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

RUNNING TITLE: High-intensity Exercise in Type 2 Diabetes

AUTHORS: Ariane Aparecida Viana¹, Bianca Fernandes¹, Cristian Alvarez², Guilherme Veiga Guimarães³, Emmanuel Gomes Ciolac¹.

AFFILIATIONS: 1. São Paulo State University – UNESP, School of Sciences, Physical Education Department, Exercise and Chronic Disease Research Laboratory, Bauru, Brazil; 2. Family Healthcare Center Tomás Rojas, Los Lagos, Chile; 2. Universidad de Los Lagos, Department of Physical Activity Sciences, Osorno, Chile; 3. University of São Paulo, School of Medicine, Heart Institute, Sao Paulo, Brazil.

CORRESPONDING AUTHOR: Emmanuel Gomes Ciolac
Universidade Estadual Paulista – UNESP, Faculdade de Ciências, Departamento de Educação Física, Laboratório de Pesquisas em Exercício Físico e Doenças Crônicas
Av. Engenheiro Luiz Edmundo Carrijo Coube 14-06, Bauru, Brazil, 17033-360.
E-mail: emmanuel.ciolac@unesp.br / Twitter: @ProfessorCiolac

DISCLOSURES: Bianca Fernandes was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP # 2016/08205-9) during this project. This work is part of Ariane A. Viana’s master of sciences dissertation under the guidance of Dr Emmanuel G. Ciolac. The current study is presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

CONFLICTS OF INTEREST: No conflicts to declare.

WORD COUNT: 6,477 (including references, tables and figures)
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 $\alpha$ 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 (20–23°C), 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 (HRMAX).
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\textsubscript{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\textsubscript{HR}, HIIE\textsubscript{RPE} and MICE) were
performed on a motorized treadmill (ATL\textsuperscript{TM}, Inbramed Inc., Porto Alegre, RS, Brazil), and the
treadmill speed was used regulate exercise intensity. The treadmill speed of HIIE\textsubscript{HR} was
regulated by an exercise specialist according to the participants' HR response during exercise.
The treadmill speed of HIIE\textsubscript{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\textsubscript{HR}, HIIE\textsubscript{RPE} and MICE sessions. The participants' HR was continuously monitored
throughout the HIIE\textsubscript{HR}, HIIE\textsubscript{RPE}, MICE and CON sessions (Polar RS800CX\textsuperscript{TM} HR monitor
system, Polar Electro Inc, Kempele, Finland), and the mean HR during the last 10 s of each stage
of HIIE\textsubscript{HR} and HIIE\textsubscript{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\textsubscript{HR}, HIIE\textsubscript{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.
Statistical Analysis

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

RESULTS

CPX was well tolerated by all participants (10.9 ± 0.8 min of exercise duration), and all participants had RPE > 18 points during peak of exercise (HR\textsubscript{PEAK} = 161 ± 14 bpm). The 50% and 85% of HR\textsubscript{RESERVE} calculated for HIIE\textsubscript{HR} session were 122 ± 10 bpm and 150 ± 13 bpm, respectively. All exercise sessions were also well tolerated by all participants. There were no significant differences in exercise HR, speed and distance between HIIE\textsubscript{HR} and HIIE\textsubscript{RPE} (Figure 1). HR and speed throughout HIIE\textsubscript{HR} and HIIE\textsubscript{RPE} were significant different (P < 0.05) from MICE; however, mean HR and speed were not different between all exercise sessions (Figure 1). Exercise distance (HIIE\textsubscript{HR} = 1.827 ± 389 m; HIIE\textsubscript{RPE} = 1.662 ± 465 m; MICE = 1.771 ± 470 m) and estimate energy expenditure (HIIE\textsubscript{HR} = 168 ± 12 kcal; HIIE\textsubscript{RPE} = 156 ± 13 kcal; MICE = 164 ± 16 kcal) were also not different between all exercise sessions.
There were significant intra-intervention differences in systolic BP ($F_{2,20} = 7.505$, $P < 0.004$, $\eta^2 = 0.43$, 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 session (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 ($F_{2,20} = 20.211$, $P < 0.0001$, $\eta^2 = 0.67$, power = 1.0). Post hoc analysis showed that there were similar reductions in capillary glycaemia after HIIE\textsubscript{RPE} (48.6±9.6 mg/dL) and HIIE\textsubscript{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 ($F_{3,30} = 2.957$, $P < 0.05$, $\eta^2 = 0.23$, 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, $P < 0.05$, $\eta^2 = 0.22$, power = 0.62) after HIIE\textsubscript{RPE} than CON, and daytime systolic BP tended to be lower (7.0±2.5 mmHg, $P = 0.06$) after HIIE\textsubscript{RPE} than CON. No significant differences between HIIE\textsubscript{RPE} and HIIE\textsubscript{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\textsubscript{RPE} and HIIE\textsubscript{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\textsubscript{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
sessions acutely reduced glycaemia, but with a longer time reduction occurring after HIIE (72 hours) than MICE (24 hours) (Tjonna et al. 2011). A 16-week HIIE program, with a weekly time commitment 25-56% lower than the minimal recommended in current exercise guidelines, improved glycemic control and other health-related outcomes in obese women with T2DM, even with a reduction in glucose-controlling medication occurring in several individuals (Alvarez et al. 2016). The similar reductions on capillary glycaemia after both HIIE_{RPE} and HIIE_{HR}, found in the present study, which were greater than the reduction after MICE, thus confirms the superiority of HIIE for reducing glycaemia in individuals with T2DM, and show for the first time that this superiority occurs similarly in HIIE session prescribed and regulated by RPE or HR response to CPX. It is also important to note that the superiority of HIIE for acutely reducing glycaemia in the present and previous study (Tjonna et al. 2011) occurred despite the lack of difference in estimate energy expenditure between interventions. Post-exercise capillary glycaemia reduction may be explained by increased glucose permeability in active muscle fibers by the insulin-independent translocation of glucose transporters (Frosig et al. 2007; Tjonna et al. 2011). The mechanism by which HIIE_{RPE} and HIIE_{HR} promoted greater blood glucose reduction than MICE was not evaluated in the present study. However, the high levels of muscle fiber recruitment (Gibala and McGee 2008) and muscle glycogen utilization (Larsen et al. 1999) previously observed during HIIE may increase exercise-induced muscle glucose absorption during and after exercise, resulting in the greater capillary glycaemia reduction found after both HIIE_{RPE} and HIIE_{HR}.

The acute hypotensive effect of exercise on resting BP is well-known (Ciolac et al. 2009; Castro et al. 2016; Costa et al. 2016; Morales-Palomo et al. 2017). However, there are few studies comparing the acute effect of HIIE versus MICE on resting BP in young normotensive (Costa et al. 2016) and in metabolic syndrome (Morales-Palomo et al. 2017) individuals, which 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<sub>RPE</sub>, HIIE<sub>HR</sub> and MICE in the present study.

Similar to which occurred with resting BP, HIIE<sub>HR</sub> 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. 2009) 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<sub>HR</sub> and MICE, 24-h systolic (but not diastolic) ABP was 6.8±2.2 mmHg lower after
HIIE<sub>RPE</sub> than CON, and daytime systolic ABP tended to be lower (7.0±2.5 mmHg, \( P = 0.06 \)) after
HIIE<sub>RPE</sub> than CON. The reason for the hypotensive effect in ABP found after HIIE<sub>RPE</sub>, but not in
HIIE<sub>HR</sub>, is unknown. However, it is possible that the pace self-regulation during HIIE<sub>RPE</sub> 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 a 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 ($\eta^2$) 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.

**ACKNOWLEDGEMENTS**

This work was partially supported by *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP # 2012/08205-4). Bianca Fernandes was supported by *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP # 2016/08205-9) during this project. This work is part of Ariane A. Viana’s master of sciences dissertation under the guidance of Dr Emmanuel G. Ciolac. The current study is presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

**CONFLICT OF INTEREST**

All authors have no conflicts of interest to declare.

**REFERENCES**


FIGURE LEGENDS

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; HIIE_{RPE}: high-intensity interval exercise prescribed and self-regulated by RPE; HIIE_{HR}: 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 HIIE_{RPE}, HIIE_{HR} and MICE (†: P < 0.001). Double dagger denotes significant difference from HIIE_{RPE} and HIIE_{HR} (‡: P < 0.05).

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; HIIE_{RPE}: high-intensity interval exercise prescribed and self-regulated by RPE; HIIE_{HR}: 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 HIIE_{RPE}, HIIE_{HR} and MICE at the same period (†: P < 0.05). Double dagger denotes significant difference from HIIE_{RPE} and HIIE_{HR} at the same period (‡: P < 0.05).

Figure 3. Ambulatory blood pressure after interventions. Data are expressed as mean ± SD. CON: control intervention; HIIE_{RPE}: high-intensity interval exercise prescribed and self-regulated 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 ($P = 0.06$).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male/female)</td>
<td>11 (2/9)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52.3 ± 3.0</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>74.1 ± 4.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4 ± 1.5</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>95.9 ± 3.9</td>
</tr>
<tr>
<td>Time elapsed from diagnosis (yr)</td>
<td>9.5 ± 1.6</td>
</tr>
<tr>
<td>Resting blood pressure (mmHg) Systolic</td>
<td>113 ± 4</td>
</tr>
<tr>
<td>Resting blood pressure (mmHg) Diastolic</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Current medication</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td></td>
</tr>
<tr>
<td>Metformin [N (mg/day)]</td>
<td>10 (1400 ± 209.1)</td>
</tr>
<tr>
<td>Glibenclamide [N (mg/day)]</td>
<td>1 (90 ± 0)</td>
</tr>
<tr>
<td>Pioglitazone [N (mg/day)]</td>
<td>1 (30 ± 0)</td>
</tr>
<tr>
<td>Dapagliflozin [N (mg/day)]</td>
<td>1 (10 ± 0)</td>
</tr>
<tr>
<td>Glicazide</td>
<td></td>
</tr>
<tr>
<td>NPH insulin [N (U/day)]</td>
<td>1 (50 ± 0)</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors [N (mg/day)]</td>
<td>3 (23.3 ± 8.8)</td>
</tr>
<tr>
<td>ARAs [N (mg/day)]</td>
<td>4 (68.8 ± 18.8)</td>
</tr>
<tr>
<td>Diuretics [N (mg/day)]</td>
<td>2 (25 ± 0)</td>
</tr>
<tr>
<td>β-blockers [N (mg/day)]</td>
<td>1 (5 ± 0)</td>
</tr>
<tr>
<td>Hypolipidemics</td>
<td></td>
</tr>
<tr>
<td>Statins [N (mg/day)]</td>
<td>3 (30 ± 10)</td>
</tr>
</tbody>
</table>

ACE: angiotensin conversor enzyme; ARAs: angiotensin II receptor antagonists; BMI: body mass index; BP: blood pressure; PWV: pulse wave velocity; EF: endothelial 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.

<table>
<thead>
<tr>
<th></th>
<th>HIIERPE</th>
<th>HIIEHR</th>
<th>MICE</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>114 ± 13</td>
<td>115 ± 17</td>
<td>116 ± 14</td>
<td>110 ± 14</td>
</tr>
<tr>
<td>Post</td>
<td>121 ± 18*</td>
<td>121 ± 17*</td>
<td>121 ± 22*</td>
<td>115 ± 17*</td>
</tr>
<tr>
<td>Recovery</td>
<td>113 ± 15†</td>
<td>116 ± 12†</td>
<td>116 ± 14†</td>
<td>113 ± 13</td>
</tr>
<tr>
<td><strong>Diastolic (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>75 ± 12</td>
<td>77 ± 12</td>
<td>78 ± 3.5</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>Post</td>
<td>79 ± 11</td>
<td>81 ± 15</td>
<td>81.8 ± 3.8</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Recovery</td>
<td>78 ± 10</td>
<td>77 ± 12</td>
<td>78.4 ± 3.3</td>
<td>78 ± 13</td>
</tr>
<tr>
<td><strong>PWV (m/s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>8.7 ± 1.5</td>
<td>9.3 ± 1.4</td>
<td>8.7 ± 1.3</td>
<td>8.4 ± 1.1</td>
</tr>
<tr>
<td>Post</td>
<td>8.9 ± 1.5</td>
<td>9.8 ± 1.6</td>
<td>8.8 ± 1.4</td>
<td>8.6 ± 1.3</td>
</tr>
<tr>
<td>Recovery</td>
<td>8.8 ± 1.6</td>
<td>9.6 ± 1.5</td>
<td>9.2 ± 1.4</td>
<td>9.0 ± 1.4</td>
</tr>
<tr>
<td><strong>Endothelial reactivity (√PV2/PV1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.21 ± 0.08</td>
<td>1.27 ± 0.19</td>
<td>1.19 ± 0.12</td>
<td>1.27 ± 0.12</td>
</tr>
<tr>
<td>Post</td>
<td>1.21 ± 0.15</td>
<td>1.29 ± 0.23</td>
<td>1.32 ± 0.09</td>
<td>1.27 ± 0.10</td>
</tr>
<tr>
<td>Recovery</td>
<td>1.28 ± 0.17</td>
<td>1.30 ± 0.15</td>
<td>1.27 ± 0.14</td>
<td>1.29 ± 0.11</td>
</tr>
</tbody>
</table>

CON: control intervention; HIIERPE: high-intensity interval exercise prescribed and self-regulated by rating of perceived exertion; HIIEHR: 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; HIIIEHR: 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, HIIIEHR and MICE (†: P < 0.001). Double dagger denotes significant difference from HIIERPE and HIIIEHR (‡: P < 0.05).
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).
Figure 3. Ambulatory blood pressure after interventions. Data are expressed as mean ± SD. CON: control intervention; HIERPE: 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).