

Original article

The effect of acute aerobic exercise on central arterial stiffness, wave reflections, and hemodynamics in adults with diabetes: A randomized cross-over design

Kimberley L. Way^{a,b,c,*}, Angela S. Lee^{b,d,e}, Stephen M. Twigg^{b,d,e}, Nathan A. Johnson^{a,b,c}

^a Faculty of Medicine and Health, Discipline of Exercise and Sports Science, University of Sydney, Lidcombe, NSW 2141, Australia

^b Charles Perkins Centre, University of Sydney, Camperdown, NSW 2006, Australia

^c Boden Collaboration for Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Camperdown, NSW 2006, Australia

^d Faculty of Medicine and Health, Central Clinical School, University of Sydney, Camperdown, NSW 2006, Australia

^e Department of Endocrinology, Diabetes Centre, Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia

Received 6 September 2019; revised 21 December 2019; accepted 22 January 2020

Available online 3 March 2020

2095-2546/© 2021 Published by Elsevier B.V. on behalf of Shanghai University of Sport. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Abstract

Background: Individuals with diabetes have greater central arterial stiffness, wave reflections, and hemodynamics, all of which promote the accelerated cardiovascular pathology seen in this population. Acute aerobic exercise has been shown to be an effective strategy for reducing central arterial stiffness, wave reflections, and hemodynamics in healthy individuals; however, the effects of acute aerobic exercise in reducing these outcomes is not well established in people with diabetes. Recently, implementation of high-intensity interval exercise (HIIE) has shown superior improvements in cardiovascular health outcomes when compared to traditional aerobic exercise. Yet, the effect of HIIE on the aforementioned outcomes in people with diabetes is not known. The purpose of this study was to (i) describe the central arterial stiffness, wave reflections, and hemodynamic responses to a bout of HIIE and moderate-intensity continuous exercise (MICE) in adults with diabetes; and (ii) compare the effects of HIIE and MICE on the aforementioned outcomes.

Methods: A total of 24 adult men and women (aged 29–59 years old) with type 1 ($n = 12$) and type 2 ($n = 12$) diabetes participated in a randomized cross-over study. All participants completed the following protocols: (i) HIIE: cycling for 4×4 min at 85%–95% of heart rate peak (HR_{peak}), interspersed with 3 min of active recovery at 60%–70% HR_{peak} ; (ii) MICE: 33 min of continuous cycling at 60%–70% HR_{peak} ; and (iii) control (CON): lying quietly in a supine position for 30 min.

Results: A significant group \times time effect was found for changes in central systolic blood pressure ($F = 3.20$, $p = 0.01$) with a transient reduction for the HIIE group but not for the MICE or CON groups. There was a significant group \times time effect for changes in augmentation index at a heart rate of 75 beats/min ($F = 2.32$, $p = 0.04$) with a decrease following for HIIE and MICE but not for CON. For all other measures of central arterial stiffness and hemodynamics, no significant changes were observed ($p > 0.05$).

Conclusion: A bout of HIIE appears to lead to a greater transient reduction in central systolic blood pressure than the reduction observed following MICE; however, both HIIE and MICE improved augmentation index at a heart rate of 75 beats/min in people with diabetes. There was no significant difference in response to HIIE and MICE in all outcomes. This provides preliminary evidence on the role of HIIE on such outcomes in people with diabetes.

Keywords: Augmentation index; Central systolic blood pressure; Diabetes; High-intensity interval exercise

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in people with diabetes, and these

individuals are 2–3 times more likely to develop CVD.¹ This accelerated cardiovascular pathology is prompted by endothelial dysfunction caused by hyperglycemia, insulin resistance, and inflammation.² Individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D) have greater central (aortic) arterial stiffness, wave reflections, and hemodynamic responses than healthy individuals,^{3,4} which contributes to the escalated

Peer review under responsibility of Shanghai University of Sport.

* Corresponding author.

E-mail address: KWay@ottawaheart.ca (K.L. Way).

<https://doi.org/10.1016/j.jshs.2020.02.009>

Cite this article: Way KL, Lee AS, Twigg SM, Johnson NA. The effect of acute aerobic exercise on central arterial stiffness, wave reflections, and hemodynamics in adults with diabetes: A randomized cross-over design. *J Sport Health Sci* 2021;10:499–506.

progression of CVD in this population. Despite the differences in underlying pathologies of T1D and T2D, there is no significant difference between the type of diabetes and the progression of arterial stiffness and central hemodynamics over time.⁴ Given the significant cardiovascular burden that is experienced by people with diabetes, there is a clear need for therapies to address the poor arterial health and, by implication, the CVD risk in these individuals.

Elevated central arterial stiffness, wave reflections, and central hemodynamics are recognized as strong predictors of all-cause mortality and cardiovascular events.^{5,6} Furthermore, these parameters are closely related to cardiac function, including left ventricular function.^{7,8} Increased central arterial stiffness (as measured by pulse wave velocity) leads to the early arrival of wave reflections from the vasculature during systole rather than during diastole reducing cardiac perfusion. Carotid–femoral pulse wave velocity (PWV) is the gold standard measure of central arterial stiffness⁹ and is a predictor of cardiovascular mortality and events.⁶ Higher PWV consequently has a detrimental impact on cardiac loading, which elevates the central systolic blood pressure (SBP) and reduces myocardial perfusion. The augmentation index (AIx), expressed as a percentage, represents the amount of augmented pressure due to wave reflections following the initial systolic peak wave. Increased AIx increases left ventricular afterload and can chronically lead to cardiovascular pathologies such as left ventricular hypertrophy.⁸

It has been well established that aerobic exercise can improve cardiovascular health outcomes and improve glucose control and insulin sensitivity in people with diabetes. There have been a few systematic reviews that suggest aerobic exercise can reduce PWV, AIx, and central blood pressure in healthy adults^{10,11} and CVD populations.¹² However, the effect of aerobic exercise on central arterial stiffness and hemodynamics in people with diabetes is less well-known. A systematic review from our lab shows there are no studies examining the effect of aerobic training on central arterial stiffness or wave reflections.¹³ In that review, we did observe conflicting findings for changes in peripheral (regional) arterial stiffness and AIx with moderate-intensity continuous exercise (MICE) training in people with T2D. It is important to note that peripheral measures are not as clinically relevant for cardiac pathologies when compared to central measurements of arterial stiffness, wave reflections, and hemodynamics.¹⁴

Investigating the effect of an acute bout of exercise gives insight into potential transient responses that may lead to health benefits for poor health outcomes. For instance, in people with diabetes, it is now well known that an acute bout of aerobic exercise improves insulin sensitivity. Examining acute responses can help inform future research by determining which interventions warrant further investigation without exhausting resources and burdening participants. An aerobic exercise bout induces many cardiovascular changes, including increasing cardiac output and shear stress on the vasculature and sympathetic neural drive, and these responses are dependent on exercise intensity.^{15–17} These cardiovascular responses during exercise have been thought to lead to a

reduction in central arterial stiffness and wave reflections. Pierce and colleagues¹⁸ observed that there was no significant change in PWV with acute aerobic exercise in young men. In contrast, they found a significant reduction in AIx with a bout of aerobic exercise. This is thought to be related to the increased vasodilatory response and nitric oxide availability induced by aerobic exercise.¹⁸ However, the acute exercise responses in central arterial stiffness and wave reflections in people with diabetes are not known. To our knowledge, no studies to date have examined the effect of an acute bout of aerobic exercise on central hemodynamics in individuals with diabetes. Evidence from Zhang et al's¹² review indicates that aerobic training can significantly reduce aortic SBP in people with CVD. Therefore, changes in central arterial stiffness, wave reflections, and hemodynamics following aerobic exercise in individuals with diabetes warrant investigation.

More recently, evidence has indicated that high-intensity interval exercise (HIIE) may be a superior mode of aerobic exercise for improving cardiovascular health outcomes such as poor cardiorespiratory fitness and vascular dysfunction.^{19,20} However, the effect of HIIE on central arterial stiffness, wave reflections, and hemodynamics, particularly in people with diabetes, is not known. A bout of HIIE induced greater antegrade shear stress on the cardiovascular system when compared to MICE.²¹ This can be attributed to the superior improvements found in vascular function following HIIE,²¹ which could lead to changes in central arterial stiffness, wave reflections, and hemodynamics. Because there is sparse evidence on the effect of HIIE on the aforementioned outcomes, this is an area where investigation is needed since HIIE could play a role in the management in these cardiovascular anomalies.

The primary aim of this study was to describe the acute changes in central arterial stiffness (as measured via PWV), central wave reflections (AIx and AIx at a heart rate of 75 beats/min (AIx@75)), and central hemodynamics in response to a bout of HIIE and MICE in adults with diabetes. A secondary aim was to compare the effect of an acute bout of HIIE and MICE (independent of exercise energy expenditure) on these responses. We hypothesized that (i) aerobic exercise would reduce central arterial stiffness, wave reflections, and hemodynamics when compared to control (CON); and (ii) HIIE would lead to superior reductions in arterial stiffness and hemodynamic responses when compared to MICE.

2. Methods

2.1. Participants

Adults (age range: 29–59 years) diagnosed with T1D or T2D by a physician (confirmed through medical records) were recruited to participate in the study. Posters advertising the study were displayed in the Charles Perkins Centre at the University of Sydney and in the Royal Prince Alfred Diabetes Centre, as well as, and local endocrinologists' rooms. A recruitment database was also used to contact individuals who may have been eligible to participate in the study. Volunteers were able to contact researchers via phone or email and were

recruited from September 2016 to December 2017. To assess eligibility, telephone screening was performed by 2 trial researchers (KLW and ASL) prior to the 1st study visit. Participants provided written informed consent on the 1st visit to the laboratory. Volunteers were excluded if they had a medical condition that contraindicated exercise (e.g. unstable cardiac conditions, poor glucose control, musculoskeletal conditions, active foot ulcers, or untreated severe diabetic retinopathy). After giving written informed consent, all volunteers underwent a physical examination by a study physician (ASL) prior to commencing the intervention. After initial measures were gathered, the experimental exercise sessions were conducted in a randomized order through a computer-generated (www.randomization.com) sequence in a cross-over design. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by the Human Research Ethics Committees of the University of Sydney and the Sydney Local Health District, Royal Prince Alfred Hospital.

2.2. Anthropometry

During the 1st visit, stature was measured by stadiometer (HR-200; Tanita, Wall-Mounted Height Rod, Arlington Heights, IL, USA). Waist circumference was measured at the level of the umbilicus after deep expiration. Blood pressure was taken manually (767 Mobile Aneroid Sphygmomanometer; Welch Allyn, Skaneateles Falls, NY, USA) on each arm after 10–15 min of quiet sitting and measured twice on each arm. A 3rd reading was taken when there was a difference of ≥ 10 mmHg between the 1st and 2nd reading, with the highest reading recorded. Body mass was measured with an electronic digital platform scale (Tanita BC-418 Body Composition Analyzer; Tanita Corporation, Tokyo, Japan). After height and weight were recorded, body mass index (BMI) was calculated using body mass (kg) divided by subject height (m^2). Glycosylated hemoglobin (HbA1c (%)) was measured from venous blood, which was analyzed by an accredited laboratory (Douglas Hanley Moir Pty Ltd., Sydney, Australia). Measurements were taken within 3 months before commencing the 1st intervention.

2.3. Graded exercise testing

All participants undertook a graded maximal exercise test (GXT) to measure cardiorespiratory fitness. This was performed on an electronically braked cycle ergometer (Lode Corival CPET; Lode B.V., Groningen, Netherlands) under the supervision of the study physician (ASL) and an accredited exercise physiologist (KLW). A breath-by-breath gas analysis (Ultima PFX pulmonary function/stress testing system; MGC Diagnostics, Saint Paul, MN, USA) was collected simultaneously to determine peak rate of volume of oxygen consumption (VO_{2peak}). Resting blood pressure, heart rate (HR) (Polar FS1; Polar, Kempele, Finland), and blood glucose measured by finger prick (using the participant's personal glucometer) were collected prior to commencing the GXT. The GXT consisted of a 3-min warm-up at 35 watts for women and 65 watts for men, with incremental increases of 25 watts every 150 s

until volitional fatigue. HR, BP, and rating of perceived exertion (RPE) (using the Borg scale) were obtained at each stage. The peak heart rate (HR_{peak}) obtained in the GXT was used to guide exercise intensity for each individual in the subsequent exercise intervention sessions.

2.4. Pulse wave analysis and central hemodynamics

Prior to collecting central arterial stiffness, wave reflections, and hemodynamic measures, all individuals were required to lie in a supine position for 5 min. Participants were asked to abstain from alcohol, caffeine, and strenuous exercise for 24 h prior to exercise sessions. A brachial pressure cuff was applied to the right arm to record brachial BP and pulse pressure via oscillatory method. Five seconds after the brachial BP was recorded, the cuff was inflated to capture the brachial waveform (pulse wave analysis) via SphyMoCor XCEL device (Version 1.3; AtCor Medical, Sydney, Australia). Central (aortic) pressures (systolic, diastolic, pulse, and mean arterial pressure), AIx, AIx@75, and HR were measured. Measurements were taken 30 min before the exercise bout (–30 min), immediately post-exercise (0 min), and 30 min (30 min) and 60 min (60 min) post-exercise.

2.5. PWV

Immediately following each pulse wave analysis measurement, carotid–femoral PWV (AtCor Medical, Sydney, Australia) was recorded. A femoral pressure cuff was placed as proximal as possible on the individual's right upper thigh, and the distance from the carotid to the femoral pulse was measured. PWV distance was calculated by the subtraction method from the (i) right carotid pulse to the sternal notch, (ii) sternal notch to the top edge of the femoral pressure cuff, and (iii) left inguinal fold to the top edge of the femoral pressure cuff. A tonometer was placed on the right carotid pulse to obtain a pulse wave reading. After a regular carotid pulse wave was detected, the femoral pressure cuff was inflated to capture a femoral pulse wave. In instances where collecting PWV was not successful on the right side, the left side was attempted.

2.6. Exercise sessions

All exercise sessions were supervised by an accredited exercise physiologist (KLW) and/or physician (ASL) using the electronically braked upright cycle ergometer. Each intervention session was performed ≥ 48 h, and all individuals undertook a CON condition involving no exercise after the completion of both exercise interventions. HR, RPE, brachial BP, and symptoms of possible hypoglycemia were intermittently monitored throughout the exercise sessions. For safety reasons, each participant's capillary blood glucose level (BGL) was measured before and after exercise using a memory glucose meter. This was to ensure that individuals were not in a hyperglycemic or hypoglycemic state. All volunteers were asked to arrive in a fed state to avoid hypoglycemic events. Individuals with T1D who arrived with hyperglycemia

(>14 mmol/L) capillary ketones levels were checked. If ketone levels were ≥ 0.5 mmol/L, the exercise session was rescheduled. In instances where ketones < 0.5 mmol/L, the participant was given a correction bolus of insulin by the study physician (ASL), and BGL was rechecked in 60 min. To commence exercise, the BGL had to fall within 7.0–14.0 mmol/L. The exercise session was rescheduled if it did not fall within this range. Volunteers completed a 5-min warm-up at 60%HR_{peak} and a 3-min cool-down at 50%HR_{peak} before and after each bout, respectively. Given the nature of exercise interventions, participants were not blinded to the intervention allocation.

The HIIE exercise session involved cycling for 4 repeated high-intensity bouts at 85%–95%HR_{peak} for 4 min, separated by 3 bouts of 3 min active–recovery cycling at 50%–70% HR_{peak}. In total, HIIE lasted 28 min. The MICE session involved 33 min of continuous cycling on the cycle ergometer at an intensity of 60%–70% of HR_{peak}. To standardize the energy expenditure of each exercise intervention, the American College of Sports Medicine metabolic equation for leg ergometry (maximal oxygen consumption (VO_{2max}) = 1.8 (work rate/body mass) + 3.5 + 3.5 (mL/kg/min)) was used to calculate the energy expenditure of the HIIE protocol to determine the duration of the MICE exercise bout that would elicit an energy expenditure equivalent to HIIE.^{17,18} The CON session involved lying quietly in the supine position for 30 min (the mean time of each exercise bout).

2.7. Statistical analysis

Power calculation was computed a priori using G*Power (Version 3.1.9.2; Universitat Kiel, Kiel, Germany). Based on a β error of 20% (power = 0.80) and an α error of 5%, a total sample size of 24 subjects was required to detect a moderate effect size of 0.25 (± 0.5 m/s) for changes in PWV using repeated measures analysis of variance (ANOVA) (within-between interaction). Responses to aerobic exercise bouts of exercise (HIIE and MICE) and the CON are reported as mean \pm SE. A one-way ANOVA was conducted to determine any baseline characteristic differences. To examine if changes in central arterial stiffness and central hemodynamic measures were observed with time, and possible group \times time

interactions, a two-way repeated measure ANOVA was conducted using IBM SPSS Statistics (Version 22.0; IBM Corp., Armonk, NY, USA). For Model 1, diabetes classification was entered as a covariate. In Model 2, diabetes classification and age were entered as covariates. Statistical significance was accepted at $p < 0.05$.

3. Results

3.1. Participants

Of the 34 individuals screened to participate in the trial, 24 eligible volunteers (11 men and 13 women; 12 with T1D and 12 with T2D) undertook initial assessment and randomization. All participants completed each exercise bout and the CON session. Central arterial stiffness and hemodynamic responses were collected from all participants during each intervention and CON session. The study population had a mean age of 48.6 ± 2.4 years (mean \pm SE), an HbA1c of $7.4\% \pm 0.2\%$ national glycohemoglobin standardization program units, and a VO_{2peak} of 25.2 ± 1.1 mL/kg/min. The majority of the participants were obese (BMI = 30.8 ± 1.4 kg/m²) and had abdominal obesity (100.7 ± 3.5 cm) and pre-hypertension (131/75 mmHg). Baseline participant characteristics showed that there were significant differences in series of characteristics between those with T1D and T2D, including age, sex, diabetes duration, BMI, and HbA1c level ($p \leq 0.05$; Table 1). All participants with T1D were on insulin ($n = 12$), and all individuals with T2D were prescribed an oral glyceemic medication ($n = 12$). Two participants were prescribed both oral glyceemic medications and insulin (T1D: $n = 1$; T2D: $n = 1$). Half the participants were on lipid-lowering medication (T1D: $n = 3$; T2D: $n = 9$), and eight of them were prescribed hypertension medication (T1D: $n = 1$; T2D: $n = 7$).

3.2. Central arterial stiffness and wave reflection

Results from Model 1 show a significant time ($F = 9.83$, $p < 0.01$) and group \times time interaction ($F = 2.32$, $p = 0.04$) for change in wave reflection, as measured by AIx@75 (Fig. 1), with a transient reduction with HIIE and MICE. Following HIIE, there was a significant increase in AIx@75 immediately

Table 1
Participant characteristics (mean \pm SE).

	T1D	T2D	Total	<i>p</i>
Age (year)	40.4 \pm 3.0	56.8 \pm 1.8	48.6 \pm 2.4	<0.01**
Sex (M/F)	3/9	8/4	11/13	0.04*
Weight (kg)	78.8 \pm 5.3	103.0 \pm 5.8	90.9 \pm 4.6	<0.01**
BMI (kg/m ²)	26.9 \pm 1.6	34.7 \pm 1.7	30.8 \pm 1.4	<0.01**
Waist circumference (cm)	89.9 \pm 4.5	111.5 \pm 3.0	100.7 \pm 3.5	<0.01**
Diabetes duration (year)	16.5 \pm 2.9	8.4 \pm 1.4	12.5 \pm 1.8	0.02*
HbA1c (%)	8.0 \pm 0.3	6.9 \pm 0.2	7.4 \pm 0.2	<0.01**
VO _{2peak} (mL/kg/min)	28.2 \pm 1.8	22.2 \pm 0.8	25.2 \pm 1.1	0.05*

* $p \leq 0.05$, ** $p < 0.01$, significant difference between groups.

Abbreviations: BMI = body mass index; F = female; HbA1c = glycosylated hemoglobin; M = male; T1D = type 1 diabetes; T2D = type 2 diabetes; VO_{2peak} = peak rate of volume of oxygen consumption.

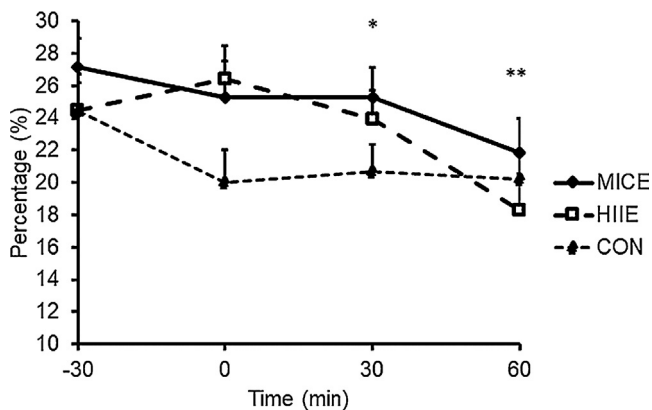


Fig. 1. The effect of an acute bout of MICE, HIIE, and CON on augmentation index at a heart rate of 75 beats/min. The results presented in the figure reflect the Model 1 statistical analysis. * $p < 0.05$, significant difference between -30 min and 30 min timepoints; ** $p < 0.01$, significant difference between -30 min and 60 min timepoints. CON = control; HIIE = high-intensity interval exercise; MICE = moderate-intensity continuous exercise.

post-exercise ($p = 0.05$) and a significant reduction at 60 min post-exercise ($p < 0.01$) when compared to the pre-intervention (-30 min) measurement. There was no significant time or group \times time interaction found for changes in PWV or AIx (Table 2). The analysis from Model 2 revealed no significant time or group \times time interactions for changes to central arterial stiffness and wave reflections.

3.3. Central hemodynamics

We observed a significant time ($F = 3.45$, $p = 0.02$) and group \times time interaction for change in central SBP ($F = 3.20$, $p = 0.01$; Fig. 2) in Model 1, which decreased in favor of HIIE below the immediate post-intervention measurement (0 min) at both 30 min ($p = 0.06$) and 60 min ($p = 0.03$) post-intervention. There was a significant time ($F = 4.06$, $p = 0.01$) and group \times time interaction for responses in central diastolic blood pressure (DBP) ($F = 2.42$, $p = 0.03$; Table 2), which significantly increased immediately following HIIE ($p < 0.01$)

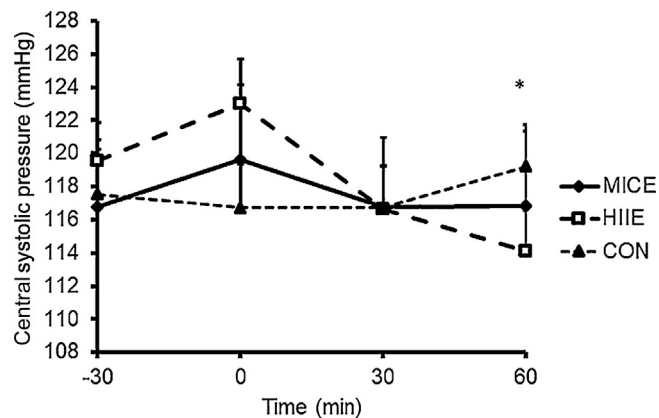


Fig. 2. The effect of an acute bout of MICE, HIIE, and CON on central systolic pressure. The results presented in the figure reflect the Model 1 statistical analysis. * $p < 0.05$, significant difference between 0 min and 60 min timepoints. CON = control; HIIE = high-intensity interval exercise; MICE = moderate-intensity continuous exercise.

and decreased at 30 min and 60 min post-exercise but did not change in CON and MICE. For pulse pressure, there was a significant time interaction ($F = 5.22$, $p < 0.01$), but no significant group \times time interaction was observed ($p = 0.28$). There were no significant time or group \times time interactions observed for mean arterial pressure (Table 2). When analyzed through Model 2, there were no significant time or group \times time interactions observed for all changes to central hemodynamic responses.

4. Discussion

This is the 1st study to examine the effect of acute aerobic exercise on central arterial stiffness, wave reflections, and hemodynamic responses in people with diabetes. We also compared the effect of acute HIIE and MICE bouts on these outcomes and the possible influence of diabetes classification. Using a cross-over randomized controlled design, we showed that HIIE led to a significant reduction in central SBP 60 min

Table 2
Results of central arterial stiffness, wave reflections, and hemodynamic responses (mean \pm SE).

	CON				MICE				HIIE				<i>p</i>
	-30 min	0min	30 min	60 min	-30 min	0min	30 min	60 min	-30 min	0min	30 min	60 min	
Arterial stiffness (m/s)													
PWV	10.2 \pm 2.2	10.1 \pm 2.0	10.3 \pm 2.2	10.5 \pm 2.1	8.2 \pm 0.3	8.3 \pm 0.4	8.1 \pm 0.2	8.3 \pm 0.3	8.1 \pm 0.2	8.1 \pm 0.2	7.9 \pm 0.2	8.0 \pm 0.2	0.40
Wave reflections (%)													
AIx	26.0 \pm 2.3	22.4 \pm 2.4	24.2 \pm 1.7	24.3 \pm 1.9	24.5 \pm 2.1	25.0 \pm 2.4	26.9 \pm 1.8	24.8 \pm 1.9	24.5 \pm 1.7	19.9 \pm 2.0	21.1 \pm 2.0	19.0 \pm 2.1	0.16
AIx@75	24.4 \pm 2.3	20.0 \pm 2.0	20.7 \pm 1.7	20.3 \pm 1.8	27.2 \pm 1.8	25.3 \pm 2.2	25.3 \pm 1.8	21.8 \pm 2.1	24.5 \pm 1.7	26.5 \pm 2.0	24.0 \pm 1.8	18.3 \pm 2.2	0.04*
Central hemodynamics (mmHg)													
SBP	117 \pm 4	120 \pm 5	117 \pm 4	117 \pm 5	117 \pm 2	116 \pm 2	117 \pm 3	119 \pm 3	120 \pm 2	123 \pm 3	117 \pm 3	114 \pm 3	0.01**
DBP	76 \pm 2	77 \pm 2	78 \pm 2	79 \pm 2	78 \pm 2	81 \pm 2	79 \pm 2	80 \pm 2	79 \pm 2	84 \pm 2	81 \pm 2	79 \pm 2	0.03*
PP	41 \pm 2	40 \pm 2	39 \pm 2	40 \pm 2	43 \pm 2	43 \pm 3	42 \pm 2	40 \pm 2	41 \pm 2	39 \pm 2	36 \pm 2	35 \pm 2	0.28
MAP	93 \pm 2	93 \pm 2	93 \pm 2	94 \pm 2	96 \pm 2	99 \pm 2	96 \pm 2	95 \pm 2	96 \pm 2	98 \pm 4	96 \pm 2	94 \pm 2	0.53

* $p < 0.05$, ** $p < 0.01$, significant difference in group \times time interaction.

Abbreviations: AIx = augmentation index; AIx@75 = augmentation index at a heart rate of 75 beats/min; CON = control; DBP = diastolic blood pressure; HIIE = high-intensity interval exercise; HR = heart rate; MAP = mean arterial pressure; MICE = moderate-intensity continuous exercise; PP = pulse pressure; PWV = pulse wave velocity; SBP = systolic blood pressure; T1D = type 1 diabetes; T2D = type 2 diabetes.

following exercise but not after MICE or CON. We also observed a significant lowering of AIx@75 following HIIE and MICE. We found a reduction in AIx@75 following the CON scenario, albeit attributed to prolonged lying in a supine position. To date, there is very limited evidence investigating central responses to aerobic exercise, particularly central blood pressure and wave reflections.

People with diabetes have significantly greater central arterial stiffness and hemodynamic responses when compared to healthy populations,^{3,4} and these responses contribute to the accelerated progression of CVD in diabetic populations. To date, these outcomes have been predominately managed through pharmacological strategies that do not necessarily treat the underlying pathology of arterial stiffness or hypertension.²² There is irrefutable evidence on the positive benefits of aerobic exercise on cardiovascular risk factors, such as poor cardiorespiratory fitness, hyperglycemia, and peripheral hypertension.^{19,20} Therefore, understanding the acute responses to aerobic exercise may give some insight into whether aerobic exercise may be an appropriate therapy for improving other markers of CVD progression, such as central arterial stiffness, wave reflections, and central hemodynamics. The significant transient reductions observed in central systolic pressure and AIx@75 indicates that an acute bout of HIIE can successfully decrease cardiac afterload in people with diabetes.²³ These are important clinical findings because HIIE transiently reduces cardiac strain, and, by implication, could have further preventative benefits for chronic pathological changes such as left ventricular hypertrophy and myocardial ischemia. Much like other transient improvements to cardiometabolic health outcomes following exercise, such as insulin sensitivity,²⁴ acute responses are pertinent in the management of diabetes.

To date, most studies examining the acute effect of aerobic exercise on AIx have been conducted in healthy individuals.^{10,11} Pierce's systematic review¹¹ revealed a significant reduction in AIx following acute aerobic exercise in healthy people (mean difference = -4.54% ; 95% confidence interval: -7.05 to -2.04 ; $p < 0.01$; 13 studies), with the majority of studies conducting MICE. Interestingly, a study by Hanssen et al.²⁵ found that HIIE, but not MICE, led to a significant reduction in AIx@75 24 h post-exercise; however, AIx@75 was significantly elevated during the immediate recovery phase post-exercise in healthy young males (which was similar to our findings). The immediate increase in AIx@75 following HIIE is not likely to be associated with a consequential effect on cardiovascular health since it was not a sustained response. Similar to the findings of Hanssen et al.,²⁵ we observed a trend toward a reduction in AIx@75 over time following HIIE; it may be possible that this could persist for at least 24 h.²⁵ Interestingly, we did observe a reduction in AIx@75 in the CON condition over time. Our findings are in contrast to Pierce's meta-analysis,¹⁸ which showed no transient change in AIx in a resting state. The lowering in AIx@75 following the CON condition was not expected but was unlikely to have been associated with the positive benefits associated with exercise, such as increased vascular function and nitric oxide availability. Given that the reduction in AIx@75 was more robust in

people with T1D, this may have been due to insulin-mediated vasodilation (due to a correction bolus). Insulin increases the availability of nitric oxide and Na^+/K^+ ATPase activity, which are essential in the signaling pathway to relax vascular smooth muscle and may therefore reduce AIx@75 .²⁶ Therefore, the reduction observed in the CON session should be interpreted with caution.

There have been few studies examining the effect of acute aerobic exercise on central hemodynamics. Three studies found no significant changes to central SBP or DBP following moderate- or maximal-intensity aerobic exercise.^{27–29} Interestingly, 2 studies revealed a significant reduction in aortic pulse pressure, which was significantly correlated with decreases in PWV following a bout of MICE.^{28,29} It should be noted that these studies were conducted in obese,²⁷ healthy,^{24,26} or post-menopausal populations.²⁵ In contrast, we observed a significant reduction in central systolic pressure following HIIE but not after MICE. Our findings suggest that the mode of aerobic exercise, i.e., HIIE is detrimental in targeting central systolic pressure. This could be due to the greater antegrade shear rate observed with interval-type exercise, which stimulates higher endothelium nitric oxide bioavailability and enhances endothelial function.^{21,30} Given the significant decrease in AIx@75 observed following HIIE in our study, the reduction in aortic systolic pressure could be explained by a reduction in the magnitude of wave reflections.

Interestingly, we did not find a significant reduction in central arterial stiffness (PWV) following an acute bout of aerobic exercise. Most of the evidence supports a decrease in PWV following acute aerobic exercise in healthy individuals.¹⁸ Kingwell et al.³¹ showed that arterial compliance improved after a bout of MICE in healthy young males, which may explain the improvements observed in other trials. Given the chronic pathological changes (fibrosis) to the aorta via advanced glycation end-products in people with diabetes,³² it is unlikely that an acute bout of exercise could lead to reductions in PWV. This is further supported by the lack of change in central pulse pressure following HIIE and MICE. Central pulse pressure is associated with aortic diameter and arterial stiffness. Therefore, chronic aerobic training may lead to changes in PWV and central pulse pressure in this population.

There are currently no exercise guidelines specifically targeting arterial stiffness, wave reflections, or central hemodynamics in people with diabetes.³³ For individuals with diabetes, it appears that the mode of aerobic exercise plays an important role for these outcomes. Our study has provided preliminary evidence that HIIE should be recommended to transiently improve central systolic pressure and AIx@75 . However, future research needs to be conducted on the different styles of interval training, such as sprint interval training, as well as on the optimal intensity and number of intervals to prescribe. Additionally, research needs to investigate how long the transient benefits last.

Our study is not without limitations. We acknowledge that generalization to chronic/adaptive effects of regular exercise training cannot be made from our study of acute aerobic exercise, which has potentially transient outcomes (measured at

60 min post-exercise). Nevertheless, in light of the lack of the evidence concerning the efficacy of aerobic exercise on central arterial stiffness and BP outcomes, understanding acute responses is important to inform future research and clinical interventions. Furthermore, we acknowledge that we did not or were not able to collect data on the possible mechanisms that led to the observed reductions in central SBP and AIx@75. Therefore, this limited our ability to explain the physiological changes that may have occurred when these outcomes decreased after HIIE or MICE. We recognize that the relatively small sample size ($n = 24$) may also limit the ability to draw conclusions regarding the efficacy of acute aerobic exercise and the changes described for central hemodynamics and wave reflection. Also, to avoid hypoglycemic events, exercise sessions were performed in a fed state; therefore, food intake may have partly impacted the response seen in these outcomes, albeit equally across the exercise and CON interventions. However, this does provide a real-world scenario for individuals with diabetes who exercise. While our group of individuals with either T1D or T2D showed significantly different characteristics (age, sex, BMI, waist circumference, HbA1c, and diabetes duration), there was no significant difference between the groups for any outcome measures. While our study has provided the important first data examining the effect of HIIE vs. traditional aerobic exercise and non-exercise CON on central hemodynamics and arterial stiffness, more studies are warranted in similar populations in order to examine the effects over the longer term.

5. Conclusion

This is the 1st study to examine the acute effect of aerobic exercise on central arterial stiffness, wave reflections, and central hemodynamics in individuals with diabetes (T1D or T2D). An acute bout of HIIE leads to transient reductions in wave reflections and central SBP, and these outcomes were not observed following MICE. There appears to be a superior benefit for post-exercise wave reflection and central blood pressure with the implementation of HIIE. Our study provides valuable insights into possible benefits that could lead to better management of cardiovascular health in people with diabetes.

Acknowledgments

Thank you to Dr Jennifer Reed for providing assistance with the statistical analysis of this manuscript.

Authors' contributions

KLW contributed to study design, supervised the exercise sessions, completed data collection, analysis, and interpretation, and drafted the manuscript; ASL contributed to study design, completed data collection and analysis, and revised the manuscript; SMT contributed to the study design and revised the manuscript; NAJ contributed to the study design, data interpretation, and revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

References

1. International Diabetes Federation. *IDF Diabetes Atlas 9th edition 2019*. Available at: <https://www.diabetesatlas.org/en/resources/>. [accessed 02.14.2020].
2. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part I. *Eur Heart J* 2013;**34**:2436–43.
3. Brooks B, Molyneaux L, Yue DK. Augmentation of central arterial pressure in type 1 diabetes. *Diabetes Care* 1999;**22**:1722–7.
4. Brooks BA, Molyneaux LM, Yue DK. Augmentation of central arterial pressure in type 2 diabetes. *Diabet Med* 2001;**18**:374–80.
5. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur Heart J* 2010;**31**:1865–71.
6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J Am Coll Cardiol* 2010;**55**:1318–27.
7. Chantler PD, Lakatta E. Arterial-ventricular coupling with aging and disease. *Front Physiol* 2012;**3**:90. doi:10.3389/fphys.2012.00090.
8. Hashimoto J, Nichols WW, O'Rourke MF, Imai Y. Association between wasted pressure effort and left ventricular hypertrophy in hypertension: Influence of arterial wave reflection. *Am J Hypertens* 2008;**21**:329–33.
9. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012;**30**:445–8.
10. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014;**9**:e110034. doi:10.1371/journal.pone.0110034.
11. Pierce DR, Doma K, Raiff H, Golledge J, Leicht AS. Influence of exercise mode on post-exercise arterial stiffness and pressure wave measures in healthy adult males. *Front Physiol* 2018;**9**:1468. doi:10.3389/fphys.2018.01468.
12. Zhang Y, Qi L, Xu L, et al. Effects of exercise modalities on central hemodynamics, arterial stiffness and cardiac function in cardiovascular disease: Systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2018;**13**:e0200829. doi:10.1371/journal.pone.0200829.
13. Way KL, Keating SE, Baker MK, Chuter VH, Johnson NA. The effect of exercise on vascular function and stiffness in type 2 diabetes: A systematic review and meta-analysis. *Curr Diabetes Rev* 2016;**12**:369–83.
14. McEnery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: Current evidence and clinical importance. *Eur Heart J* 2014;**35**:1719–25.
15. Åstrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac output during submaximal and maximal work. *J Appl Physiol* 1964;**19**:268–74.
16. Niebauer J, Cooke JP. Cardiovascular effects of exercise: Role of endothelial shear stress. *J Am Coll Cardiol* 1996;**28**:1652–60.
17. Nobrega ACL, O'Leary D, Silva BM, Marongiu E, Piepoli MF, Crisafulli A. Neural regulation of cardiovascular response to exercise: Role of central command and peripheral afferents. *BioMed Res Int* 2014;**2014**:478965. doi:10.1155/2014/478965.
18. Pierce DR, Doma K, Leicht AS. Acute effects of exercise mode on arterial stiffness and wave reflection in healthy young adults: A systematic review and meta-analysis. *Front Physiol* 2018;**9**:73. doi:10.3389/fphys.2018.00073.
19. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: A systematic review and meta-analysis. *Br J Sports Med* 2014;**48**:1227–34.
20. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: A systematic review and meta-analysis. *Sports Med* 2015;**45**:679–92.

21. Ghardashi Afousi A, Izadi MR, Rakhshan K, Mafi F, Biglari S, Gandomkar Bagheri H. Improved brachial artery shear patterns and increased flow-mediated dilatation after low-volume high-intensity interval training in type 2 diabetes. *Exp Physiol* 2018;**103**:1264–76.
22. Chen Y, Shen F, Liu J, Yang GY. Arterial stiffness and stroke: De-stiffening strategy, a therapeutic target for stroke. *Stroke Vasc Neurol* 2017;**2**:65–72.
23. Heusinkveld MHG, Delhaas T, Lumens J, et al. Augmentation index is not a proxy for wave reflection magnitude: Mechanistic analysis using a computational model. *J Appl Physiol* 2019;**127**:491–500.
24. Way KL, Hackett DA, Baker MK, Johnson NA. The effect of regular exercise on insulin sensitivity in type 2 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Metab J* 2016;**40**:253–71.
25. Hanssen H, Nussbaumer M, Moor C, Cordes M, Schindler C, Schmidt-Trucksäss A. Acute effects of interval versus continuous endurance training on pulse wave reflection in healthy young men. *Atherosclerosis* 2015;**238**:399–406.
26. Yki-Järvinen H, Utriainen T. Insulin-induced vasodilatation: Physiology or pharmacology? *Diabetologia* 1998;**41**:369–79.
27. Bunsawat K, Ranadive SM, Lane-Cordova AD, et al. The effect of acute maximal exercise on postexercise hemodynamics and central arterial stiffness in obese and normal-weight individuals. *Physiol Rep* 2017;**5**:e13226. doi:10.14814/phy2.13226.
28. Akazawa N, Ra SG, Sugawara J, Maeda S. Influence of aerobic exercise training on post-exercise responses of aortic pulse pressure and augmentation pressure in postmenopausal women. *Front Physiol* 2015;**6**:268. doi:10.3389/fphys.2015.00268.
29. Sugawara J, Komine H, Miyazawa T, Imai T, Ogoh S. Influence of single bout of aerobic exercise on aortic pulse pressure. *Eur J Appl Physiol* 2015;**115**:739–46.
30. Whyte JJ, Laughlin MH. The effects of acute and chronic exercise on the vasculature. *Acta Physiol (Oxf)* 2010;**199**:441–50.
31. Kingwell BA, Berry KL, Cameron JD, Jennings GL, Dart AM. Arterial compliance increases after moderate-intensity cycling. *Am J Physiol* 1997;**273**:H2186–91.
32. Ziemann SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;**25**:932–43.
33. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes Care* 2010;**33**:e147–67.