine decline in HFpEF patients, which correlate with skeletal muscle fatigue (plantar flexion), peak VO₂ and 6 min walk performance.²⁴

Table 3 VO₂ kinetics and submaximal exercise haemodynamics in controls and HFpEF patients

Variable	Control	HFpEF	HF MRT <60 s	HF MRT ≥60 s
VO ₂ kinetics				
Amplitude (L/min)	0.61 (0.15)	0.63 (0.15)	0.63 (0.15)	0.63 (0.15)
MRT (s)	40.1 (14.2)	65.4 (27.7)*	45.6 (14.7)	85.2 (23.2)*†
O ₂ deficit (L)	0.38 (0.23)	0.63 (0.28)*	0.47 (0.20)	0.80 (0.28)*†
Steady state				
SBP (mm Hg)	153 (27)	156 (28)	145 (28)	158 (24)
DBP (mm Hg)	86 (16)	76 (16)	80 (14)	70 (17)
MAP (mm Hg)	110 (15)	102 (16)	102 (16)	100 (16)
HR (beats/min)	98 (16)	99 (17)	101 (21)	97 (12)
Q _c (L/min)	8.6 (1.7)	9.7 (2.2)	8.7 (2.0)	10.7 (2.1)*†
Q _c index (L/min/m ²)	4.6 (0.8)	4.6 (1.0)	4.1 (0.9)	5.1 (0.7)†
SV (mL)	89 (28.4)	99 (20)	87 (14)	111 (18)*†
TPR (dyne/s/cm ⁵)	1048 (253)	876 (192)*	962 (179)*	791 (163)*
SV index (mL/m ²)	48 (13)	47 (10)	41 (6)	53 (10)†
VO ₂ (L/min)	0.81 (0.1)	0.85 (0.2)	0.83 (0.2)	0.84 (0.2)
VO ₂ (mL/kg/min)	11.4 (1.3)	8.7 (1.9)*	8.3 (1.6)*	9.0 (2.2)*
VO ₂ (% peak)	52 (12)	61 (12)*	59 (9)*	61 (14)*
a-vO ₂ difference (mL/100 mL)	9.8 (1.8)	8.9 (1.9)	9.7 (2.1)	7.9 (1.1)*†
Δ a-vO ₂ difference (mL/100 mL)	4.1 (1.1)	2.5 (1.7)*	2.7 (1.9)*	2.2 (1.5)*

Means (SD).

*P<0.05 versus control.

†P<0.05 versus MRT <60 s.

a-vO₂, arterial-venous oxygen difference; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HF, heart failure; HR, heart rate; MAP, mean arterial pressure; Q_c, cardiac output; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; VO₂, oxygen utilisation.

To further explore the relationship between MRT and submaximal exercise haemodynamics, we stratified HFpEF patients into two groups based on an MRT cut-off of 60 s. Previous studies investigating the predictive value of MRT indicate that HFrEF patients with an MRT ≥ 60 s have lower rates of survival, transplant free survival and survival free of hospitalisation compared with HFrEF patients with an MRT < 60 s.^{2 3 25} Additionally, HFrEF patients with an MRT ≥ 60 s have significantly worse indices of cardiac function including lower ejection fraction and elevated pulmonary arterial pressure during exercise.^{4 21 26} In this investigation, HFpEF patients with normal MRT experienced similar reductions in peak exercise capacity as patients with MRT ≥ 60 s (peak VO_2 : control: 22.2 ± 4 , MRT < 60 s: 14.6 ± 3.1 , MRT ≥ 60 s: 14.7 ± 2.5 mL/kg/min; both $p < 0.05$ vs control), demonstrating that slowed MRT is not merely a generalised consequence of deconditioning.

Rather, slow MRT identified a unique phenotype within HFpEF patients characterised by disproportionately impaired peripheral oxygen extraction. Clinically, patients from each 'subtype' of HFpEF (slower vs faster MRT) would have appeared to be identical based solely on peak VO_2 measured during standard CPET. However, incorporation of VO_2 kinetics was able to further distinguish between these HFpEF phenotypes. The 'peripherally limited' HFpEF phenotype with impaired MRT may be particularly susceptible to exercise intolerance and fatigue given the presence of impaired oxidative capacity during submaximal exercise intensities compared with HFpEF with normal MRT. Assessment of MRT may identify those patients that are well suited for training interventions targeted at improving skeletal muscle function.

Potential mechanisms for reduced kinetics in HFpEF

In healthy individuals, VO_2 kinetics are largely independent of oxygen delivery and instead constrained by mitochondrial capacity.¹ However, in the case of pathophysiological limitations of $\dot{Q}_c$, like that observed in HFrEF, VO_2 kinetics may become oxygen delivery dependent. Recently, Chatterjee *et al*⁴ assessed both central and peripheral determinants of oxygen uptake concurrently with MRT to identify the factors related to slow MRT in patients with HFrEF. They report that slowed kinetics (MRT ≥ 60 s) are associated with reduced $\dot{Q}_c$ and exaggerated peripheral oxygen extraction during submaximal and peak exercise. The presence of reduced $\dot{Q}_c$ and exaggerated peripheral extraction is consistent with a significant limitation of $\dot{Q}_c$ and bulk oxygen delivery to contracting skeletal muscle, which is partially compensated by elevated peripheral oxygen extraction in HFrEF patients.²⁷ In contrast to HFrEF, impaired MRT in HFpEF was present despite a normal or exaggerated $\dot{Q}_c$ response to *submaximal* exercise and was associated with an attenuated rise in a- vO_2 difference ($\Delta \text{a-vO}_2$ diff: control: 4.1 ± 1.1 , HFpEF: 2.5 ± 1.7 mL/100 mL; $p = 0.002$) suggestive of a primary contribution of impaired skeletal muscle oxidative capacity.

Importantly, the finding of preserved *submaximal* $\dot{Q}_c$ and reduced a- vO_2 difference during exercise is not isolated to this cohort of HFpEF patients. A recent meta-analysis indicates that HFpEF patients have normal or slightly smaller changes in a- vO_2 difference at *peak* exercise in the supine position, whereas during exercise in the upright posture (the position of most activities of daily living), a- vO_2 difference at *peak* exercise is consistently lower.¹² In regards to $\dot{Q}_c$, all studies to date have found that HFpEF patients display a preserved or exaggerated $\dot{Q}_c$ response during *submaximal* exercise.^{9 10 14 18} Specifically, the majority of these studies indicate that the rise in $\dot{Q}_c$ in response

to a change in VO_2 ($\dot{Q}_c/\text{VO}_2$ relationship) is preserved in HFpEF patients compared with healthy controls.^{10 15–18 28 29} These findings indicate that at sufficiently mild exercise intensities when $\dot{Q}_c$ is not limited, skeletal muscle and vascular maladaptations may be important for understanding the impairment in VO_2 kinetics and exercise intolerance in HFpEF.

Furthermore, Kitzman and colleagues⁸ show reduced capillary-to-fibre ratio, and a shift towards glycolytic type II muscle fibres in skeletal muscle of HFpEF patients. Greater percentage of type II fibres has been tied mechanistically to slower VO_2 kinetics in healthy individuals (see online supplementary material). Several studies also report a smaller change in VO_2 in response to a given change in external work rate in HFpEF,^{10 14 28} consistent with impaired oxidative capacity and greater prevalence of type 2 fibres. These skeletal muscle fibre type, and structural abnormalities may be compounded further by dysregulated mitochondrial function related to obesity and excessive skeletal muscle fat deposition^{24 30} that result in cellular metabolic impairment, rapid depletion of high energy phosphates and muscular fatigue.²⁴ Emerging evidence suggests that these pathophysiological skeletal muscle abnormalities may be primary features of an obese HFpEF phenotype.¹⁵ In some HFpEF patients, skeletal muscle abnormalities are present during submaximal exercise intensities and manifest prominently during metabolic transitions.^{7 24 30} Future studies using more direct measures of skeletal muscle oxidative function will be important to determine the mechanisms and extent of skeletal muscle impairments in HFpEF patients. Significant limitations may also exist upstream of skeletal muscle in the oxygen cascade including ventilatory gas exchange, vascular convective oxygen delivery, the distribution of blood flow to, and within active skeletal muscle, and diffusive capacity of oxygen from blood to skeletal muscle.

Limitations and considerations

HFpEF patients demonstrate reduced chronotropy at peak exercise (table 4),¹² and it is possible that slower HR kinetics during the transition from rest to steady state could contribute to lower $\dot{Q}_c$ and thus slower VO_2 kinetics. This study is not able to exclude a possible contribution of impaired $\dot{Q}_c$ to slowed uptake kinetics. However, it is unlikely that chronotropic incompetence can explain the observed decrements in VO_2 kinetics considering there was no evidence of lower HR during submaximal exercise in this study, and even at peak exercise, the lower HR did not reduce peak $\dot{Q}_c$. However, further studies are warranted to fully characterise the relative contribution of on-transient cardiac responses to impairments in MRT in HFpEF patients. Finally, larger prospective studies will be necessary to validate the phenotypic findings of the MRT > 60 s subanalysis in this investigation.

CONCLUSION

The MRT of VO_2 kinetics, an independent predictor of hospitalisation and mortality in HF, is significantly prolonged in HFpEF patients and may be related to impairments in peripheral oxidative capacity. Furthermore, stratification by MRT identified a subset of HFpEF patients with particularly severe peripheral oxidative limitations to submaximal exercise capacity. Given the complex multifactorial nature of HFpEF, the primary mechanism of exercise intolerance is likely to be heterogeneous among patients. In contrast to a- vO_2 difference, MRT can be assessed without measurement of $\dot{Q}_c$ and may be useful clinically in conjunction with CPET to determine the 'physiological phenotype' of an individual HFpEF patient and

Table 4 Haemodynamics at peak exercise in controls and HFpEF patients

Variable	Control	HFpEF	HF MRT <60 s	HF MRT ≥60 s
SBP (mm Hg)	192 (24)	178 (36)	159 (34)*	188 (28)†
DBP (mm Hg)	88 (16)	83 (12)	77 (12)	88 (11)
MAP (mm Hg)	122 (13)	114 (16)	105 (14)*	122 (13)†
HR (beats/min)	158 (13)	132 (23)*	129 (28)*	134 (19)*
Q _c (L/min)	13.4 (4.0)	13.9 (3.5)	13.3 (3.8)	14.5 (3.2)
Q _c index (L/min/m ²)	7.2 (1.8)	6.6 (1.47)	6.2 (1.7)	6.9 (1.2)
SV (mL)	85 (25)	104 (15)*	100 (2)	108 (17)*
SV index (mL/m ²)	45 (12)	49 (8)	47 (6)	52 (10)
TPR (dyne/s/cm ⁵)	801 (287)	695 (151)	679 (141)	709 (167)
VO ₂ (L/min)	1.65 (0.44)	1.44 (0.48)	1.46 (0.5)	1.42 (0.5)
VO ₂ (mL/kg/min)	22.2 (4.0)	14.6 (3.1)*	14.6 (3.8)*	14.7 (2.5)*
a-vO ₂ difference (mL/100 mL)	12.7 (2.9)	10.4 (2.2)*	11.1 (2.5)	9.71 (1.7)*
Δ a-vO ₂ difference (mL/100 mL)	7.0 (1.6)	4.1 (2.3)*	4.3 (2.4)*	4.0 (2.4)*

Means (SD).

*P<0.05 versus control.

†P<0.05 versus MRT <60 s.

a-vO₂, arterial-venous oxygen difference; Δ AvO₂ difference, change from baseline; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; MAP, mean arterial pressure; MRT, mean response time; Q_c, cardiac output; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; VO₂, oxygen utilisation.

identify patients who may benefit from exercise interventions tailored to improve skeletal muscle function. Finally, utilising MRT as a gauge of intervention efficacy may identify strategies that improve the integrative cardiovascular response to submaximal exercise intensities that are in line with activities of daily living, which may be missed when focusing solely on changes in peak VO₂.

Key messages

What is already known on this subject?

- O₂ kinetics are an integrative marker of the efficiency of the cardiovascular system and skeletal muscle to adapt to changes in metabolic demand. Addition of VO₂ kinetics analysis to maximal exercise testing results improves prognostic capacity in heart failure with reduced ejection fraction.

What might this study add?

- In heart failure with preserved ejection fraction (HFpEF), VO₂ kinetics are considerably slowed despite preserved cardiac output during *submaximal* exercise and are related to impairments in peripheral oxygen utilisation.

How might this impact on clinical practice?

- O₂ kinetics assessed during submaximal exercise intensities can be incorporated into standard cardiopulmonary exercise testing to provide a more integrative assessment of cardiovascular and skeletal muscle function in addition to peak oxygen uptake. In HFpEF, VO₂ kinetics may be used to phenotype patients with significant peripheral limitations to exercise capacity and inform decisions regarding treatment and exercise rehabilitation.

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