

Original Scientific Paper

Impaired postexercise cardiovascular autonomic modulation in middle-aged women with type 2 diabetes

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Background Type 2 diabetes is associated with cardiovascular autonomic dysfunction. Postexercise autonomic modulation may be different in obese individuals with and without type 2 diabetes. We examined postexercise responses in nondiabetic and diabetic women aged 40–60 years.

Methods Hemodynamics, high-frequency and low-frequency of RR interval, low-frequency of systolic blood pressure variability and baroreflex sensitivity were evaluated before and after a 20 min walk at ~65% of $\dot{V}O_2$ peak in eight lean, 12 obese without type 2 diabetes and eight women with type 2 diabetes. Postexercise measurements were obtained at 10–15, 20–25 and 30–35 min.

Results Systolic blood pressure decreased at 10 ($P < 0.001$) and 20 min ($P < 0.01$) in all groups. Total peripheral resistance decreased at 10 min in all women, but the subsequent increase at 20 min was greater ($P < 0.01$) in lean than in diabetic women. Log-transformed low-frequency of systolic blood pressure increased ($P < 0.01$) at 10 and 20 min in all women, but the increase at 10 min was smaller ($P < 0.05$) in diabetic than in lean women. Heart rate was increased ($P < 0.001$) at 10 min in all women and at 20 min in both obese groups. Both log-transformed high-frequency of RR interval and baroreflex sensitivity decreased at 10 and 20 min of recovery in all groups. A group-by-time interaction ($P < 0.05$) was observed for heart rate and baroreflex sensitivity as a lower heart rate and higher baroreflex sensitivity were observed in lean women than in women with type 2 diabetes.

Conclusions Reduced postexercise baroreflex sensitivity and responses to autonomic cardiovascular activity contribute to an attenuated recovery of heart rate and total peripheral resistance after brisk walking in middle-aged obese women with type 2 diabetes. *Eur J Cardiovasc Prev Rehabil* 14:237–243 © 2007 The European Society of Cardiology

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Keywords: autonomic nervous system, baroreflex sensitivity, heart rate variability, obesity, postexercise recovery, type 2 diabetes

Introduction

Cardiovascular autonomic nervous system (ANS) dysfunction, characterized by reduced parasympathetic (vagal) modulation of the heart rate (HR), coupled with an increased sympathetic vascular modulation, has been reported to occur in obese individuals with and without

type 2 diabetes (T2D) [1–4]. It appears that obesity *per se* may not affect ANS function in individuals with [5,6] and without [4,7] diabetes, but rather metabolic abnormalities such as high hemoglobin A_{1c} (HbA_{1c}) levels [8–10] and fasting hyperglycemia [11] may be the cause of cardiovascular ANS dysfunction in this population.

Spectral analysis of HR and blood pressure (BP) variability provide quantitative indices of cardiovascular autonomic activities during and after physiological perturbations [2,12–17]. After cessation of exercise,

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important hemodynamic changes lead to adjustments in the ANS activity [12–14,18]. HR and BP return to preexercise levels induced by changes in vagal tone and sympathetic vascular activity [13,14,18]. These adjustments occur during the first 30 min after low-intensity exercise [19], whereas it takes 60 min or more with moderate to maximal intensities in healthy and hypertensive individuals [12,13,20]. Postexercise autonomic control is influenced not only by exercise intensity and duration, but also by the individual's health status [12,14]. Despite extensive investigation on hemodynamic responses, relatively little is known about the cardiovascular autonomic regulation after exercise in individuals with chronic health conditions other than cardiovascular diseases [12,14,21–23]. In addition, most of the previous studies have used maximal dynamic exercise [12,14,18], whereas, the autonomic responses after submaximal intensity have been less well studied.

The aim of this study is to evaluate the ANS adjustments after an acute bout of submaximal exercise in middle-aged women, using spectral analysis of HR and BP variability. As autonomic dysfunction is present in patients with T2D without evident neuropathy [7], we hypothesized that postexercise cardiovascular regulation would be impaired in women with T2D compared with nondiabetic obese and lean women.

Methods

Participants

Twenty-eight women (40–60 years) were classified into one of the following three groups: T2D ($n = 8$), obese ($n = 12$) and lean ($n = 8$) without T2D. Obese nondiabetic women and women with T2D had a body mass index (BMI) $> 30 \text{ kg/m}^2$, whereas the lean women had a BMI $< 25 \text{ kg/m}^2$. Fasting glucose values were $> 7.0 \text{ mmol/l}$ in women with T2D, but were $< 5.5 \text{ mmol/l}$ in lean and obese women. Medications included the following: oral hypoglycemic agents (six T2D), angiotensin-converting enzyme inhibitors (three T2D, one obese and two lean), statins (one T2D and one obese). Premenopausal women were studied in the first 10 days of their menstrual cycle. Postmenopausal women on hormone replacement therapy ($n = 2$, T2D and obese) were included. Participants gave written informed consent, which was approved by the Institutional Review Boards at Syracuse University and SUNY Upstate Medical University.

Experimental design

As a part of preliminary testing, participants had blood samples taken after a 12 h fast, and body composition was measured using air plethysmography (Bod Pod; Life Measurements Instruments, Concord, California, USA). Peak aerobic capacity (VO_2 peak) was also assessed on the first visit [24]. All subjects had a normal ECG during a

graded maximal treadmill test following a protocol described previously [24].

On the study day, participants reported to the laboratory within 3 h after their last meal and abstained from caffeinated beverages for 12 h. Women on medication were asked to take their medication as normally prescribed. After 15 min of quiet rest, cardiovascular parameters were collected for 5 min in the supine position. Thereafter, participants exercised on a treadmill for 20 min at $\sim 65\%$ of the previously determined VO_2 peak. Immediately after exercise, participants assumed the supine position for 35 min of recovery. Postexercise measurements were carried out in 5 min segments between 10–15 min (10), 20–25 min (20) and 30–35 min (30). A metronome was used to set the breathing frequency at 12 breaths/min during data recording.

Anthropometric testing

Height and weight were taken and BMI was calculated. Percentage body fat was measured using the Bod Pod (Life Measurements Instruments). Measurements were taken according to the guidelines established by the manufacturer, with all participants wearing a swimsuit.

Autonomic and hemodynamic measurements

We obtained continuous recordings of HR using a modified CM5 ECG lead interfaced with a Biopac data acquisition system (Biopac, Santa Barbara, California, USA). Hemodynamic parameters were measured using finger plethysmography (Portapres, TNO Biomedical Instrumentation, Amsterdam, The Netherlands) from the right middle finger. The ECG and BP signals were sampled at a frequency of 1000 and 200 Hz, respectively, and stored in a computer. Stroke volume (SV) was assessed from the BP waveform obtained from the Portapres by employing the modelflow method [25]. Cardiac output (CO) was calculated as $\text{HR} \times \text{SV}$ and total peripheral resistance (TPR) was calculated as mean arterial pressure/CO.

Data analysis was performed on 5 min segments from preexercise and three postexercise periods (10, 20 and 30 min). The RR interval (RRI) and systolic blood pressure (SBP) signals were manually inspected and edited for ectopic beats and artifacts using linear interpolation. Fast Fourier transformation was used to obtain power spectrums of the RRI and SBP [15,26] using the winCPRS software (Absolute Aliens, Turku, Finland). We used two spectral components of the total power: low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.40 Hz) in absolute units (ms^2) as described previously [27]. Vagal activity, cardiac sympatho-vagal balance and vascular sympathetic modulation were evaluated by HF_{RR} , the LF/HF ratio [27,28] and LF_{SBP} [2,12,13], respectively.

We also calculated baroreflex sensitivity (BRS) using cross-spectral analysis of RRI and SBP variability in the LF band. The transfer function at LF was used as index of spontaneous BRS if coherence was >0.5 and the phase shift was negative [13,29].

Blood sampling and analysis

Fasting blood samples were analyzed for glucose and HbA_{1c} concentration. Blood glucose levels were measured using the glucose oxidase method with a YSI 2300 STAT glucose analyzer (Yellow Springs Inc., Ohio, USA). HbA_{1c} was analyzed with a commercial kit using high-performance liquid chromatography (Diabetes Technologies Inc., Thomasville, Georgia, USA).

Statistical analysis

Normal distribution of the data was confirmed by creating a histogram. Natural log transformation (Ln) was used if the data were not normally distributed. Group differences in patient characteristics and resting cardiovascular parameters were analyzed using one-way analysis of variance. A 3×4 analysis of variance with repeated measures [group (T2D, obese and lean) by time (preexercise, 10, 20 and 30 min)] was used to evaluate the time-dependent changes and interactions in autonomic and hemodynamic variables. The Tukey's HSD test was used to identify significant group differences when appropriate. Values are shown as mean \pm SEM, and statistical significance was set at $P < 0.05$. SPSS version 12.0 (SPSS Inc., Chicago, Illinois, USA) was used.

Results

Participant characteristics are shown in Table 1. The three groups were of similar age and height, but body weight, BMI, percentage body fat and waist circumference were higher ($P < 0.05$) and VO₂ peak was lower in the obese women with and without T2D than in the lean women. Plasma glucose levels were higher ($P < 0.05$) in women with T2D than in the nondiabetic obese and lean women, whereas HbA_{1c} was higher in the women with T2D than in lean women.

Resting hemodynamics and autonomic parameters are shown in Table 2. CO was greater in women with T2D compared with lean women ($P < 0.05$). There were no significant differences between groups in any of the other variables at rest.

The 20 min average exercise intensity (% of VO₂ peak) was similar between groups (women with T2D $63 \pm 2\%$, obese $64 \pm 2\%$ and lean $58 \pm 2\%$). A significant main effect was observed for SBP, TPR and HR with a complete recovery at 30 min after exercise (Fig. 1). SBP was significantly reduced at 10 ($P < 0.001$) and 20 min ($P < 0.01$) in all women (Fig. 1a). TPR was decreased at 10 min ($P < 0.01$) in all groups, followed by an increase

Table 1 Participant characteristics

	Type 2 diabetes (n=8)	Obese (n=12)	Lean (n=8)
Age (years)	50 \pm 1	48 \pm 2	49 \pm 3
Height (m)	1.60 \pm 0.02	1.65 \pm 0.01	1.65 \pm 0.02
Weight (kg)	90.3 \pm 4.2*	102.6 \pm 4.4*	60.1 \pm 1.8
BMI (kg/m ²)	35.2 \pm 1.7*	37.6 \pm 1.4*	22.0 \pm 0.5
Body fat (%)	44.9 \pm 2.3*	47.6 \pm 1.1*	31.1 \pm 1.1
Waist circumference (cm)	114 \pm 4*	110 \pm 3*	78 \pm 2
Fasting glucose (mmol/l)	7.9 \pm 0.6* [†]	5.2 \pm 0.2	4.7 \pm 0.2
Hemoglobin A _{1c} (%)	7.5 \pm 0.4*	6.1 \pm 0.5	5.4 \pm 0.1
VO ₂ peak (ml/kg per min)	21.9 \pm 1.0*	21.4 \pm 0.6*	30.5 \pm 1.4

BMI, body mass index; VO₂ peak, peak oxygen consumption. * $P < 0.05$ vs. lean women; [†] $P < 0.05$ vs. obese.

Table 2 Resting hemodynamic and autonomic function parameters

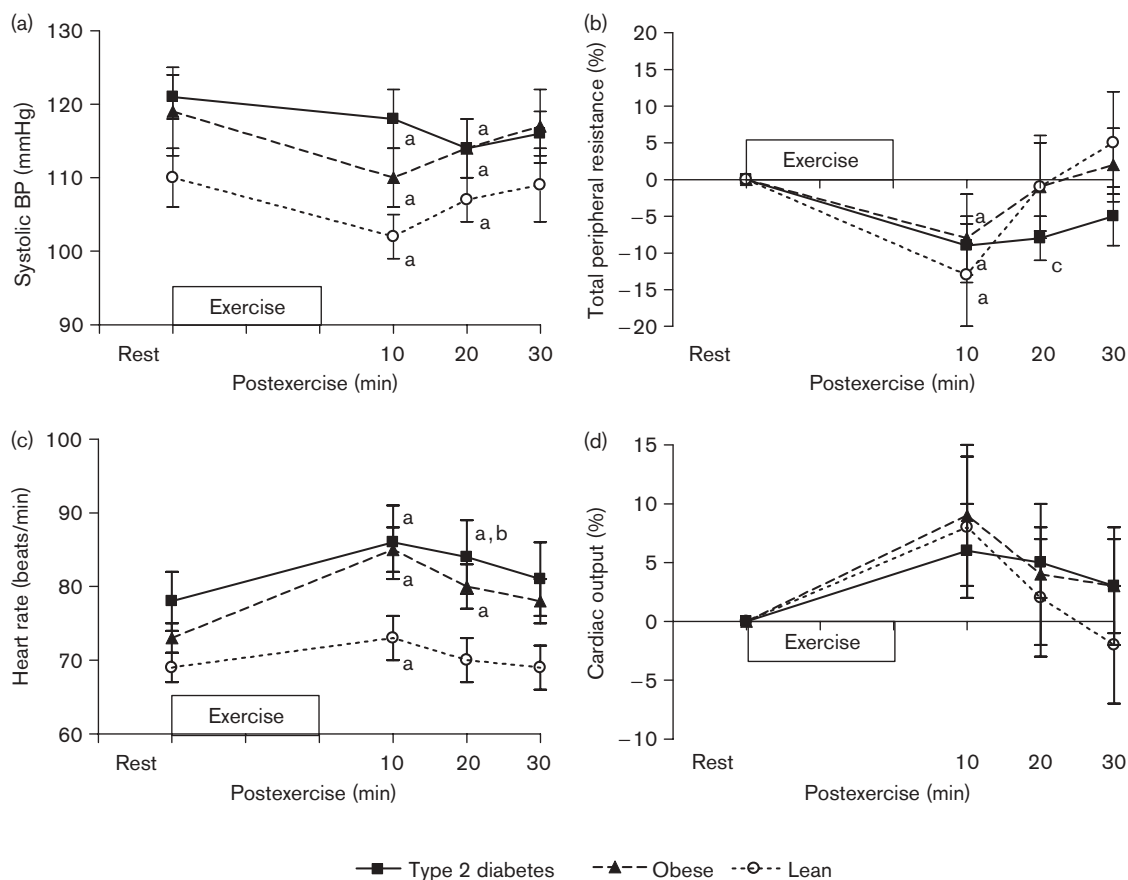
	Type 2 diabetes (n=8)	Obese (n=12)	Lean (n=8)
Heart rate (beat/min)	78 \pm 4	73 \pm 2	69 \pm 3
Stroke volume (ml)	108 \pm 5	102 \pm 6	87 \pm 4
Cardiac output (l/min)	8.4 \pm 0.6*	7.4 \pm 0.5	6.0 \pm 0.3
TPR (mmHg/min per l)	10.2 \pm 0.9	11.6 \pm 0.9	13.0 \pm 0.7
SBP (mmHg)	120 \pm 3	122 \pm 6	114 \pm 4
LF _{RR} (Ln ms ²)	4.0 \pm 0.1	4.4 \pm 0.1	4.3 \pm 0.1
HF _{RR} (Ln ms ²)	4.4 \pm 0.4	5.2 \pm 0.2	5.2 \pm 0.3
LF/HF (ratio)	0.9 \pm 0.3	0.8 \pm 0.1	0.8 \pm 0.2
LF _{SBP} (Ln mmHg ²)	1.3 \pm 0.3	0.9 \pm 0.3	0.4 \pm 0.3
BRS (ms/mmHg)	4.5 \pm 0.7	5.4 \pm 0.8	8.5 \pm 2.3

BRS, baroreflex sensitivity; HF, high frequency; LF, low frequency; RR, R-R interval; SBP, systolic blood pressure; TPR, total peripheral resistance. * $P < 0.05$ vs. lean.

($P < 0.001$) in TPR from 10 to 20 min in obese and lean women. This change in TPR was higher ($P < 0.01$) in lean than in diabetic women (Fig. 1b). HR was increased at 10 min ($P < 0.001$) in all groups and also at 20 min ($P < 0.01$) after exercise in both obese groups. A significant group-by-time interaction ($P < 0.05$) was observed for HR as women with T2D had a higher HR than lean women at 20 min (Fig. 1c). SV (data not shown) and CO showed no significant changes after exercise (Fig. 1d).

A significant main effect was observed for Ln LF_{SBP}, Ln HF_{RR} and BRS with a complete recovery at 30 min (Fig. 2). Ln LF_{SBP} was increased at 10 ($P < 0.01$) and 20 min ($P < 0.001$) in all women, but diabetic women displayed a lower increase than lean women at 10 min (Fig. 2a). Ln HF_{RR} was decreased by 10 ($P < 0.001$) and 20 min ($P < 0.05$) in all women and approached significance time-by-group interaction ($P = 0.054$), such that obese women with and without T2D had a greater decrease in Ln HF_{RR} than lean women (Fig. 2b). A reduction in BRS at 10 ($P < 0.01$) and 20 min ($P < 0.05$) in all women was seen (Fig. 2d). A group-by-time interaction was observed for BRS as the changes over time were lower in diabetic than in lean women. Ln LF_{RR} (data not shown) increased ($P < 0.05$) at 10 min in all groups. SV (data not shown)

Fig. 1



Systolic blood pressure (BP), total peripheral resistance, heart rate, cardiac output in postexercise recovery in type 2 diabetes, obese and lean groups. Panels (a) and (c) are actual measured data and panels (b) and (d) are percentage (%) changes from rest. ^aSignificantly different than preexercise, ^bsignificantly different than lean women, ^csignificantly different from previous measurement compared with lean women.

and LF/HF ratio showed no significant changes after exercise (Fig. 1c).

Discussion

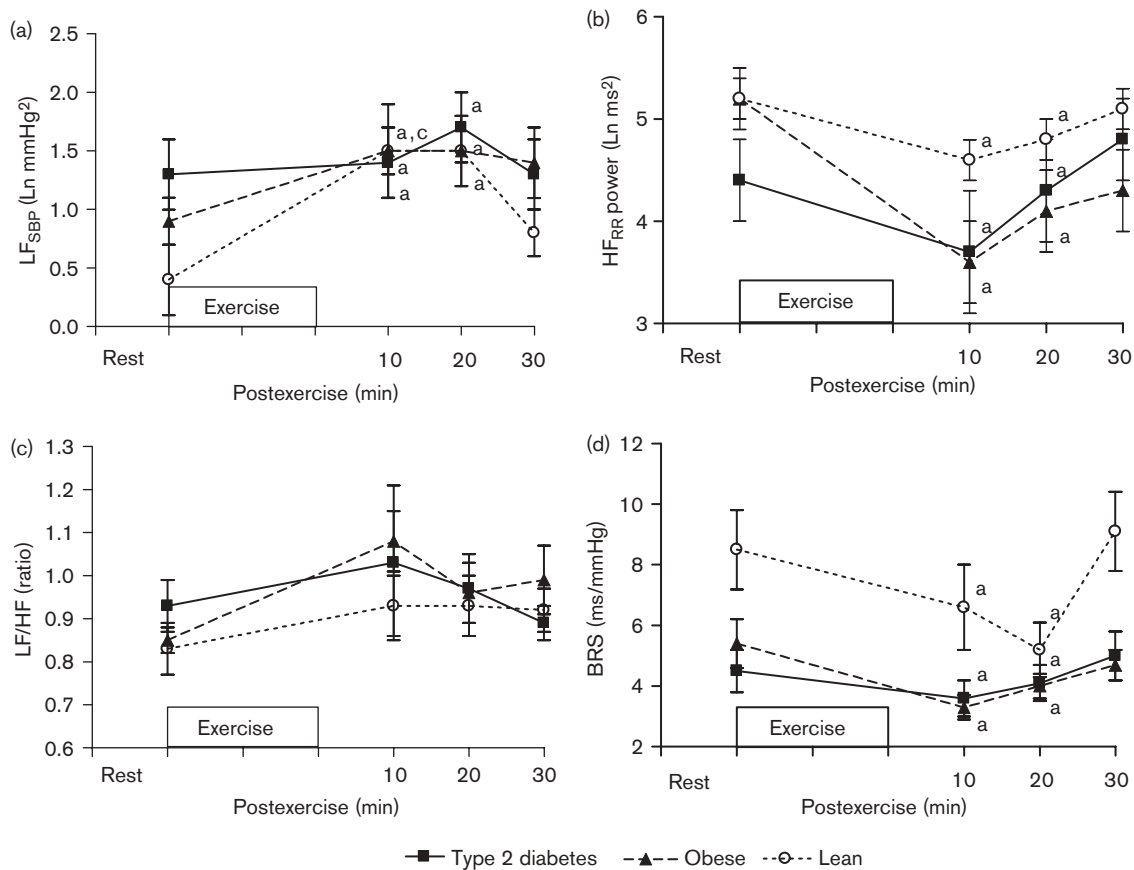
The major finding of this study was that middle-aged women with T2D without apparent autonomic cardiovascular dysfunction at rest had abnormal responses to an acute bout of brisk walking compared with lean women. A slower return of TPR and HR to preexercise levels was present that were associated with impaired autonomic regulation in obese women with T2D.

After exercise, increased muscle vasodilator substances and cardiovascular autonomic adjustments contribute to progressive changes in arterial pressure and vascular resistance [30,31]. A 20 min bout of brisk walking decreased SBP after 10 and 20 min of recovery in all participants. SBP decreased by 9 mmHg in our obese and lean women and 6 mmHg in obese diabetic women, which is in agreement with previous studies [21,32,33]. The lowest SBP value in the nondiabetic groups was,

however, observed at 10 min, whereas a progressive decrease in SBP was observed from 10 to 20 min in women with T2D. Postexercise hypotension (PEH) has been attributed to peripheral vasodilation caused by local substances released by the exercised muscle [30], which consequently reduces TPR for a short period of time [23,33]. Consistent with previous studies that included submaximal [23,33] and maximal exercise [12,18], the PEH observed during early recovery is explained by decreased TPR. TPR returned to the preexercise level 20 min after exercise in nondiabetic lean and obese women. The increase in TPR was, however, smaller in women with T2D, which may explain the progressive decrease in SBP from 10 to 20 min in this group.

The reduction in postexercise SBP is accompanied by sympathetic enhancement of vasomotor tone after a 20 min bout of exercise at submaximal intensity [13]. Consistent with previous studies [12,13,18], we found an increase in $\ln \text{LF}_{\text{SBP}}$ 10 and 20 min after exercise in all groups, which returned to preexercise levels by 30 min of

Fig. 2



Log-transformed (Ln) low-frequency (LF) component of systolic blood pressure ($Ln LF_{SBP}$) (a), Ln high frequency (HF) power (b), the LF/HF of heart rate variability (c), and baroreflex sensitivity (BRS) (d) in postexercise recovery in type 2 diabetes, obese and lean groups. ^aSignificantly different than preexercise, ^csignificantly different from previous measurement compared with lean women. A group-by-time interaction was detected for BRS between lean women and women with type 2 diabetes.

recovery. The increase in this index of vascular sympathetic tone and subsequent vasoconstriction explain the normalization of SBP after 30 min of recovery. The increase in vascular sympathetic tone during 10 min of recovery was lower in diabetic than in lean women. Yet, a small additional increase in $Ln LF_{SBP}$ was observed in women with T2D from 10 to 20 min of recovery, whereas nondiabetic women maintained the same elevated level reached at 10 min. The reduced increase in TPR observed in women with T2D after 20 min of recovery may be related to reduced vasoconstrictive response to sympatho-excitation [12] or reduced sympathetic activity [22,34]. Previous studies have reported sustained vasodilation 60 min after moderate intensity exercise, which occurs concurrently with decreased muscle sympathetic nerve activity [31,34]. Although there is no information on the ANS modulation during PEH in individuals with T2D, blunted increase in $Ln LF_{SBP}$ during orthostatic hypotension may be a pattern of early autonomic dysfunction in diabetic patients [29]. In our study, the attenuated $Ln LF_{SBP}$ response at 10 min after exercise in

women with T2D may explain the delayed SBP hypotension and the persistent reduced TPR [22] at 20 min after walking. These findings may indicate an early autonomic vascular complication in women with T2D.

Increased HR is a reflex response induced by the decrease in SBP during the early recovery of exercise [13,18]. We observed that HR was increased after 10 min of recovery in all women. Although HR remained elevated in both obese women with and without T2D at 20 min after exercise, HR was higher only in diabetic than in lean women. Following submaximal exercise, HR returned to preexercise levels after 20 min of recovery [32] mainly because of vagal reactivation [13]. Recently, HR recovery after exercise has been considered as an indicator of reduced parasympathetic reactivation [35]. In this study, a reduction in vagal activity ($Ln HF_{RR}$) with unchanged sympatho-vagal balance (LF/HF) occurred after 10 min of recovery in all women. We observed that $Ln HF_{RR}$ remained lower than preexercise levels after 20 min of

recovery in all groups, particularly in obese women with and without T2D. A reduced cardiac responsiveness to parasympathetic activity linked to hyperinsulinemia in obese individuals [36] may explain the higher HR at 20 min after exercise in both obese groups. Furthermore, parasympathetic function is more severely affected than sympathetic function in individuals with T2D [37]. Therefore, our results suggest that the delayed HR recovery after exercise in women with T2D may be attributed to incipient parasympathetic dysfunction.

The arterial baroreflex is the main mechanism involved in short-term cardiovascular control after exercise [12,13,18,27]. Studies using the spontaneous methods to determine baroreflex function have shown reduced BRS during 10–20 min after a single bout of cycling [13,18]. Consistent with these findings [13,18], we found a decreased BRS after 10 and 20 min of recovery, which returned to preexercise values after 30 min in all groups. This indicates that during the early recovery period, the unloading of the baroreceptors by PEH led to a decrease in cardiovagal activity and an increase in vascular sympathetic activity [13,18]. After an increase in SBP, the reset of BRS toward increased gain [18] was followed by the return of autonomic modulation and hemodynamics to preexercise levels at 30 min of recovery, except for HR in both obese women with and without T2D. The overall changes in postexercise BRS were, however, lower in women with T2D compared with lean women, but not significantly ($P = 0.07$) different than nondiabetic obese. Therefore, considering that spontaneous BRS methods reflect mainly on cardiovagal baroreflex responses [12], the slow HR recovery after submaximal exercise may be explained by an attenuated baroreflex modulation in women with T2D.

It would have been ideal to have selected only women not on medications for this study. There would, however, be ethical consideration for taking these women off their medications for a prolonged period of time. Thus we included women on oral glycemic agents. We do not feel that the use of medications confounded our finding as we still observed postexercise reduced hemodynamic responses in women with T2D [38]. Some of our participants were also on antihypertensive medication (angiotensin-converting enzyme inhibitors), which by reducing BP levels may improve autonomic function. This medication may have altered our findings slightly, but it also provided a better reflection of the autonomic control in this population.

In conclusion, reduced postexercise BRS and responses to autonomic cardiovascular activity contribute to an attenuated recovery of HR and TPR after brisk walking in middle-aged obese women with T2D.

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