Differential responses of post-exercise recovery leg blood flow and oxygen uptake kinetics in HFPEF versus HFREF

Richard B Thompson1*, Joseph J Pagano1, Ian Paterson3, Jason Dyck4, Dalane Kitzman5, Mark Haykowsky2

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Background
Delayed oxygen uptake (VO2) kinetics during recovery from a bout of endurance exercise have been shown to be an important prognostic marker of all-cause mortality in chronic heart failure (HF), where skeletal muscle is the predominant O2 consumer. Few studies have examined skeletal muscle O2 delivery/utilization, and no previous study has evaluated the differences between HF patients with reduced LVEF (HFREF) versus those with preserved LVEF (HFPEF). We used novel MRI-based techniques to non-invasively measure quadriceps (leg) blood flow, O2 extraction and VO2 recovery kinetics in clinically stable patients diagnosed with HFREF or HFPEF.

Methods
Leg flow and venous O2 saturation (%SaO2) were measured in the femoral vein post-exercise (knee-extension) using MRI (Fig. 1A, B) as previously described (Magn Reson Med. 2014 Dec 22. doi: 10.1002/mrm.25564). These values in conjunction with arterial oxygen saturation (% SaO2, pulse oximeter), hemoglobin (Hgb) and hematocrit (from blood sampled prior to exercise) are used to calculate leg VO2, from the Fick equation (Fig. 1B). All subjects performed 4 min. of single-leg knee-extension exercise at 85% of their pre-determined peak power output. Leg blood flow, oxygen extraction and VO2 were measured continuously during recovery for 3 minutes, starting within 1 second of exercise cessation. Recovery kinetics were quantified as the mean response time (MRT - defined in Fig. 1E, lower right panel) for all parameters, with comparison to healthy younger male controls (HC) from a previous study using the same methodology.

Results
HFPEF (n = 5, LVEF = 36 ± 11%, 69 ± 9 yrs) and HFREF (n = 5, LVEF = 57 ± 6%, 67 ± 11 yrs) patients were recruited from the Alberta HEART study. Quadriceps muscle mass, peak leg flow, A-VO2 difference and VO2 were not significantly different between HFPEF and HFREF (p > 0.05 for all). However, HFREF patients had severe impairment of VO2 recovery kinetics (increased MRT), while HFPEF had a moderate impairment, as compared to HC (p < 0.05 for all comparison, Fig. 1E, bottom right). This is understood by considering the underlying flow and oxygen extraction kinetics. From Fig. 1D) both HF groups showed similarly impaired A-VO2 recovery kinetics compared to controls (p < 0.05), however, the HFREF group had marked impairment in leg blood flow recovery dynamics, compared to both HFPEF and control groups (p < 0.05 for both comparisons, Fig. 1C). Thus, it is the impaired recovery of flow in HFREF group which distinguishes the HFREF and HFPEF groups.

Conclusions
Whole body VO2 recovery kinetics are related to the degree of functional impairment and are strongly predictive of mortality. We show for the first time that muscle-specific VO2 recovery kinetics are significantly more delayed in HFREF compared to HFPEF (reflecting a larger oxygen debt for a similar amount of work). These findings suggest distinct mechanisms may underlie the reduced exercise capacity in HFREF vs HFPEF, with potentially distinct diagnostic metrics and therapeutic approaches.
**Figure 1**

A) Anatomic image from a patient showing femoral vein location used for evaluation of flow and venous O2 saturation. B) O2 saturation images from a patient at two time points (2 sec. and 60 sec.) following exercise, and the Fick equation for calculation of VO2.

C to E) show the average recovery curves for flow, venous O2 saturation and calculated leg VO2, for HFPEF (black), HFrEF (red) and healthy controls (HC, blue). MRT = mean response time, which is the sum of the delay term (Δ), to the onset of exponential recovery, and time constant of the best-fit mono-exponential decay function (t), as shown in E. HFPEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, Hgb = hemoglobin concentration.
Authors’ details
1Biomedical Engineering, University of Alberta, Edmonton, AB, Canada.
2College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, TX, USA. 3Medicine, University of Alberta, Edmonton, AB, Canada.
4Pediatrics, University of Alberta, Edmonton, AB, Canada. 5Cardiology and Geriatrics, Wake Forest University, Wake Forest, NC, USA.

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