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Prescribing High-intensity Interval Exercise by RPE in Individuals with Type 2 Diabetes: Metabolic and Hemodynamic Responses

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TITLE: Prescribing High-intensity Interval Exercise by RPE in Individuals with Type 2 Diabetes: Metabolic and Hemodynamic Responses

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ABSTRACT

We tested the hypothesis that rating of perceived exertion (RPE) is a tool as efficient as heart rate (HR) response to cardiopulmonary exercise test (CPX) for prescribing and self-regulating high-intensity interval exercise (HIIE), and that metabolic and hemodynamic response to HIIE is superior than to continuous moderate-intensity exercise (MICE) in individuals with type 2 diabetes mellitus (T2DM). Eleven participants (age=52.3±3yr) underwent HIIE prescribed and self-regulated by RPE ($HIIE_{RPE}$; 25 min), HIIE prescribed and regulated by individuals' HR response to CPX ($HIIE_{HR}$; 25 min), MICE prescribed and self-regulated by RPE (30 min) and control (CON; 30 min of seated resting) intervention in random order. HR, blood pressure (BP), capillary glucose, endothelial reactivity and carotid-femoral pulse wave velocity (PWV) were assessed before, immediately after and 45 min after each intervention. Exercise HR, speed and distance were measured during exercise sessions. 24-h ambulatory BP was measured after each intervention. Exercise HR, speed and distance were similar between $HIIE_{RPE}$ and $HIIE_{HR}$. BP response was not different among $HIIE_{RPE}$, $HIIE_{HR}$, and MICE. Capillary glycaemia reduction was greater ($P < 0.05$) after $HIIE_{RPE}$ (48.6±9.6 mg/dL) and $HIIE_{HR}$ (47.2±9.5 mg/dL) than MICE (29.5±11.5 mg/dL). Reduction ($P < 0.05$) in 24-h (6.7±2.2 mmHg) and tendency toward reduction ($P = 0.06$) in daytime systolic (7.0±2.5 mmHg) ambulatory BP were found only after $HIIE_{RPE}$. These results suggest that HIIE is superior to MICE for reducing glycaemia and ambulatory BP, and that the 6 to 20 RPE scale is an useful tool for prescribing and self-regulating HIIE in individuals with T2DM.

Keywords: arterial stiffness; blood pressure; capillary glycaemia; high-intensity interval exercise; rating of perceived exertion; type 2 diabetes mellitus.

INTRODUCTION

Physical exercise is a first-line nonpharmacological treatment for type 2 diabetes mellitus (T2DM), resulting in improvements on glycemic control, body composition and functional capacity (Colberg et al. 2010; Alvarez et al. 2016). A minimum of 150 min/wk (30 min, 5 d/wk) of moderate to vigorous aerobic exercise, in association with 2 to 3 sessions/wk of resistance training, is thus recommended in the current American Diabetes Association and American College of Sports Medicine guidelines (Colberg et al. 2010). Moderate-intensity continuous exercise (MICE) with sustained increases in heart rate (HR) (i. e., walking, cycling or jogging at 40–60% of reserve HR) has been commonly recommended to meet this aerobic exercise recommendation Colberg et al. 2010).

However, high-intensity interval exercise (HIIE) training (repeated bouts of vigorous exercise interspersed with periods of rest or active recovery) has shown greater improvements than energy expenditure-matched MICE programs in hemoglobin glycated (Mitranun et al. 2014), fasting insulin (Karstoft et al. 2013; Mitranun et al. 2014), glucose control assessed by continuous glucose monitoring (Karstoft et al. 2013) and others cardiovascular risk factors (Karstoft et al. 2013; Mitranun et al. 2014) in T2DM patients. The time-efficiency of HIIE is also noteworthy, whereas substantial benefits occurs with a weekly time commitment markedly lower (Francois and Little. 2015; Alvarez et al. 2016) than current recommendations (Colberg et al. 2010). Given that lack of time is the most frequently cited barrier to regular exercise participation (Trost et al. 2002), HIIE may thus be an attractive option for increasing physical activity levels in this predominantly sedentary or insufficiently active population (Morrato et al. 2007).

HIIE prescription is commonly based on HR, oxygen consumption or ventilatory threshold response during cardiopulmonary exercise testing (CPX) (Ciolac et al. 2015b), which requires expensive equipment and has measurements dependent on calibration procedures before

testing (Atkinson et al. 2005; Meyer et al. 2005). These limitations may reduce individuals' access to exercise testing and, consequently, HIIE. In contrast, rating of perceived exertion (RPE) (Borg 1982) is a simple and inexpensive tool associated with several exercise intensity markers (i.e.: heart rate, oxygen consumption, and metabolic thresholds) (Seip et al. 1991; Green et al. 2006; Ciolac et al. 2015a), independently of training and health status (Seip et al. 1991; Ciolac et al. 2015a; Ciolac et al. 2015b), and thus may be an attractive option for exercise prescription and self-regulation. Accordingly, a recent pilot study showed that RPE may be an effective tool for prescribing and self-regulating HIIE in healthy young subjects (Ciolac et al. 2015b). However, the usefulness of RPE for prescribing and self-regulating HIIE, as well as the metabolic and hemodynamic response to RPE-regulated HIIE sessions, have not been studied in T2DM individuals.

Thus, our aim was to test, in T2DM individuals, the hypothesis that 1) RPE is a tool as efficient as HR response to CPX for prescribing and self-regulating HIIE, and that 2) metabolic and hemodynamic response to HIIE is superior than to MICE, independently if prescribed and regulated by individuals' RPE or HR response to CPX.

METHODS

Population and study design

We studied physically inactive (non-involvement in regular physical activity or exercise program for at least 6 months) T2DM individuals (established diagnosis for at least 6 months), with unchanged drug therapy during the previous 3 months and absence of long-term diabetic complications (history of foot injury, retinopathy, nephropathy, and diabetic peripheral neuropathy). Individuals with musculoskeletal disorders, uncontrolled cardiovascular and/or metabolic disease, asthma, chronic obstructive pulmonary disease, pregnancy and cardiovascular

contraindications to exercise were not included in the study. Pacemaker users and smokers were also not included in the study. A 100% of intervention sessions compliance was required for all participants in order to be included in the final statistical analysis.

The present study was a randomized four crossover intervention conducted in a single center in Brazil. The primary outcome was capillary glycaemia response to exercise, and secondary outcomes were blood pressure (BP), HR, carotid-femoral pulse wave velocity (PWV) and endothelial reactivity response to exercise. The size effect estimation was based on preliminary results of the present study (Viana et al. 2017), which suggested that an overall sample of 10 individuals would be required to provide a power of 85% to detect of 44.9±31.1 mg/dl reduction on capillary glycaemia after exercise interventions, with two-sided α of < 0.05. Forty-one individuals answered the call for participation in the study, which was performed through folders displayed at social networks, and public transportation and local health centers of the city of Bauru, Brazil. After a telephone call with explanations about the study protocol and inclusion criteria, 25 individuals volunteered to undergo a structure history, medical record review, and physical examination for eligibility criteria. Seventeen T2DM individuals who met all of the inclusion criteria were included in the present study. During the evaluations, six individuals dropped out from the study for personal reasons. Thus, 11 (two men) T2DM individuals age 32 to 68 yr completed all the proceedings and were included in final analysis (Table 1).

All participants were referred for CPX to determine HR dynamics. Three to 7 days after CPX, participants were allocated to HIIE session prescribed and regulated by their HR response to CPX ($HIIE_{HR}$), HIIE session prescribed and self-regulated by RPE ($HIIE_{RPE}$), MICE session prescribed and self-regulated by RPE (MICE) or nonexercise control session (CON). The

participants underwent all interventions in random order (1:1:1:1), using a drawing of lots (envelops in bag), and with 3 to 7 days between interventions. BP, HR, capillary glycaemia, PWV and endothelial reactivity were measured before (pre), immediately after (post) and 45 min after (recovery) each session. HR was also measured throughout each intervention. 24-h ambulatory BP (ABP) monitoring was performed after each intervention and measurements began 90 min after the session. All interventions began between 2:00 and 3:00 p.m. and participants leaved laboratory between 5:00 and 6:00 p.m.. Participants were asked to have a light meal (lunch) up to 2 hours before beginning interventions, and to refrain from strenuous physical activities and caffeine and alcoholic beverages for 24 hours prior each intervention. Participants were also instructed to maintain the same medication treatment during the entire study period and to have similar meals (breakfast and lunch) in the day of the interventions. The Ethics Committee of the São Paulo State University (School of Sciences) approved all procedures. Volunteers read a detailed description of the protocol and provided written informed consent.

Cardiopulmonary Exercise Testing (CPX)

Participants performed a symptom-limited maximal CPX (between 2:00 and 4:00 p.m.) on treadmill (ATL™, Inbramed Inc., Porto Alegre, RS, Brazil) using a Balke modified protocol (Ciolac et al. 2010a) at controlled room temperature (20–23ºC), 3 to 7 days before beginning the interventions. Continuous measures of cardiac rhythm were performed by 12-lead ECG (Ergo13™, HeartWare Inc., Belo Horizonte, MG, Brazil) throughout CPX phases (resting, warm-up, exercise and recovery). BP measurements (Premium Aneroid Sphygmomanometer™, Accumed Inc., China) were measured at ending of resting, exercise and recovery stages. The highest HR level during the exercise phase of CPX was considered the maximal value (HR_{MAX}).

All participants were asked to have a light meal (lunch) up to 2 hours before the start of the test, and to refrain from strenuous physical activities and caffeine and alcoholic beverages for 24 hours prior CPX.

Resting Blood Pressure and Heart Rate

Resting BP and HR were measured at pre (after a 10-min seated rest), post and recovery phase of each intervention, using an automatic monitor (Omron HEM 7200™, Omron Healthcare Inc., Dalian, China) and a digital telemetry system (Polar RS800CX™ HR monitor system, Polar Electro Inc, Kempele, Finland), respectively. Pre intervention BP and HR were measured in triplicate (2 min interval between each measurement), whereas post and recovery BP and HR were measured only once. The mean of the three BP and HR measurements at pre were calculated and used for intra- and inter-intervention assessment. Participants' resting BP and HR were the mean of the nine measurements performed before each intervention.

Capillary Glycaemia

Capillary glycaemia was obtained using a digital glycosimeter (FreeStyle Optium Neo™, Abbott, Oxon, UK), and measurements were taken during pre, post and recovery periods of each session, with the patient in seated position.

Arterial Stiffness

Arterial stiffness was assessed by carotid-femoral PWV measurements, with a noninvasive, and previously validated (Hickson et al. 2009), automatic device (Vicorder™, SMT Medical GmbH & Co., Wuerzburg, Germany), with participants quietly in supine position, and

after measurement of BP and HR. The measurements were performed at pre (after a 10-min seated rest), post and recovery phase of each intervention, by an experienced observer blinded to the intervention assignment, as previously described (Pascoalino et al. 2015). Briefly, common carotid artery and femoral artery pressure waveforms were estimated noninvasively using a pressure-sensitive cuff. The distance between the recording sites (D) was measured in a straight line with a flexible meter, and PWV was automatically calculated as PWV=D/t, where (t) means pulse transit time.

Endothelial Reactivity

Endothelial reactivity was evaluated by flow-mediated slowing with the Endocheck™, which is embedded within the Vicorder™ device (SMT Medical GmbH & Co., Wuerzburg, Germany), with participants quietly in supine position. The Endocheck™ records brachial pulse volume wave forms at baseline and during reactive hyperemia, which was provoked through pulse volume displacement, obtained by inflating a cuff (occlusion cuff) positioned distally around the forearm (just above the wrist). Pulse volume wave-forms were measured by a second cuff (test cuff) positioned distally around the arm (just above the elbow). The pulse wave-forms were firstly recorded at baseline for 10 s. The occlusion cuff was then inflated to 200 mmHg for 5 min, and pulse volume wave-forms were recorded for 3 min after occlusion cuff release. Pulse volume displacement was calculated as a percent change in the pulse volume wave-form between during and before hyperemia through the equation $\sqrt{PV2/PV1}$, where PV1 represents pulse volume wave-form at the baseline and PV2 represents pulse volume wave-form during hyperemia (Day et al. 2013). Endothelial reactivity measurements were performed at pre (after a

10-min seated rest), post and recovery phase of each intervention, by an experienced observer blinded to the intervention assignment, and after measurement of PWV.

Ambulatory Blood Pressure Monitoring

24-h ABP monitoring started 90 min after each intervention, at the same time of the day (5:00 to 6:00 p.m.), and was performed on a weekday other than Friday with a Dyna-Mapa™ ABP monitor (*Cardio Sistemas Comercial e Industrial Ltda*, Sao Paulo, Brazil), as previously described (Castro et al. 2016). In brief, the monitor was programmed to measure BP every 15 min during daytime and every 20 min during nighttime periods (based on participants' time from getting into and out of bed). Participants were asked to do their habitual daily activities, not to engage in formal physical activity, and to relax and straighten out the arm during the recording interval for daytime 24-h ABP monitoring. Participants were also asked to document the time at work, hours of sleep, time at leisure activities, and time of medication. Individual BP measurements were reviewed for missing and erroneous value readings by an experienced examiner who was blinded to the patient intervention (Castro et al. 2016). The average 24-h, daytime, nighttime and hourly BP (systolic and diastolic) measurements were compared between interventions.

Exercise and Control Interventions

All participants performed $HIIE_{HR}$, $HIIE_{RPE}$, MICE and CON interventions in random order, at a controlled room temperature (21-23°C), 3 to 7 days after CPX and with 2 to 5 days interval between interventions. The $HIIE_{HR}$ intensity was determined according to the HR dynamics during CPX, and consisted in 4 min walking (warm-up) at 50% (± 5bpm) of reserve

HR, followed by 21 min of HIIE, alternating 1 min of jogging/running at 85% (± 5bpm) of reserve HR with 2 min of walking at 50% (± 5bpm) of reserve HR. The $HIIE_{RPE}$ intensity was based on the association between RPE (6-20 RPE scale) and reserve HR (Ciolac et al. 2015b), and consisted in 4 min walking (warm-up) at 9 level of RPE, followed by 21 min of HIIE, alternating 1 min of jogging/running at 15-17 level with 2 min of walking at 9-11 level of RPE. The MICE intensity was also based on the association between RPE (6-20 RPE scale) and reserve HR (Ciolac et al. 2015b), and consisted in 4 min walking (warm-up) at 9 level, followed by 26 min of walking/jogging at 11-14 level of RPE. The CON session consisted in 30 min of resting quietly in the seated position. All exercise sessions ($HIIE_{HR}$, $HIIE_{RPE}$ and MICE) were performed on a motorized treadmill (ATL™, Inbramed Inc., Porto Alegre, RS, Brazil), and the treadmill speed was used regulate exercise intensity. The treadmill speed of $HIIE_{HR}$ was regulated by an exercise specialist according to the participants' HR response during exercise. The treadmill speed of $HIIE_{RPE}$ and MICE was self-regulated by the volunteer according to the RPE perception during exercise. All participants were blinded to the treadmill speed during both $HIIE_{HR}$, $HIIE_{RPE}$ and MICE sessions. The participants' HR was continuously monitored throughout the $HIIE_{HR}$, $HIIE_{RPE}$, MICE and CON sessions (Polar RS800CX™ HR monitor system, Polar Electro Inc, Kempele, Finland), and the mean HR during the last 10 s of each stage of $HIIE_{HR}$ and $HIIE_{RPE}$, and the corresponding period of MICE and CON sessions were used for comparisons between sessions. Exercise speed throughout the exercise sessions, as well as mean speed and total distance performed during exercise were recorded for comparisons among $HIIE_{HR}$, HII_{RPE} and MICE. Energy expenditure during exercise sessions were estimated by a previously validated calculation (Pescatello 2014), accordingly to participants' exercise speed and body mass.

238

239 **Statistical Analysis**

240 The software SPSS 17.0 ™ for Windows (SPSS Inc., Chicago, IL, USA) was used for
241 statistical analysis. The Shapiro-Wilk and Levene′s test were used to test the data normality and
242 homoscedasticity, respectively. Data are expressed as mean ± standard deviation (SD) or standard
243 error (SE). Two-way ANOVA with repeated measures (intervention *vs*. time) was used to
244 indicate inter- and intra-interventions differences in data measured at pre, post and recovery
245 phase of interventions. One-way ANOVA with repeated measures was used to indicate inter-
246 interventions differences in the 24-h ABP data, and in data measured during interventions. The
247 Bonferroni *post hoc* analysis was used to identify significant differences were indicated by one-
248 and two-way ANOVA. The level of significance was set at $P < 0.05$.

249

250 **RESULTS**

251 CPX was well tolerated by all participants (10.9 ± 0.8 min of exercise duration), and all
252 participants had RPE > 18 points during peak of exercise (HR_{PEAK} = 161 ± 14 bpm). The 50%
253 and 85% of $HR_{RESERVE}$ calculated for $HIIE_{HR}$ session were 122 ± 10 bpm and 150 ± 13 bpm,
254 respectively. All exercise sessions were also well tolerated by all participants. There were no
255 significant differences in exercise HR, speed and distance between $HIIE_{HR}$ and $HIIE_{RPE}$ (Figure
256 1). HR and speed throughout $HIIE_{HR}$ and $HIIE_{RPE}$ were significant different ($P < 0.05$) from
257 MICE; however, mean HR and speed were not different between all exercise sessions (Figure 1).
258 Exercise distance ($HIIE_{HR}$ = 1.827 ± 389 m; $HIIE_{RPE}$ = 1.662 ± 465 m; MICE = 1.771 ± 470 m)
259 and estimate energy expenditure ($HIIE_{HR}$ = 168 ± 12 kcal; $HIIE_{RPE}$ = 156 ± 13 kcal; MICE = 164
260 ± 16 kcal) were also not different between all exercise sessions.

There were significant intra-intervention differences in systolic BP ($F_{2,20}$ = 7.505, P < 0.004, η^2 = 0.43, power = 0.91). Post hoc analysis showed that BP response was similar between exercise interventions, with a significant increase in systolic BP immediately after each exercise sessions (post), followed by its reduction to pre-exercise levels at recovery (Table 2). No significant intra- and intervention difference were observed in diastolic BP.

There were significant inter- and intra-intervention differences in capillary glycaemia ($F_{2,20}$ = 20.211, P < 0.0001, η^2 = 0.67, power = 1.0). Post hoc analysis showed that there were similar reductions in capillary glycaemia after $HIIE_{RPE}$ (48.6±9.6 mg/dL) and $HIIE_{HR}$ (47.2±9.5 mg/dL), which were greater (P < 0.05) than the observed after MICE (29.5±11.5 mg/dL) (Figure 2).

No significant changes in endothelial reactivity and PWV were found during all interventions (Table 2). Diastolic ABP levels were also not different between interventions. However, there were significant differences between interventions in 24-h systolic BP ($F_{3,30}$ = 2.957, P < 0.05, η^2 = 0.23, power = 0.63), as well as a tendency toward inter-intervention difference in daytime systolic BP ($F_{3,30}$ = 2.807, P = 0.056). Post hoc analysis showed that 24-h systolic BP was lower (6.7±2.2 mmHg, P < 0.05, η^2 = 0.22, power = 0.62) after $HIIE_{RPE}$ than CON, and daytime systolic BP tended to be lower (7.0±2.5 mmHg, P = 0.06) after $HIIE_{RPE}$ than CON. No significant differences between $HIIE_{RPE}$ and $HIIE_{HR}$ sessions were found in 24-h, daytime, and nighttime ABP (Figure 3).

DISCUSSION

The main finding of the present study was that 1) there were no significant differences in hemodynamic (HR, PWV, endothelial reactivity and HRV) and metabolic (capillary glycaemia) response, as well as walking/running speed and exercise distance, between $HIIE_{RPE}$ and $HIIE_{HR}$;

2) HIIE were more effective than MICE for acutely reducing capillary glycaemia independently of the mode of prescription (RPE *vs* HR response to CPX); and 3) only $HIIE_{RPE}$ was effective for reducing 24-h systolic BP. These findings suggests that the RPE scale is a simple, inexpensive and useful tool for prescribing and self-regulating HIIE in patients with T2DM. To the best of our knowledge, this is a pioneer study in analyzing the usefulness and efficiency of RPE (Borg 1982) for prescribing and self-regulating HIIE in patients with T2DM.

The usefulness of RPE (Borg 1982) for prescribing and self-regulating exercise has been previously shown in studies with healthy (Chen et al. 2002; Ciolac et al. 2015b) and cardiovascular disease populations (Carvalho et al. 2009; Ciolac et al. 2015a). For example, we and others showed that RPE is useful for prescribing and self-regulating land and water-based MICE in heart transplant (Ciolac et al. 2015a) and chronic heart failure (Carvalho et al. 2009) patients. RPE was also effective and reproducible for monitoring and regulating steady-state running in physically active individuals (Chen et al. 2002). A pilot study by our group also showed no differences in HR response and walking/running speed between HIIE sessions prescribed and self-regulated by RPE or HR response to CPX in young healthy individuals (Ciolac et al. 2015b). The findings of present study are in agreement with above-mentioned studies with MICE and HIIE, and thus confirm our hypothesis that RPE is as effective as HR response to CPX for prescribing and self-regulating HIIE in patients with T2DM.

Blood glucose control is a key goal of T2DM treatment that reduces incidence of diabetic-related complications, including risk of cardiovascular events (Mannucci et al. 2013). The potential of HIIE for improving glycemic control has been shown in both acute and chronic intervention studies (Tjonna et al. 2011; Gillen et al. 2012; Alvarez et al. 2016). For example, a single HIIE session reduced mean 24-hour glucose and postprandial glycaemia in T2DM individuals (Gillen et al. 2012). In individuals with metabolic syndrome, HIIE and MICE

309 sessions acutely reduced glycaemia, but with a longer time reduction occurring after HIIE (72
310 hours) than MICE (24 hours) (Tjonna et al. 2011). A 16-week HIIE program, with a weekly time
311 commitment 25-56% lower than the minimal recommended in current exercise guidelines,
312 improved glycemic control and other health-related outcomes in obese women with T2DM, even
313 with a reduction in glucose-controlling medication occurring in several individuals (Alvarez et al.
314 2016). The similar reductions on capillary glycaemia after both $HIIE_{RPE}$ and $HIIE_{HR}$, found in the
315 present study, which were greater than the reduction after MICE, thus confirms the superiority of
316 HIIE for reducing glycaemia in individuals with T2DM, and show for the first time that this
317 superiority occurs similarly in HIIE session prescribed and regulated by RPE or HR response to
318 CPX. It is also important to note that the superioty of HIIE for acutely reducing glycaemia in the
319 present and previous study (Tjonna et al. 2011) occurred despite the lack of difference in estimate
320 energy expenditure between interventions. Post-exercise capillary glycaemia reduction may be
321 explained by increased glucose permeability in active muscle fibers by the insulin-independent
322 translocation of glucose transporters (Frosig et al. 2007; Tjonna et al. 2011). The mechanism by
323 which $HIIE_{RPE}$ and $HIIE_{HR}$ promoted greater blood glucose reduction than MICE was not
324 evaluated in the present study. However, the high levels of muscle fiber recruitment (Gibala and
325 McGee 2008) and muscle glycogen utilization (Larsen et al. 1999) previously observed during
326 HIIE may increase exercise-induced muscle glucose absorption during and after exercise,
327 resulting in the greater capillary glycaemia reduction found after both $HIIE_{RPE}$ and $HIIE_{HR}$.

328 The acute hypotensive effect of exercise on resting BP is well-known (Ciolac et al. 2009;
329 Castro et al. 2016; Costa et al. 2016; Morales-Palomo et al. 2017). However, there are few
330 studies comparing the acute effect of HIIE *versus* MICE on resting BP in young normotensive
331 (Costa et al. 2016) and in metabolic syndrome (Morales-Palomo et al. 2017) individuals, which
332 have shown similar hypotensive effect between interventions (Costa et al. 2016) or a superior

effect of HIIE (Morales-Palomo et al. 2017). In contrast, no reductions in resting BP were found after any intervention in the present study. Differences in studied population, exercise protocol and exercise duration may explain differences between present and previous studies. In addition, all participants in the present study had resting BP at normotensive levels. Indeed, hypertensive individuals in present study were under anti-hypertensive therapy, and showed similar resting BP levels than normotensive individuals (data not shown). The acute hypotensive effect of exercise appears to be more pronounced in individuals with higher baseline BP levels, regardless of exercise modality (Ciolac et al. 2009), which may explain the absence of BP reduction after both $HIIE_{RPE}$, $HIIE_{HR}$ and MICE in the present study.

Similar to which occurred with resting BP, $HIIE_{HR}$ and MICE did not shown a hypotensive effect on ABP. Few studies assessed the acute hypotensive effect of HIIE *versus* MICE on 24-h ABP in middle-aged (Ciolac et al. 209) and older (Carvalho et al. 2015) hypertensive individuals, which showed that both interventions promote systolic and diastolic ABP reduction when compared with CON, but with similar hypotensive effect between interventions (Ciolac et al. 2015), or a superior hypotensive effect of HIIE (Carvalho et al. 2015). Again, differences in exercise protocol, exercise duration and ABP levels may explain differences between present and previous studies. Previous studies have used longer duration interventions (Ciolac et al. 2009; Carvalho et al. 2015) and exercise protocol with a longer period at high-intensity (Carvalho et al. 2015), as well as have assessed individuals with greater ABP levels (Ciolac et al. 2009; Carvalho et al. 2015) than present study. Despite the no hypotensive effect of $HIIE_{HR}$ and MICE, 24-h systolic (but not diastolic) ABP was 6.8±2.2 mmHg lower after $HIIE_{RPE}$ than CON, and daytime systolic ABP tended to be lower (7.0±2.5 mmHg, $P = 0.06$) after $HIIE_{RPE}$ than CON. The reason for the hypotensive effect in ABP found after $HIIE_{RPE}$, but not in $HIIE_{HR}$, is unknown. However, it is possible that the pace self-regulation during $HIIE_{RPE}$ may be

involved in the ABP reduction, although it was not significantly different from the imposed pace during $HIIE_{HR}$. Future studies are thus necessary to better understand present results.

Arterial stiffness and endothelial dysfunction are important cardiovascular risk factors that increase progressively during aging and in the presence of cardiometabolic diseases, including T2DM (Ciolac et al. 2010a; Ciolac et al. 2010b; Guimaraes et al. 2010; Francois and Little 2017). The present study found no changes on endothelial reactivity and PWV during all interventions. Although little is known about the acute effect of both HIIE and MICE on arterial stiffness in T2DM individuals, the lack of exercise-induced change on carotid-femoral PWV observed in the present study is in accordance with a recent meta-analysis that found no acute effect of aerobic exercise on carotid-femoral PWV in healthy young adults (Pierce et al. 2018). In contrast, HIIE and MICE sessions were similarly effective to acutely improve flow-mediated dilation in individuals with cardiovascular disease (Currie et al. 2012). However, in agreement with present findings, a recent study showed no changes in markers of endothelial function in sedentary and trained T2DM individuals submitted to a HIIE session (Francois and Little. 2017). The results of present and previous studies (Currie et al., 2012; Francois and Little 2017) thus suggest that exercise may acutely improve endothelial function markers in individuals with cardiovascular, but not in T2DM individuals, which may be due the deleterious effect of hyperglycemia and the heterogeneity of medication (dosage and type) and comorbidities. However, future studies are necessary to confirm this hypothesis.

The limitations of present study include its design, where the use of a single session does not allow to state that the similar hemodynamic and performance response between $HIIE_{RPE}$ and $HIIE_{HR}$, as well as the reduction in capillary glycaemia and ABP may persist after a long period of HIIE training. However, the initial step to evaluate the response to any exercise intervention is to analyze the acute responses that this intervention produces, and training studies may not be

justified without demonstrating an efficient acute response first. The small sample size of physically inactive T2DM individuals is also limitation of present study, because it does not guarantee similar results in other T2DM populations, especially those that are physically active or have long-term diabetic complications. However, it is important to note that sample power estimation was based on the primary outcome, and that the statistical analysis of secondary outcomes showed high effect sizes (η^2) and power (see results). One can argue that the no standardization of the meals prior each intervention may have influenced the capillary glucose response to interventions, and thus may also be a limitation of present study. However, all participants were instructed to have similar meals (breakfast and lunch) in the day of the interventions. In addition, the lack of significant difference on baseline capillary glycaemia between interventions suggest that participants followed the instructions.

Most T2DM patients are sedentary or insufficient actives (Morrato et al. 2007) and lack of time is the most frequently cited barrier to regular exercise participation (Trost et al. 2002). Thus, the greater capillary glycaemia decrease after $HIIE_{RPE}$ and $HIIE_{HR}$ than MICE with lower time commitment may have important implications for a public health perspective. In addition to improved glycaemic control, cardiovascular risk reduction also have positive effects in T2DM morbidity, mortality and health care expenditure (Turnbull et al. 2005; Shaw et al. 2010; Zhang et al. 2010). For example, 2.1/0.9 mmHg decrease on systolic/diastolic BP resulted in a 10% reduction of major cardiovascular events in T2DM patients (Turnbule et al. 2005). In this context, the $HIIE_{RPE}$-induced 6.7 mmHg decrease in 24-h systolic BB may have important clinical implications. Finally, the lack of difference between $HIIE_{RPE}$ and $HIIE_{HR}$ HR, speed and distance during exercise, as well as post-exercise hemodynamic and metabolic response, suggest that RPE is a useful tool for prescribing and self-regulating HIIE in T2DM. This simple and inexpensive tool may then increase access and adherence to this exercise modality, and consequently, increase

benefits to the general population, given that methods commonly used to prescribe HIIE have high cost and low access (Atkinson et al. 2005; Meyer et al. 2005; Ciolac et al. 2015b). In this context, future multicenter randomized controlled trials focused on analyzing adherence and health-related benefits to long-term $HIIE_{RPE}$ programs in T2DM are welcome.

In summary, HR, speed and distance during exercise, as well as BP response to exercise, were similar between $HIIE_{RPE}$ and $HIIE_{HR}$. In addition, HIIE was superior to MICE to acutely reduce capillary glycaemia, independently if it was prescribed and regulated by RPE or HR response to CPX. Indeed, $HIIE_{RPE}$ was superior to $HIIE_{HR}$ and MICE to acutely reduce ambulatory BP. These results suggest that HIIE may be superior to MICE for reducing glycaemia and BP in T2DM individuals, and that the 6 to 20 RPE scale may be an useful tool for prescribing and self-regulating HIIE in this population.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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571

572 **FIGURE LEGENDS**

573 **Figure 1.** Heart rate (A e C) and speed (B e D) during interventions. Data are expressed as mean
574 ± SE (A e B) or mean ± SD (C e D). CON: control intervention; $HIIE_{RPE}$: high-intensity interval
575 exercise prescribed and self-regulated by RPE; $HIIE_{HR}$: high-intensity interval exercise
576 prescribed and regulated by heart rate response to cardiopulmonary exercise testing; MICE:
577 moderate-intensity continuous exercise. Asterisk denotes significant difference from high-
578 intensity intervals and active recovery intervals (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.01$). Dagger
579 denotes significant difference from $HIIE_{RPE}$, $HIIE_{HR}$ and MICE (†: $P < 0.001$). Double dagger
580 denotes significant difference from $HIIE_{RPE}$ and $HIIE_{HR}$ (‡: $P < 0.05$).

581

582 **Figure 2.** Capillary glycaemia (A) and its absolute (B) and relative (C) changes (Δ) during
583 interventions. Data are expressed as mean ± SD. CON: control intervention; $HIIE_{RPE}$: high-
584 intensity interval exercise prescribed and self-regulated by RPE; $HIIE_{HR}$: high-intensity interval
585 exercise prescribed and regulated by heart rate response to cardiopulmonary exercise testing;
586 MICE: moderate-intensity continuous exercise. Asterisk denotes significant difference from pre
587 at the same intervention (*: $P < 0.05$; **: $P < 0.01$). Dagger denotes significant difference from
588 $HIIE_{RPE}$, $HIIE_{HR}$ and MICE at the same period (†: $P < 0.05$). Double dagger denotes significant
589 difference from $HIIE_{RPE}$ and $HIIE_{HR}$ at the same period (‡: $P < 0.05$).

590

591 **Figure 3.** Ambulatory blood pressure after interventions. Data are expressed as mean ± SD.
592 CON: control intervention; $HIIE_{RPE}$: high-intensity interval exercise prescribed and self-regulated
593 by RPE; $HIIE_{HR}$: high-intensity interval exercise prescribed and regulated by heart rate response

to cardiopulmonary exercise testing; MICE: moderate-intensity continuous exercise. #: significant difference from CON ($P < 0.05$). °: tendency toward difference from CON ($P = 0.06$).

Tabel 1: Subjects' characteristics.

Variable	
N (male/female)	11 (2/9)
Age (yr)	52.3 ± 3.0
Body mass (kg)	74.1 ± 4.4
Height (m)	1.62 ± 0.04
BMI (kg/m^2)	28.4 ± 1.5
Waist circumference (cm)	95.9 ± 3.9
Time elapsed from diagnosis (yr)	9.5 ± 1.6
Resting blood pressure (mmHg)	
Systolic	113 ± 4
Diastolic	76 ± 3
Current medication	
Hypoglycemics	
Metformin [N (mg/day)]	10 (1400 ± 209.1)
Glibenclamide [N (mg/day)]	1 (90 ± 0)
Pioglitazone [N (mg/day)]	1 (30 ± 0)
Dapagliflozin [N (mg/day)]	1 (10 ± 0)
Glicazide	1 (20 ± 0)
NPH insulin [N (U/day)]	1 (50 ± 0)
Anti-hypertensives	
ACE inhibitors [N (mg/day)]	3 (23.3 ± 8.8)
ARAs [N (mg/day)]	4 (68.8 ± 18.8)
Diuretics [N (mg/day)]	2 (25 ± 0)
β-blockers [N (mg/day)]	1 (5 ± 0)
Hypolipidemics	
Statins [N (mg/day)]	3 (30 ± 10)

ACE: angiotensin conversor enzyme; ARAs: angiotensin II receptor antagonists; BMI: body mass index; BP: blood pressure; PWV: pulse wave velocity; EF: endotelial function; NPH: Neutral Protamine Hagedorn; SSRIs: selective serotonin reuptake inhibitors.

Table 2. Blood pressure, pulse wave velocity and endothelial reactivity response to exercise and control interventions.

	$HIIE_{RPE}$	$HIIE_{HR}$	MICE	CON
Systolic (mmHg)				
Pre	114 ± 13	115 ± 17	116 ± 14	110 ± 14
Post	121 ± 18*	121 ± 17*	121 ± 22*	115 ± 17*
Recovery	113 ± 15†	116 ± 12†	116 ± 14†	113 ± 13
Diastolic (mmHg)				
Pre	75 ± 12	77 ± 12	78 ± 3.5	76 ± 11
Post	79 ± 11	81 ± 15	81.8 ± 3.8	78 ± 12
Recovery	78 ± 10	77 ± 12	78.4 ± 3.3	78 ± 13
PWV (m/s)				
Pre	8.7 ± 1.5	9.3 ± 1.4	8.7 ± 1.3	8.4 ± 1.1
Post	8.9 ± 1.5	9.8 ± 1.6	8.8 ± 1.4	8.6 ± 1.3
Recovery	8.8 ± 1.6	9.6 ± 1.5	9.2 ± 1.4	9.0 ± 1.4
Endothelial reactivity (√PV2/PV1)				
Pre	1.21 ± 0.08	1.27 ± 0.19	1.19 ± 0.12	1.27 ± 0,12
Post	1.21 ± 0.15	1.29 ± 0.23	1.32 ± 0.09	1.27 ± 0,10
Recovery	1.28 ± 0.17	1.30 ± 0.15	1.27 ± 0.14	1.29 ± 0,11

CON: control intervention; $HIIE_{RPE}$: high-intensity interval exercise prescribed and self-regulated by rating of perceived exertion; $HIIE_{HR}$: high-intensity interval exercise prescribed and regulated by heart rate response to cardiopulmonary exercise testing. MICE: moderate-intensity continuous exercise; PWV: carotid-femoral pulse wave velocity. Asterisk denotes significant difference from pre (*: $P < 0.05$). Dagger denotes significant difference from post (†: $P < 0.05$).

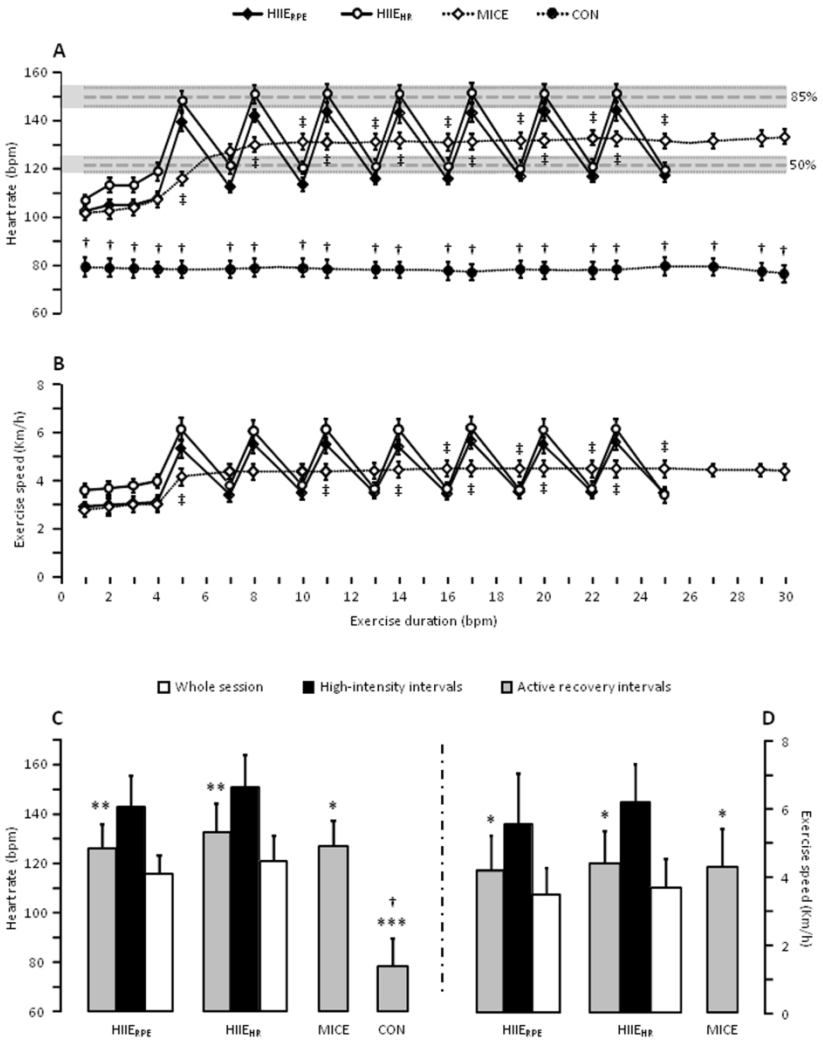

Figure 1. Heart rate (A e C) and speed (B e D) during interventions. Data are expressed as mean ± SE (A e B) or mean ± SD (C e D). CON: control intervention; HIIERPE: high-intensity interval exercise prescribed and self-regulated by RPE; HIIEHR: high-intensity interval exercise prescribed and regulated by heart rate response to cardiopulmonary exercise testing; MICE: moderate-intensity continuous exercise. Asterisk denotes significant difference from high-intensity intervals and active recovery intervals (*: P < 0.05; **: P < 0.01; ***: P < 0.01). Dagger denotes significant difference from HIIERPE, HIIEHR and MICE (†: P < 0.001). Double dagger denotes significant difference from HIIERPE and HIIEHR (‡: P < 0.05).

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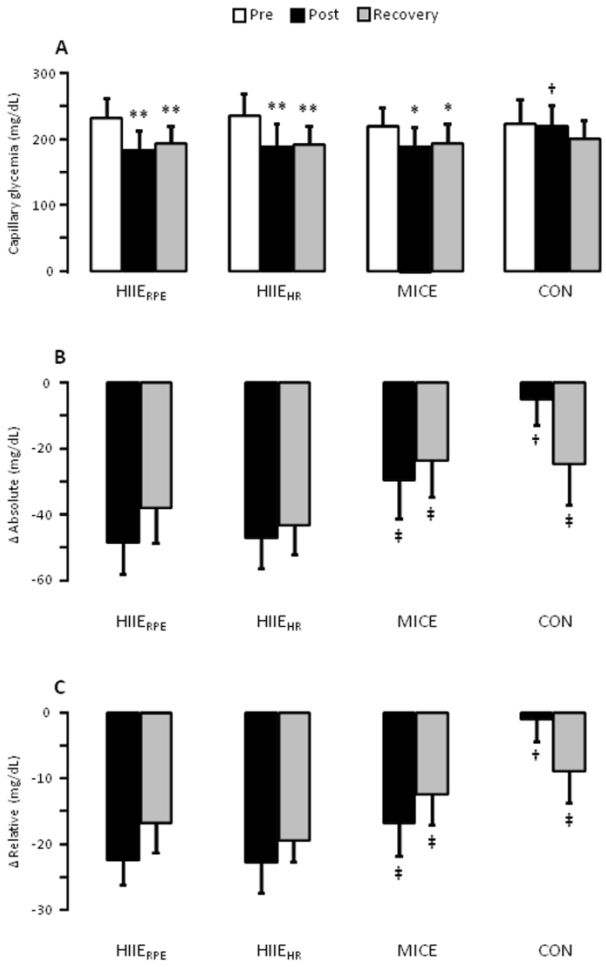

Figure 2. Capillary glycaemia (A) and its absolute (B) and relative (C) changes (Δ) during interventions. Data are expressed as mean ± SD. CON: control intervention; HIIERPE: high-intensity interval exercise prescribed and self-regulated by RPE; HIIEHR: high-intensity interval exercise prescribed and regulated by heart rate response to cardiopulmonary exercise testing; MICE: moderate-intensity continuous exercise. Asterisk denotes significant difference from pre at the same intervention (*: P < 0.05; **: P < 0.01). Dagger denotes significant difference from HIIERPE, HIIEHR and MICE at the same period (†: P < 0.05). Double dagger denotes significant difference from HIIERPE and HIIEHR at the same period (‡: P < 0.05).

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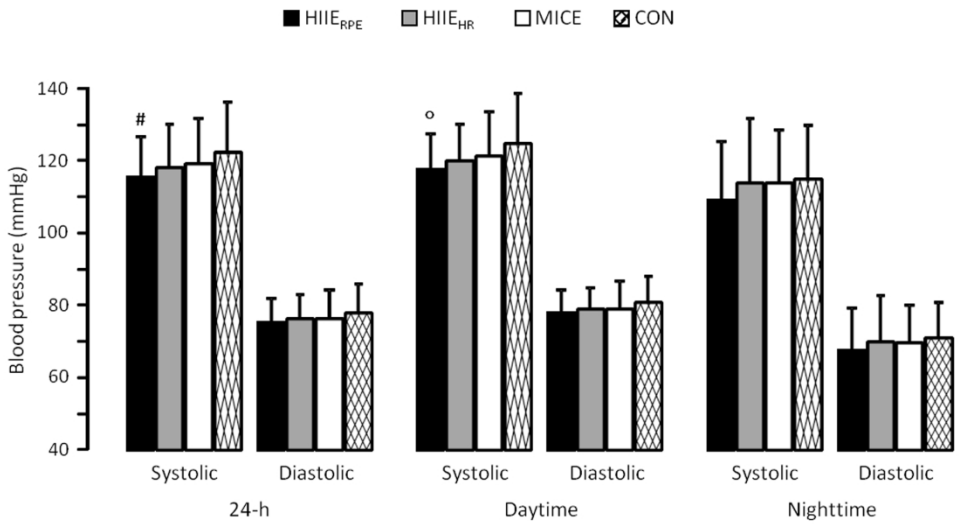

Figure 3. Ambulatory blood pressure after interventions. Data are expressed as mean ± SD. CON: control intervention; HIIERPE: high-intensity interval exercise prescribed and self-regulated by RPE; HIIEHR: high-intensity interval exercise prescribed and regulated by heart rate response to cardiopulmonary exercise testing; MICE: moderate-intensity continuous exercise. #: significant difference from CON ($P < 0.05$). □: tendency toward difference from CON ($P = 0.06$).

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