

Beta-Blocker Type Effect on Substrate Oxidation during HIIE in Heart Failure Patients: Pilot Data

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Abstract

The effect of third and second-generation type of beta-blocker on substrate oxidation especially during high-intensity exercises are scarce.

The objective of the study is to explore differences of beta-blocker regimens (vasodilating vs. non-vasodilating beta-blockers) for substrate oxidation during in high-intensity intermittent exercise (HIIE) in chronic heart failure and reduced ejection fraction (HFrEF).

Eighteen CHF males (58.8 ± 9 years), 8 under use of β_1 specific beta-blockers+alfa 1-blocker and 10 using β_1 non-specific beta-blockers, were randomly assigned to 4 different HIIE, in a cross-over design. The 4 protocols were: 30 seconds (A and B) or 90 seconds (C and D) at 100% peak power output, with passive (A and C) or active recovery (50% of PPO; B and D). Energy expenditure (EE; kcal/min), quantitative carbohydrate (CHO) and lipid oxidation (g/min) and qualitative (%) contribution were calculated. Two-way ANOVA and Bonferroni post-hoc test were used (p -value ≤ 0.05) to compare CHO and lipid oxidation at rest and at 10min.

Total exercise time or EE did not show differences for beta-blocker use. The type of beta-blocker use showed impact in CHO (%) and lipid (g/min and %) for rest and 10 min, but absolute contribution of CHO (g/min) was different just at 10min (Interaction $p = 0.029$). Higher CHO oxidation was found in vasodilating beta-blockers when comparing to non-vasodilating.

According to our pilot data, there is an effect of beta-blocker type on substrate oxidation during HIIE, but no influence on EE or exercise total time in HFrEF patients.

Introduction

To reduce sympathetic nervous system activation and improve myocardium contractility, morbidity and mortality,

Keywords

Heart Failure, Adrenergic beta-Antagonists; Stroke Volume, Chemical Oxidation, Exercise.

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Manuscript received January 27, 2018, revised manuscript April 26, 2018, accepted August 15, 2018

DOI: 10.5935/abc.20190039

most of the chronic heart failure (CHF) patients are under beta-blocker use.¹ Besides all benefits, there is some evidence showing reduced glycemic control, weight gain, insulin secretion inhibition and resistance and dyslipidemia in resting states in patients under beta-blocker regimen.^{2,3} Also, it was showed that the use of beta blockers could remodel substrate use during moderate-intensity continuous exercise.⁴

The third generation of beta-blockers, described as vasodilating β -blockers (i.e. β non-selective + α -1 blocker), seem to have a beneficial effect comparing to previous ones (β -selective). Because of its lack of effect on α -1 adrenergic receptors, non-vasodilating beta blockers can induce vasoconstriction, reducing blood flow and glucose uptake at muscular level.^{2,3} But when comparisons between carvedilol vs. metoprolol were made concerning NYHA no changes were found.⁵ However, there is a lack of evidence of comparison of the type of beta-blocker during exercise, especially during high-intensity exercises (i. e. vasodilating vs. non-vasodilating).

Regarding exercise intensity, there is an increasing use of high-intensity interval training programs in cardiac rehabilitation sites. Enough evidence is provided about the superior benefits of this modality for maximal oxygen uptake (VO_2 max) and quality of life when compared to moderate continuous training.⁶ However, still a lack of evidence about different high-intensity interval exercise (HIIE) prescriptions in terms of optimal intensity, duration of bouts, recovery time and type (passive or active).⁷ Also, not enough evidence about substrate utilization in cardiac rehabilitation context, especially what concerns to medication use.^{4,8} We believe that vasodilating beta-blockers could especially influence carbohydrate (CHO) oxidation, and this may reflect in total time of exercise session.

Therefore, for this study, we compared substrate oxidation, energy expenditure (EE) and total time of HIIE protocols performed by CHF with reduced left ejection fraction (HFrEF), under two different beta-blocker regimens (vasodilating vs. non-vasodilating).

Methods

Participants

Twenty stable HFrEF were recruited from the heart failure ambulatory at the Montreal Heart Institute. This is a sub-study, inclusion criteria and exclusion criteria have been detailed in the previous publication,⁷ and clinical information was

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obtained from medical records. The study was performed in a cross-over design, all patients participated in the same exercise sessions in random order (generated by randomizer.org), and every single session being separated by one week (5 weeks for complete protocol). No changes in medication were made during the evaluations. The protocol was accepted by the Ethics Committee of the Montreal Heart Institute (08-1023), all procedures in agreement with Helsinki declaration and written informed consent was obtained from all patients.

Maximal cardiopulmonary exercise test

Maximal cardiopulmonary exercise testing was performed according to previously published methodology.⁷⁻⁹ In short, the maximal exercise protocol was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany), speed was settled at 60 RPM, and the power was increased by 10 W every minute until exhaustion. Gas exchanges variables were measured breath by breath during testing and then averaged every 15s. Peak power output (PPO) was defined as the power output reached the last fully completed stage. Electrocardiographic activity was monitored continuously using an 8-lead ECG (Marquette, Missouri, USA).

HIIE sessions

The exercise sessions were based on previously published methodology in patients with HFrEF.⁷ HIIE protocols were all prescribed at 100% PPO, based on CPET and differed in interval duration (30 seconds for protocols A and B vs 90 seconds for protocols C and D) and type of recovery (active recovery at 50% of PPO for protocols B and D vs passive recovery [0% of PPO] for protocols A and C). The exercise time and recovery were designed as 1:1 ratio. Each patient exercised for a maximal time of 30 min or until exhaustion due to fatigue, dyspnea, dizziness, or inability to maintain pedal cadence at 60 rpm.⁷

Substrate oxidation and energy expenditure calculation

EE was calculated using Weir equation.¹⁰ Substrate oxidation (CHO and lipid) was calculated from gas exchange using the Frayn equation¹¹ (in g/min) and with a respiratory exchange ratio values (in %) using a table of non-protein respiratory quotient.¹²

Statistical analysis

Results are expressed as mean \pm SD for clinical characteristics and described as n (%) for beta blocker regimen (Table 1). This is an exploratory analysis from our previous studies,⁷⁻⁹ all HIIE sessions that lasted more than 10 min of exercise were included. The substrates were compared in two time-points: rest and end of 10 min, both averages of 3 min measurements. EE (Kcal/min; EE), CHO and lipid oxidation, in g/min and total contribution (%), were compared during HIIE protocols using a two-way ANOVA for beta-blocker type and time factors. The Bonferroni *post-hoc* test with a p value ≤ 0.05 was used. Student's *t*-test was used to compare the exercise total time between types of beta-blocker. All analyses were performed using IBM SPSS Statistics software, version 21 and Statview.

Results

The patients' characteristics are described in Table 1, two patients were excluded for this analysis because did not achieve the minimum of 10 min exercise. Both groups were similar for clinical characteristics, except for systolic and diastolic blood pressures. Total exercise time was not different between the beta-blockers types (non-vasodilating group = 1377 ± 505 s; vasodilating group = 1371 ± 503 s; $p = 0.962$). Also, no differences were found for EE for group or interaction (group $p = 0.203$; time $p < 0.0001$ and interaction $p = 0.867$). Differences in CHO (mg/min*Kg⁻¹ and %; $p = 0.012$ and $p = 0.0006$) and lipids (mg/min*Kg⁻¹ and %; $p = 0.0017$ and $p = 0.0083$) were found for group and time analysis, and interaction was found just for CHO (mg/min*Kg⁻¹; $p = 0.03$) (Figure 1).

Discussion

Our results showed a different effect on substrate oxidation depending on the type of beta-blocker generation. We believe that the decision of beta-blocker use can benefit the substrate oxidation during exercise and can be chosen accordingly with patients' necessity. Because of their effect on α_1 - adrenergic receptors, vasodilating beta-blockers like carvedilol could benefit CHO oxidation, as shown in our results for absolute and relative values, comparing to non-vasodilation beta-blockers. Because these blocking agents can have a different effect on the circulatory and respiratory systems, previously they were known to potentially reduce exercise capacity in heart failure patients.¹³ Recent evidence has shown some improvement, with a different combination of drugs, vasodilating beta-blockers demonstrated positive effect increasing insulin sensitivity comparing to non-vasodilating ones¹⁴ and probably remodelling substrate oxidation.

According to literature, HIIE requires greater energetic demand from the muscular system,¹⁵ and therefore should be accompanied by higher CHO oxidation. The increasing use of HIIE in a clinical context is due to its superiority compared to continuous exercise training to improve VO_{2peak} with similar effects on left ventricular function, safety and exercise compliance.^{6,16} In our previous work,⁹ we showed substrate oxidation differences between HIIE protocols, and the individual variances lead us to explore the potential muscle metabolism differences that could be related to beta-blocker use. Also, there is still little data available on substrate oxidation and the effect of pharmacological agents in heart failure patients,³ especially during high-intensity exercise, so we believe we are providing interesting initial data to raise interest on the subject.

The major limitation of our study is the sample size, but we believe appropriate for a pilot study to encourage further investigation. Also, because of the lack of a placebo group, we cannot investigate the actual effect of beta-blocker on substrate oxidation, but differences between different regimens. Since more than 90% of our HFrEF patients are under some beta-block medication, we did not consider the possibility to suspend or change patients' medication.

Table 1 – Baseline Clinical Characteristics according to the type of beta-blocker class

Clinical Variables	Beta-blocker class	
	Non-vasodilating n = 10	Vasodilating n = 8
Age (years)	59.3 ± 9.8	58.0 ± 8.5
BMI (kg/m ²)	30.0 ± 4.0	28.0 ± 3.7
LVEF (%)	29 ± 7	27 ± 6
SBD (mmHg)	129 ± 20	108 ± 17*
DBP (mmHg)	75 ± 10	61 ± 15*
NYHA functional class		
I	1 (10%)	4 (50%)
II	9 (90%)	3 (37.5%)
III	0	1 (12.5%)
Etiology of heart failure		
Ischemic heart disease	6 (60%)	4 (50%)
Idiopathic dilated cardiomyopathy	4 (40%)	4 (50%)
Medical history		
Diabetes mellitus	1 (10%)	3 (37.5%)
Hypertension	6 (60%)	4 (50%)
Medications		
ACE inhibitors or ARBs	10 (100%)	8 (100%)
Digoxin	2 (20%)	4 (50%)
Furosemide	8 (80%)	6 (75%)
Spironolactone	4 (40%)	4 (50%)
Devices		
ICD	7 (70%)	6 (75%)
CRT	1 (10%)	3(37.5%)
Maximal exercise variables		
Peak power output (Watts)	108 ± 33	110 ± 31
VO _{2peak} (L/min)	1598 ± 507	1478 ± 422
VO _{2peak} (% predicted)	63 ± 13	59 ± 12
VO _{2peak} (mL/min/kg)	17.3 ± 4.6	18.3 ± 4.6

Values are presented as means ± SDs, or numbers of patients (percentages). BMI: body mass index; LVEF: left ventricle ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; VO₂: oxygen uptake; VO_{2peak}: peak oxygen uptake. * p < 0.05.

Conclusion

In short, according to our pilot data, carvedilol seems to facilitate CHO oxidation during HIIE and should be considered when possible, for patients under high-intensity exercise programs. However, how the use of different beta-blockers agents (ex: vasodilating) could impact muscle metabolism during various acute and chronic exercise training programs in these patients need to be better explored.

Acknowledgement

The authors are grateful to ÉPIC Foundation, Montreal Heart Institute Foundation and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq– Brazil) for grant support.

Author contributions

Conception and design of the research: Ribeiro PAB, Juneau M, White M, Nigam A, Gayda M; acquisition of data: Normandin E, Meyer P; analysis and interpretation of the data: Ribeiro PAB, Normandin E, Meyer P, White M, Nigam A, Gayda M; statistical analysis: Ribeiro PAB; obtaining funding: Ribeiro PAB, Juneau M, Gayda M; writing of the manuscript: Ribeiro PAB, Gayda M; critical revision of the manuscript for intellectual content: Ribeiro PAB, Normandin E, Meyer P, Juneau M, White M, Nigam A, Gayda M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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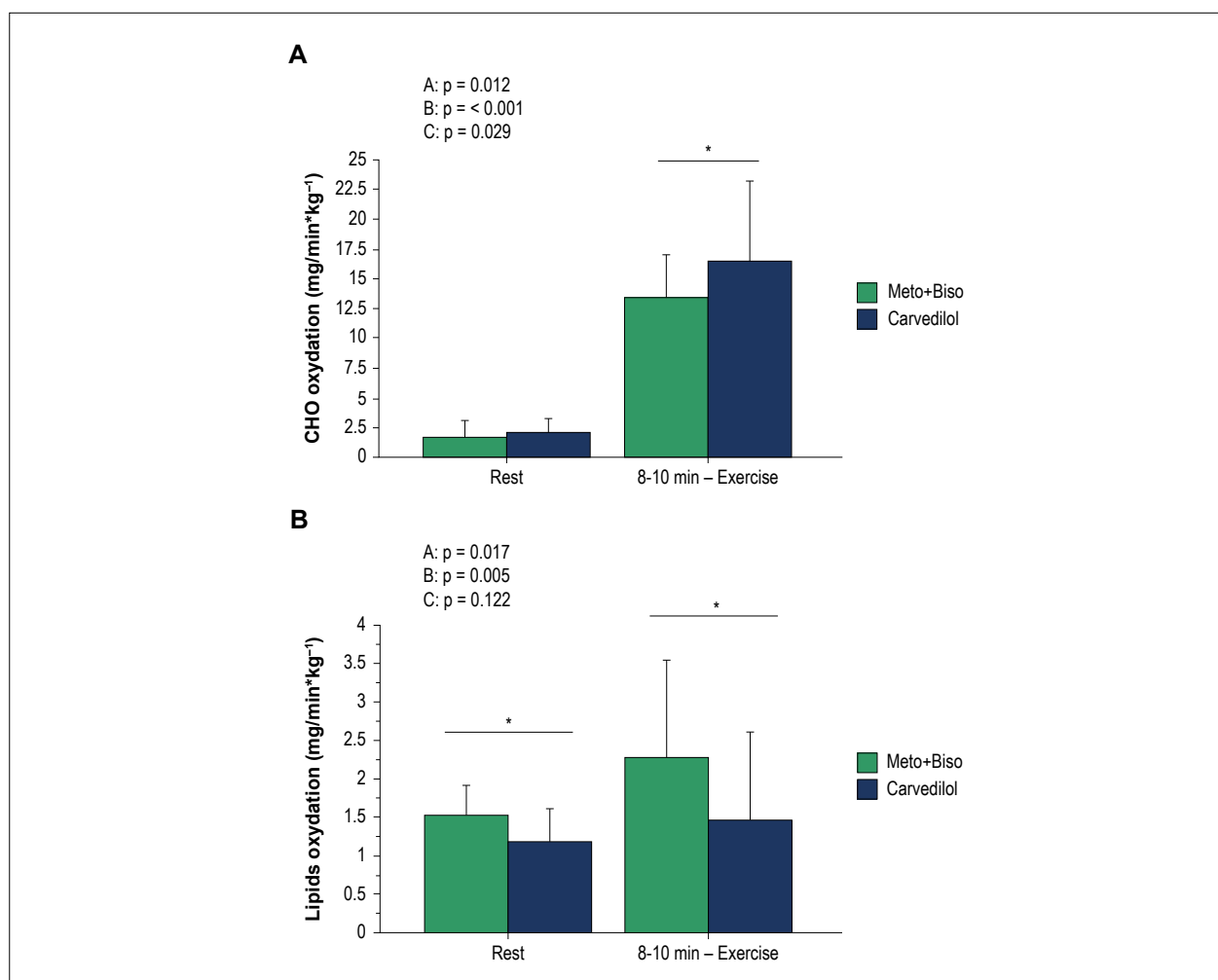


Figure 1 – A) Carbohydrate oxidation by group at rest and 8-10 minutes high-intensity interval exercise. B) Lipids oxidation by groups at rest and 8-10 minutes high-intensity interval exercise. * $p < 0.05$ for groups; ANOVA p value results: A: group; B: time; C: interaction.

Sources of Funding

This study was funded by the ÉPIC Fondation, the Montreal Heart Institute Foundation and the CNPq.

Study Association

This article is part of the Post-Doctoral fellowship submitted by Paula Aver Bretanha Ribeiro, from University of Montreal.

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