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Brief Rapid Report

Comparison of Carbohydrate and Lipid Oxidation During Continuous and Intermittent Exercise in Patients With Chronic Heart Failure

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ABSTRACT

Skeletal muscle substrate oxidation was compared during moderate-intensity continuous exercise (MICE) and high-intensity intermittent exercise (HIIE) in patients with heart failure and reduced ejection fraction (HFREF). Eighteen patients (aged 60 ± 9 years; LVEF, 26 ± 7%) randomly performed MICE (22 minutes at 60% of peak power) and HIIE (30 seconds at 100% of peak power interspersed by 30 seconds' rest for 16 minutes). Carbohydrate and lipid oxidation calculated using the Frayn equation were 4.8- and 1.42-fold higher during MICE and 5- and 1.22-fold higher during HIIE ($P < 0.0001$). HIIE and MICE can similarly and favourably increase carbohydrate and lipid oxidation in patients with HFREF.

RÉSUMÉ

L'oxydation des substrats par le muscle squelettique a été comparée durant l'exercice continu d'intensité modérée (ECIM) et l'exercice par intervalles de haute intensité (EIHI) chez les patients ayant une insuffisance cardiaque à fraction d'éjection diminuée (IC-FÉD). Dix-huit (18) patients (âgés de 60 ± 9 ans; fraction d'éjection ventriculaire gauche [FÉVG], 26 ± 7 %) ont effectué de manière aléatoire l'ECIM (22 minutes à 60 % de la puissance maximale) et l'EIHI (30 secondes à 100 % de la puissance maximale entrecoupées de période de repos de 30 secondes durant 16 minutes). L'oxydation des glucides et des lipides calculée par l'équation Frayn a été de 4,8 et 1,42 fois plus élevée durant l'ECIM, et de 5 et 1,22 fois plus élevée durant l'EIHI ($P <$ 0,0001). L'EIHI et l'ECIM peuvent similairement et favorablement augmenter l'oxydation des glucides et des lipides chez les patients ayant une IC-FÉD.

Exercise training is a main component of cardiac rehabilitation for patients with heart failure and reduced ejection fraction (HFREF) and benefits functional capacity, quality of life, and risk of (re)hospitalization and death.[1] High-intensity interval exercise (HIIE) is as a new, safe exercise training modality for patients with HFREF[1-4] and has superior benefits for physiological function and quality of life.[1] In patients with HFREF, insulin resistance, reduced skeletal muscle glucose use, and a high plasma fatty acid concentration are associated with reduced functional capacity, diminished cardiac metabolism efficiency,[5] and progression of HF.[6,7] Previous studies demonstrated that patients with HFREF have reduced glucose oxidation and higher plasmatic free fatty acids and lipid oxidation at rest[7] and that exercise training improves skeletal muscle glucose uptake,[6] underlying the potential therapeutic role of exercise to improve skeletal muscle metabolism in those patients.[5-7] Skeletal muscle substrate use (eg, carbohydrates and lipids) during either HIIE or moderate-intensity continuous exercise (MICE) is unknown in patients with HFREF. Substrate use during HIIE and MICE reported in 2 previous studies in healthy young subjects showed conflicting results.[8,9] Christmass et al.[8] found greater carbohydrate (CHO) oxidation and lower lipid oxidation during HIIE compared with MICE,[8] whereas Essen et al.[9] reported no difference.[9] The aim of this study was to compare CHO and lipid oxidation increase during MICE and HIIE in patients with HFREF.

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See page 992 for disclosure information.

Methods

Participants

Eighteen clinically stable HFREF patients were recruited at the Montreal Heart Institute. Inclusion criteria, exclusion

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criteria,[2-4] and baseline characteristics are presented in Supplemental Table S1 and Supplementary Material A. Patients performed randomly 1 optimized HIIE and 1 MICE session under medical supervision, each session being separated by 1 week. The protocol was accepted by the ethics committee of the Montreal Heart Institute, and written informed consent was obtained from all patients.

Maximal cardiopulmonary exercise test

Maximal cardiopulmonary exercise testing was performed according to previously published methodology.[2-4] More details are available in Supplementary Material B.

MICE and HIIE session

The exercise sessions were based on previously published methodology in patients with HFREF,[2-4] detailed in Supplementary Material C.

Substrate oxidation calculation

Substrate oxidation was calculated by the Frayn equation and gas exchange analysis data (see Supplementary Material D).

Statistical analysis

Mean and standard deviation were reported for continuous variables, while frequencies and percentages were reported for categorical values. CHO and lipid oxidation were compared during HIIE and MICE by repeated measure analysis of variance with time and group factors. Statistical analyses were performed with StatView software, version 5.0 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics

Patients were on optimal medical therapy (New York Heart Association class II or III), with a majority having ischemic heart disease or idiopathic dilated cardiomyopathy (Supplemental Table S1).

Maximal cardiopulmonary exercise variables

Mean peak oxygen consumption and peak power output were 17.43 ± 5.51 mL/min/kg (or 1523 ± 475 mL/min) and 93 ± 35 watts, respectively.

Gas exchange and substrate oxidation variables

Compared with resting values, CHO oxidation was 4.8- and 5-fold higher for MICE and HIIE second bloc, respectively ($P < 0.0001$), and lipid oxidation was 1.42- and 1.22-fold higher for MICE and HIIE second bloc, respectively ($P < 0.0001$; Table 1). Energy expenditure (kilocalories per minute) and CHO and lipid oxidation (in grams per minute and percentages) did not differ at rest or during exercise and recovery ($P > 0.05$) during MICE and HIIE (Table 1).

Discussion

The main findings of this study are that (1) compared with rest values, MICE and HIIE were responsible for 4.8- to 5-fold higher CHO oxidation and 1.22- to 1.42-fold higher lipid oxidation compared with resting values (Table 1) and (2) carbohydrate and lipid oxidation were equivalent in terms of absolute and relative value during isocaloric HIIE and MICE sessions in patients with HFREF. Those results underlie the potential therapeutic role of MICE and HIIE to increase glucose oxidation and metabolism in patients with HFREF, as well as their use in training programs to improve metabolic abnormalities.[5-7] Our results disagree with a previous study in healthy subjects demonstrating lower lipid oxidation and higher carbohydrate oxidation during HIIE vs MICE.[8] This divergence may be due to different HIIE exercise intensity (120% of peak oxygen consumption), carbohydrate and lipid oxidation during exercise being mainly dependent on exercise intensity.[8,10] Our results agree with those of another previous study in healthy subjects, demonstrating similar carbohydrate

Table 1. Energy expenditure and carbohydrate and lipid oxidation measured during MICE and HIIE in patients with HFREF

Parameters	Rest	Fist bloc	Second bloc	Recovery	ANOVA *P* value
EE (kcal/min)					
MICE	1.78 ± 0.36	6.08 ± 1.45	6.29 ± 1.53	4.76 ± 1.27	a = 0.1037
HIIE	1.78 ± 0.34	5.26 ± 1.21	5.37 ± 1.28	4.36 ± 0.82	b < 0.0001
					c = 0.0267
CHO oxidation (g/min)					
MICE	0.30 ± 0.12	1.66 ± 0.48	1.46 ± 0.37	1.17 ± 0.37	a = 0.0906
HIIE	0.24 ± 0.11	1.39 ± 0.45	1.20 ± 0.39	1.07 ± 0.31	b < 0.0001
					c = 0.1292
Lipid oxidation (g/min)					
MICE	0.07 ± 0.04	0.05 ± 0.06	0.10 ± 0.09	0.06 ± 0.06	a = 0.6350
HIIE	0.09 ± 0.03	0.06 ± 0.05	0.11 ± 0.06	0.06 ± 0.04	b < 0.0001
					c = 0.6425
CHO oxidation (%)					
MICE	68 ± 21	92 ± 10	86 ± 13	88 ± 14	a = 0.1553
HIIE	50 ± 17	90 ± 11	84 ± 13	89 ± 13	b < 0.0001
					c = 0.041
Lipid oxidation (%)					
MICE	31 ± 21	7 ± 10	13 ± 13	11 ± 14	a = 0.1562
HIIE	49 ± 17	9 ± 11	15 ± 13	10 ± 13	b < 0.0001
					c = 0.042

CHO, carbohydrate; EE, energy expenditure; HFREF, heart failure with reduced ejection fraction; HIIE, high-intensity intermittent exercise; MICE, moderate-intensity continuous exercise; a, mode effect; b, time effect; c, interaction effect (mode × time).

and lipid oxidation during MICE (55% of peak power output) and HIIE (15 seconds at 100% peak power output, 15 seconds of passive recovery).[9] Despite this metabolic similarity, 2 studies have suggested some minor differences in intramuscular and extramuscular sources of substrate[9,11] during HIIE and MICE. A higher contribution of blood free fatty acids as a lipid source has been suggested during HIIE, with similar contribution of blood glucose and muscle glycogen.[9] Absolute values of carbohydrate and lipid oxidation (in grams per minute, dependent on oxygen consumption and carbon dioxide elimination values) during acute exercise are lower compared with those reported in healthy controls.[12] Patients with HFREF have structural and metabolic skeletal muscle abnormalities including fibre atrophy, decreased type I myosin heavy chain fibre, and reduced oxidative capacity,[13] as well as a reduced skeletal muscle glucose uptake associated with insulin resistance. Those abnormalities may contribute to reduced quantitative carbohydrate oxidation observed during exercise.[12] Aerobic exercise training has been shown to increase type I myosin heavy chain, oxidative enzyme, and insulin sensitivity and skeletal muscle glucose uptake in patients with HFREF.[6,13] In HFREF patients, HIIE training has been shown to be superior to MICE training to improve mitochondrial function and skeletal muscle oxygen extraction[14] and would be potentially more beneficial for glucose metabolism and oxidation during exercise via an increased level of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). This study has several limitations, including the small number of patients in New York Heart Association class II-III HF. Even if patients were told to take their usual breakfast before testing, meal composition was not standardized. Also, intramuscular and extramuscular sources of substrate (carbohydrate and lipid) could not be determined in this study. In conclusion, HIIE and MICE can favourably increase carbohydrate and lipid oxidation in patients with HFREF; further studies will be required to document which exercise training modalities (interval and/or continuous) and/or nutritional components of recent meals would better improve glucose oxidation and metabolism in those patients and intramuscular and extramuscular sources of substrate modifications after training.

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Disclosures

The authors have no potential conflicts of interest.

References

1. Arena R, Myers J, Forman DE, Lavie CJ, Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? Heart Fail Rev 2013;18:95-105.
2. Gayda M, Normandin E, Meyer P, et al. Central hemodynamic responses during acute high-intensity interval exercise and moderate continous exercise in patients with heart failure. Appl Physiol Nutr Metab 2012;37: 1171-8.
3. Meyer P, Normandin E, Gayda M, et al. High-intensity interval exercise in chronic heart failure: protocol optimization. J Card Fail 2012;18: 126-33.
4. Normandin E, Nigam A, Meyer P, et al. Acute responses to intermittent and continous exercise in heart failure patients. Can J Cardiol 2013;29: 466-71.
5. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. Lancet 2004;364:1786-8.
6. Kemppainen J, Stolen K, Kalliokoski KK, et al. Exercise training improves insulin stimulated skeletal muscle glucose uptake independent of changes in perfusion in patients with dilated cardiomyopathy. J Card Fail 2003;9:286-95.
7. Norrelund H, Wiggers H, Halbirk M, et al. Abnormalities of whole body protein turnover, muscle metabolism and levels of metabolic hormones in patients with chronic heart failure. J Intern Med 2006;260:11-21.
8. Christmass MA, Dawson B, Passeretto P, Arthur PG. A comparison of skeletal muscle oxygenation and fuel use in sustained continuous and intermittent exercise. Eur J Appl Physiol Occup Physiol 1999;80:423-35.
9. Essen B, Hagenfeldt L, Kaijser L. Utilization of blood-borne and intramuscular substrates during continuous and intermittent exercise in man. J Physiol 1977;265:489-506.
10. Romijn JA, Coyle EF, Sidossis LS, et al. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am J Physiol 1993;265(Pt 1):E380-91.
11. Essen B, Kaijser L. Regulation of glycolysis in intermittent exercise in man. J Physiol 1978;281:499-511.
12. Malatesta D, Werlen C, Bulfaro S, Cheneviere X, Borrani F. Effect of high-intensity interval exercise on lipid oxidation during postexercise recovery. Med Sci Sports Exerc 2009;41:364-74.
13. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. J Am Coll Cardiol 1997;29: 1067-73.
14. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2012.11.005.

Supplementary Material

A) Inclusion and exclusion criteria

Inclusion criteria were: age ≥ 18 years, left ventricular ejection fraction (LVEF) <40% (measured within 6 months of enrolment by echocardiography, radionuclide ventriculography or cardiac magnetic resonance), New York Heart Association (NYHA) functional class I to III, stable optimal medical therapy including a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers for at least 6 weeks, ability to perform an maximal cardiopulmonary exercise test and capacity and willingness to sign the informed consent formed. Exclusion criteria included any relative or absolute contraindications to exercise training in chronic HFREF patients, fixed-rate pacemaker or internal cardioverter-defibrillator devices with heart rate limits set lower than exercise training target heart rate, major cardiovascular event or procedure within the 3 months preceding enrolment, chronic atrial fibrillation, HF secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to LV dysfunction) and HF secondary to congenital heart disease or obstructive cardiomyopathy.

B) Maximal cardiopulmonary exercise test

A continuous progressive exercise protocol was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany). The pedaling speed was settled at 60 revolutions per minute (RPM) during the entire test. A 2 min warm up at 20 W was performed before the test and the power was increased by 10 W every minute until exhaustion. Peak power

output (PPO) was defined as the power output reached at the last fully completed stage. Gas exchanges variables were measured breath by breath during testing, and then averaged every 15 s has previously described [3-5]. All subjects were encouraged to provide a maximal effort. Heart rate, manual brachial blood pressure and rating of perceived exertion using the Borg scale (level 6 to 20) were recorded before the test and at 2 min intervals during exercise and recovery. Electrocardiographic activity was monitored continuously using an 8-lead ECG (Marquette, Missouri, USA). The average value of the $\dot{V}O_2$ recorded during the last 15 seconds of exercise was considered as the $\dot{V}O_2$peak [3-5].

C) MICE and HIIE session

The intensity and duration incorporated in this study was 60% of PPO and 22 min, respectively [3-5]. Gas exchanges variables were measured breath by breath during MICE session, and then averaged every 15 sec. [4,5]. HIIE session consisted of a 2 minute warm-up at 50% of PPO, followed by two sets of 8 min intervals at 100% of PPO. Each interval block was composed of repeated bouts of 30 s at 100% of PPO interspersed by 30s of passive recovery [3-5]. Four minutes of passive recovery were allowed between the two sets, as well as a 1 min cool-down at 25% of PPO after the last 30s exercise bout [3-5]. Gas exchanges variables were measured breath by breath during HIIE session, and then averaged every 15 sec. [4,5].

D) Substrate oxidation calculation

Energy expenditure and substrate oxidation were calculated as mean values corresponding to the last 2 minutes of rest, HIIE blocs and recovery and for the same

exercise time period on MICE. Energy expenditure was calculated using Weir equation (EE kcal/min = [(3.9 ×VO_2 ml/min) + (1.1×VCO_2)]×1.44]÷1440 [9]. Quantitative CHO and lipid oxidation (g/min) were calculated from VO_2 and VCO_2 using the Frayn equations valid for high intensity exercise [7,10,11], protein oxidation was neglected.

CHO (g/min) = 4.55×(VCO_2 L/min) – 3.21×(VO_2 L/min)

Lipid (g/min) = 1.67×(VO_2 L/min) – 1.67×(VCO_2 L/min)

Qualitative CHO and lipid oxidation (in %) were calculated from R.E.R values using a table of non-protein respiratory quotient [12].

Supplemental Table S1. Baseline characteristics of the patients with chronic heart failure.

Clinical Variables	**n=18**
Age (years)	60±9
Male	17 (94%)
Body mass index (kg/m^2)	30±6
LVEF (%)	26±7
Duration of heart failure (years)	5±4
NYHA functional class	
I	5 (27%)
II	8 (44%)
III	8 (44%)
Etiology of heart failure	
Ischemic heart disease	8 (44%)
Idiopathic dilated cardiomyopathy	8 (44%)
Other cause	2 (11%)
Risk factors	
Diabetes mellitus	6 (33%)
Hypertension	12 (66%)
Smoking	1 (5%)
Dyslipidemia	14 (77 %)
Obesity (BMI ≥30 kg/m^2)	8 (44%)
Medical history	
Previous myocardial infarction	8 (44%)
Previous CABG	1 (5 %)
Previous PCI	6 (33%)
Medications	
ACE inhibitors	11 (61 %)
ARB's	6 (33%)
Betablockers	18 (100 %)
Digoxin	11 (61%)
Oral hypoglycemic agents	1 (5%)
Insulin	3 (16 %)
Spironolactone	9 (50 %)
Devices	
ICD	14(77 %)
CRT	3 (16 %)

Values are means ± SD or numbers of patients (%). ACE: angiotensin-converting enzyme; ARB's: angiotensin II receptor blockers; BMI: body mass index; CABG: coronary artery bypass grafting, CRT: cardiac resynchronization therapy, ICD: internal

cardioverter-defibrillator, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, PCI: percutaneous coronary intervention.