# Does Type 1 Diabetes alter postexercise thermoregulatory and cardiovascular function in young adults?

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**Running Title:** Postexercise responses in Type 1 Diabetes

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**ABSTRACT**

Recent data demonstrated that individuals with Type 1 Diabetes (T1DM) exhibit impaired sweating and increased rectal temperature (i.e., heat storage) during exercise compared to healthy Controls. Our purpose in this study was to investigate the consequences of T1DM on postexercise thermal homeostasis. Sixteen participants (8 Controls matched with 8 T1DM) performed 90-min of cycling followed by 60-min of seated recovery. Esophageal and rectal temperatures, sweating (forearm, chest, and upper back), skin blood flow [forearm and upper back; presented as cutaneous vascular conductance (CVC)], and blood pressure (MAP) were measured at baseline and throughout recovery. Esophageal temperature was similar during baseline and recovery between groups (P=0.88). However, rectal temperature was elevated in our T1DM group throughout recovery (P=0.048). Sweating and CVC were similar between groups at all sites from 10-min postexercise until the end of recovery (P≥0.16). While absolute MAP was similar between groups (P=0.43), the overall decrease in MAP postexercise was greater in Controls from 20-min (T1DM: -8±5 *vs*. Control: -13±6 mmHg, P=0.03) until the end of recovery. We conclude that despite increased heat storage during exercise, individuals with T1DM exhibit a similar suppression in heat loss to their healthy counterparts during recovery.

## INTRODUCTION

It has been well established that the postexercise period is associated with substantial perturbations to thermoregulatory control in healthy individuals as demonstrated by a sustained elevation in core body and muscle temperatures (Kenny et al. 2008). This persistent hyperthermia is the result of rapid reductions in heat loss responses (i.e., skin blood flow and sweating) towards baseline levels during the early stages (within ~20 minutes) of recovery. While exercise is often prescribed as a key component to the management of Type 1 Diabetes Mellitus (T1DM) (Chimen et al. 2012), the impact of exercise on thermoregulatory control in these individuals has not been well examined. To date, research has demonstrated that local skin blood flow and sweating may be impaired in otherwise healthy individuals with T1DM (Yardley et al. 2013). In fact, a recent study reported that a group of individuals with T1DM had a lower capacity to dissipate heat as evidenced by an attenuated local sweating response (albeit exhibiting regional differences) (Carter et al. 2014). These impairments were paralleled by greater heat storage in individuals with T1DM compared to healthy counterparts as evidenced by greater rectal temperature following 90-min of continuous incremental exercise at fixed rates of metabolic heat production. However, it remains unclear whether these impairments in heat loss persist into the postexercise period.

In healthy individuals, the disturbance in postexercise thermoregulatory control is paralleled by alterations in cardiovascular function, commonly characterized by a rapid reduction in mean arterial pressure below baseline levels in the early stages of recovery (Halliwill et al. 2013). This phenomenon, known as postexercise hypotension, is generally due to persistent peripheral vasodilation that is not completely offset by increases in cardiac output and can persist for up to 2 hours into recovery (Halliwill 2001). Recent reports have attributed the peripheral vasodilation, and thereby postexercise hypotension, to histamine ($H_1$ and $H_2$) receptor activation during recovery (McCord & Halliwill 2006). While this response has been well examined in

88 healthy individuals, it is unknown whether those with T1DM would exhibit similar responses
89 during the postexercise period. Considering that individuals with T1DM have been shown to
90 exhibit substantial reductions in postexercise muscle blood flow compared to healthy controls
91 (Menon et al. 1992), it is plausible that postexercise cardiovascular responses in individuals with
92 T1DM may not parallel those of their healthy counterparts.

93 Empirical evidence has identified a possible link between perturbations in postexercise
94 thermoregulatory control and postexercise hypotension (Kenny & Jay 2013). Specifically, the
95 change in baroreceptor loading status associated with postexercise hypotension has been shown to
96 modulate the level of heat dissipation, and therefore core temperature during recovery. In fact, it
97 is well documented that baroreflex sensitivity can be independently modulated by both exercise
98 and heat stress (Brenner et al. 1997; Parekh & Lee 2005). Furthermore, Armstrong et al. (2010)
99 recently demonstrated that recovery from exercise-induced heat stress is associated with
100 pronounced reductions from baseline in baroreflex sensitivity in young healthy physically active
101 males. It has been shown that individuals with T1DM without clinically diagnosed autonomic
102 neuropathy exhibit lower levels of baroreflex sensitivity during supine resting (Weston et al. 1998;
103 Weston et al. 1996) relative to their healthy counterparts. However, the extent to which these
104 differences in baroreflex activity exist following exercise in T1DM and how they may affect
105 postexercise thermoregulatory function remains unclear.

106 We have previously examined thermoregulatory responses in detail during exercise in the
107 heat (Carter et al. 2014). The purpose of this study was to evaluate the consequences of an exercise-
108 induced heat stress on postexercise thermoregulatory function, and the relationship to postexercise
109 hemodynamics, in individuals with T1DM. We hypothesized that the impairments in heat
110 dissipation associated with T1DM during exercise would extend into recovery such that despite a

111 greater end-exercise rectal temperature in T1DM, heat loss responses would be attenuated to a
112 similar extent as Control leading to a sustained state of hyperthermia during the 60-min recovery
113 in individuals with T1DM. We further hypothesized that this response would be paralleled by a
114 greater reduction in baroreflex sensitivity and postexercise hypotension.
115

## METHODS

### *Ethical Approval*

The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board, and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers prior to their participation in the study.

### *Participants*

A total of 16 individuals participated in the study. Eight participants (5 males, 3 females) with T1DM were matched for sex, height, body mass, body surface area, body composition, maximal oxygen consumption, and training status with eight healthy Control participants (Table 1). Our participants were the same individuals who participated in our previous study (Carter et al. 2014). Two T1DM participants (1 male and 1 female) were taking Levothyroxine (0.125 $mg \cdot day^{-1}$ and 0.1 $mg \cdot day^{-1}$, respectively) for the treatment of hypothyroidism. The female participant was also taking metformin (500 $mg \cdot day^{-1}$) for polycystic ovarian syndrome. These medications have not been reported to alter skin blood flow and sweating responses. All participants were non-smoking and were free from any cardiovascular, respiratory, and other metabolic diseases.

[*Please insert Table 1 around here*]

### *Experimental Design*

All participants volunteered for one preliminary and one experimental session. The preliminary session consisted of measurements for body height, mass, and surface area as well as training status and maximal oxygen consumption. Body height was determined using a stadiometer (Detecto, model 2391, Webb City, MO, USA) whereas body mass was measured using a digital

high-performance weighing terminal (model CBU150X, Mettler Toledo, Mississauga, ON, Canada). Body surface area was calculated from body height and mass (Du Bois & Du Bois 1989). Training status was evaluated by having participants complete both the Kohl's Fitness Questionnaire and the Baecke Sport Index Questionnaire (Baecke et al. 1982; Kohl et al. 1988). Maximal oxygen consumption ($VO_{2max}$) was determined by indirect calorimetry (MOXUS system, Applied Electrochemistry, Pittsburgh, PA, USA) during a progressive incremental exercise protocol performed on a constant-load upright cycle ergometer (Corival, Lode BV, Groningen, The Netherlands). The workload was set at 80 W for 1 min and participants were instructed to cycle continuously at ~85-90 rpm (Canadian Society for Exercise Physiology 1986). The work rate was increased by 20 W every minute thereafter until pedaling cadence of at least 60 rpm could not be maintained.

Participants reported to the laboratory between 7h00 and 11h00 for the experimental session. The participants were asked to drink 500 mL of water the night before, as well as the morning of the experimental session and to refrain from alcohol, caffeine, and exercise for 24 hours prior to experimentation. Participants with T1DM were instructed to take their normal bolus of insulin adjusted for exercise and eat a normal breakfast prior to arriving at the laboratory. Upon arrival, participants provided a urine sample and a nude body mass measurement before changing into shorts, sandals, and a sports bra for females. Urine specific gravity was assessed in duplicate using a refractometer (Reichert TS 400 total solids refractometer, Reichert Inc., Depew, NY, USA). At this point participants rested supine on a bed while an intravenous catheter was inserted into the left antecubital vein for the collection of blood samples at baseline, end of exercise, and at minute 30 and 60 of recovery. Participants subsequently sat upright for a 60-min instrumentation

period in temperate conditions (~24°C) before moving to an environmental chamber regulated at 35°C and 20% humidity for a 30-min adaptation period.

Figure 1 depicts a detailed schematic of the protocol. Following the adaptation period, 30-min of baseline data collection ensued. Thereafter, participants performed 90-min of continuous incremental exercise on a semi-recumbent cycle ergometer. The exercise intensity was set at progressively greater rates of metabolic heat production of 200, 250, and 300 $W \cdot m^{-2}$ of body surface area for 30-min each. Participants with T1DM experiencing capillary blood glucose <4.5 $mmol \cdot L^{-1}$ were supplemented with glucose (i.e., Gatorade) as a safety measure. Consequently, each participant with T1DM performed the experimental session prior to the matched Control so that both participants could be given the same amount of Gatorade at the same time point. Six of eight individuals with T1DM required glucose supplementation during exercise. The exercise bout was immediately followed by a 60-min recovery period in the semi-recumbent position. Following the experimental protocol, participants remained seated for a period of local heating to assess maximal skin blood flow. The local skin heaters were heated to 42°C for an initial 15-min and subsequently to 44°C for an additional 30-min until a stable plateau of skin blood flow was observed for at least 5-min. A final nude body mass measurement and urine sample were obtained at the end of the experimental session.

*Measurements*

Esophageal and rectal temperatures were measured using a pediatric thermocouple probe of ~2 mm in diameter (Mon-a-therm, Mallinckrodt Medical Inc., St. Louis, MO, USA) inserted 40 cm past the entrance of the nostril and 12 cm pas the anal sphincter, respectively. Skin temperature was measured at four sites using thermocouples (Concept Engineering, Old Saybrook, CT, USA)

184 attached to the skin with surgical tape. Mean skin temperature was subsequently calculated using
185 a four-point weighting of regional proportions as previously determined (Ramanathan 1964): chest
186 (30%), biceps (30%), calf (20%), and quadriceps (20%). Temperature data were collected using
187 an HP Agilent data acquisition module (model 3497A; Agilent Technologies Canada Inc.,
188 Mississauga, ON, Canada) every 15 seconds. Data were simultaneously recorded and displayed in
189 spreadsheet format on a personal computer with LabVIEW software (Version 7.0, National
190 Instruments, TX, USA).

191 Local sweat rate was measured as described previously (Carter et al. 2014) on the mid-
192 anterior forearm, upper back (superior trapezius), and chest (medial to the nipple) on the left side
193 using capsules attached to the skin with adhesive rings and topical skin glue (Collodian HV,
194 Mavidon Medical products, Lake Worth, FL, USA). Local sweat rate was calculated using the
195 difference in water content from the effluent and influent air multiplied by the flow rate and
196 normalized for the skin surface area under the capsule, presented in $mg \cdot min^{-1} \cdot cm^{-2}$. Local skin
197 blood flow was estimated at 32 Hz using laser-Doppler velocimetry (PeriFlux System 5000,
198 Perimed AB, Stockholm, Sweden) adjacent to the sweat capsules on the mid-anterior forearm and
199 upper back (superior trapezius) as previously described (Carter et al. 2014). Cutaneous vascular
200 conductance (CVC) was subsequently calculated from the ratio of skin blood flow (perfusion units)
201 to mean arterial pressure and presented as a percentage of maximum, as determined during local
202 heating.

203 Heart rate was monitored, recorded every 15 seconds, and stored using a Polar coded
204 WearLink and transmitter, Polar RS400 interface, and Polar Trainer 5 software (Polar Electro, Oy,
205 Finland). Mean arterial pressure was determined during baseline and recovery using a Finometer
206 (Finapres Medical Systems, Amsterdam, The Netherlands) from beat-to-beat recording of the right

middle finger arterial pressure waveform with the volume-clamp method (Penaz 1973) and physiocal criteria (Wesseling et al. 1995). Blood pressure was verified by auditory inspection with an automated monitor (Tango+, SunTech Medical Inc., Morrisville, NC, USA). The Finometer was also used to measure baroreflex sensitivity which expresses the change in inter-beat interval for a simultaneously occurring change in blood pressure and was calculated as previously described in $ms \cdot mmHg^{-1}$ (Westerhof et al. 2006). Baroreflex sensitivity is presented every 10-min throughout recovery as an average of the preceding 3-min.

Metabolic energy expenditure was assessed using indirect calorimetry during exercise (Nishi 1981). Expired gas was analyzed for oxygen (error of ± 0.01%) and carbon dioxide (error of ± 0.02%) concentrations using electrochemical gas analyzers (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA, USA). Prior to each session, gas mixtures of known concentrations (~17% $O_2$ and ~4% $CO_2$, balance $N_2$) were used to calibrate the gas analyzers and a 3 L syringe was used to calibrate the turbine ventilometer (error ± 1%).

An intravenous catheter was inserted, secured in place with a 6 x 7 cm film dressing (Tegaderm Film, 3M Health Care, St. Paul, MN, USA), and connected to a Luer-Lock extension (Microbore Extension, Clave™, Locking Spin Collar, Non-DEHP). Venous blood samples were taken (~10 mL) during baseline, at the end of exercise, and at min 30 and 60 of recovery. Blood samples were collected into K2 EDTA™ and Serum™ vacutainers (BD Vacutainer, Franklin Lakes, NJ, USA) for the determination of plasma volume and osmolality, respectively. Samples in the K2 EDTA™ vacutainers were immediately analyzed for hemoglobin (Hb) concentration and hematocrit (Hct) ratio to calculate changes in plasma volume as described previously (Dill & Costill 1974). Samples in the Serum™ vacutainers were allowed to sit for 20-min before being centrifuged. Plasma aliquots were collected, frozen at -20 °C and stored at -70 °C until analysis of

plasma osmolality using the freezing-point method (Osmometer, Advance Instruments, Norwood, MA, USA).

Cardiac output was measured non-invasively during baseline (in triplicate and presented as an average) and at 10-min intervals during recovery using an Innocor$^{TM}$ inert gas-rebreathing unit (Innovisions, Odense, Denmark) which has been previously validated against the direct Fick method and thermodilution (Peyton & Thompson 2004). Heart rate and arterial oxygen saturation were measured during each test which consisted of breath-by-breath ergospirometry with 5% nitrous oxide and 1% sulphur hexafluoride diluted with ambient air (Ayotte et al. 1970). The participant was asked to breathe through a breathing filter (Pro-Tec Filters, PF30S, 30 mm ports, Odense, Denmark) connected to a 3-way valve, an anti-static rubber bag, and a gas analyzer. Stroke volume was calculated as cardiac output divided by heart rate.

*Data Analysis*

All variables were compared between groups (T1DM vs Control) to evaluate the influence of T1DM on the recovery from exercise in the heat. Local sweat rate, CVC, and esophageal, mean skin, and rectal temperatures are presented for the end of exercise (i.e., minute 90 of exercise) as well as in 10-min intervals for the duration of the 60-min recovery. The time constant (tau) for the reduction in sweat rate and skin blood flow was also calculated using an exponential, one-phase association non-linear regression analysis and represented the exponential decay observed during recovery. Mean arterial pressure (absolute and relative change from baseline), baroreflex sensitivity, cardiac output, stroke volume, heart rate, and total peripheral resistance are also presented in 10-min intervals for the duration of the 60-min recovery. Plasma osmolality and venous blood glucose are presented at baseline, end-exercise, and at minutes 30 and 60 of recovery

whereas changes in plasma volume from baseline are presented at the end of exercise, and at minutes 30 and 60 of recovery.

*Statistical Analysis*

A two-way repeated measures analysis of variance (ANOVA) was conducted to evaluate whether a main effect of time (6 levels: 10, 20, 30, 40, 50, and 60 minutes of recovery) and group (2 levels: T1DM and Control) was present for local sweat rate, CVC, heart rate, mean arterial pressure (absolute and relative change from baseline), esophageal, mean skin, and rectal temperatures, baroreflex sensitivity, cardiac output, stroke volume, and total peripheral resistance. A two-way ANOVA was also conducted with factors of time (4 levels: baseline, end-exercise, and minutes 30 and 60 of recovery) and group (2 levels: T1DM and Control) for plasma osmolality, and venous blood glucose. Finally, a two-way ANOVA was conducted to evaluate changes in plasma volume from baseline with factors of time (3 levels: end-exercise and minutes 30 and 60 of recovery). When a significant main effect was observed, post-hoc comparisons were carried out using Student's paired samples *t*-tests corrected for multiple comparisons with the Holm-Bonferroni procedure. The level of significance for all analyses was set at $P<0.05$. Curve fitting analysis was performed using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). All other statistical analyses were completed using the software package SPSS 21.0 for Windows (IBM Corp. Armonk, NY, USA). Values are presented as mean ± standard error of the mean unless otherwise indicated.

## RESULTS

*Experimental session*

No differences were observed between groups for age (P=0.685), height (P=0.377), mass (P=0.288), body surface area (P=0.840), maximal oxygen consumption (P=0.964), or training status (Kohl's score: P=0.826; Baeke's score: P=0.458) (see Table 1). No differences were found between groups for metabolic heat production (P=0.257) or percentage of maximal oxygen consumption (P=0.849) throughout the exercise bout. Further, urine specific gravity did not differ between groups at the start (T1DM: 1.021 ± 0.007; Control: 1.016 ± 0.006, P=0.400) or end (T1DM: 1.022 ± 0.005; Control: 1.017 ± 0.006, P=0.180) of the experimental session.

*Thermoregulatory variables*

*Core and skin temperatures*. Esophageal, mean skin, and rectal temperature responses are depicted in Figure 2. There was a main effect of time observed for esophageal temperature throughout recovery (P=0.018), but not for group (P=0.875). Similarly, a main effect of time (P<0.001), but not group (P=0.484) was observed for mean skin temperature postexercise. In contrast, a main effect of time (P<0.001) and group (P=0.048) was observed for rectal temperature during recovery. Despite being similar at baseline (T1DM: 36.99 ± 0.08°C; Control: 37.07 ± 0.16°C, P=0.425), the increase in rectal temperature during exercise was greater in T1DM at the end of exercise compared to Control (1.51 ± 0.15ºC vs. 1.00 ± 0.10ºC, P=0.046, respectively) and remained elevated throughout recovery.

[*Please insert Figure 2 around here*]

*Cutaneous vascular conductance*. There was a main effect of time at the forearm (P=0.001) and upper back P=0.001) CVC during the postexercise period. However, no effect of group was

observed at either site (forearm: P=0.160; upper back: P=0.652) (see Figure 3). Furthermore, tau for CVC during recovery from exercise was similar between groups at the forearm (T1DM: 21 ± 7 min; Control: 17 ± 5 min, P=0.382) and upper back (T1DM: 14 ± 5 min; Control: 17 ± 5 min, P=0.517).

[*Please insert Figure 3 around here*]

*Local sweat rate.* Local sweat rate responses for baseline, end-exercise, and throughout recovery are depicted in Figure 4. While a main effect of time was observed for local sweat rate at the forearm (P=0.002), chest (P<0.001), and upper back sites (P=0.006), there was no main effect of group during the postexercise period (forearm: P=0.752; chest: P=0.702; upper back: P=0.259). This was despite the significantly lower local sweat rate at the end of exercise at the forearm (P=0.029) and chest (P=0.047) sites in the T1DM group compared to the Control group. Further, the tau value for sweat rate during recovery was similar between groups at the forearm (T1DM: 12 ± 5 min; Control: 13 ± 4 min, P=0.856), chest (T1DM: 16 ± 6 min; Control: 14 ± 4 min, P=0.628), and upper back (T1DM: 17 ± 5 min; Control: 15 ± 4 min, P=0.660). However, it should be noted that the magnitude of decrease in local sweat rate was greater in the Control group at the forearm (T1DM: 0.58 ± 0.20 $mg \cdot min^{-1} \cdot cm^{-2}$; Control: 0.84 ± 0.20 $mg \cdot min^{-1} \cdot cm^{-2}$, P=0.003) and the chest (T1DM: 0.51 ± 0.14 $mg \cdot min^{-1} \cdot cm^{-2}$; Control: 0.85 ± 0.29 $mg \cdot min^{-1} \cdot cm^{-2}$, P=0.035) compared to the T1DM group.

[*Please insert Figure 4 around here*]

*Cardiovascular variables*.

*Mean arterial pressure.* Postexercise mean arterial pressure exhibited a main effect of time (P=0.047), but not group (P=0.430) (Table 2). However, when presented relative to baseline levels, there was a main effect of time (P=0.049) and group (P=0.024) for mean arterial pressure (Figure

5). Despite being similar between groups (T1DM: -11 ± 7 mmHg; Control: -11 ± 6 mmHg, P=0.953) at 10-min into recovery, the magnitude of postexercise hypotension became progressively lower in T1DM compared to Control. Specifically, the relative change in mean arterial pressure from baseline levels was reduced in T1DM (-8 ± 5 mmHg) compared to Control (-13 ± 6 mmHg, P=0.026) at 20-min of recovery, and this difference persisted until the end of the 60-min recovery (T1DM: -1 ± 3 mmHg; Control: -9 ± 3 mmHg, P=0.002).

[*Please insert table 2 and Figure 5 around here*]

*Stroke volume, heart rate, cardiac output, and total peripheral resistance*. Cardiovascular responses are presented in Table 2. During the postexercise period, there was a main effect of time (P=0.024), but not group (P=0.719) for stroke volume such that stroke volume was reduced from baseline levels at 10-min of recovery (T1DM: -20 ± 5 mL; Control: -21 ± 6 mL, P<0.001) and progressively returned towards baseline levels. Similarly, there was also a main effect of time (P<0.001), but not group (P=0.382) for heart rate during recovery. Heart rate was elevated from baseline levels at 10-min into recovery (by T1DM: 34 ± 5 bpm; Control: 29 ± 8 bpm, P<0.001) and progressively decreased towards baseline levels. In parallel with these observations, cardiac output exhibited a main effect of time (P<0.001), but not group (P=0.378) during recovery. Specifically, cardiac output was increased at 10-min postexercise (by T1DM: 1.1 ± 0.4 $L \cdot min^{-1}$; Control: 1.2 ± 0.3 $L \cdot min^{-1}$) compared to baseline levels (P<0.023). Finally, there was also a main effect of time (P<0.001), but not group (P=0.210) observed for total peripheral resistance during recovery such that resistance was reduced at 10-min into recovery (by T1DM: -3 ± 1 $mmHg \cdot L^{-1} \cdot min^{-1}$; Control: -3 ± 1 $mmHg \cdot L^{-1} \cdot min^{-1}$) compared to baseline levels (P≤0.001) and progressively increased until the end of recovery.

343 *Baroreflex sensitivity*. There was a main effect of time (P<0.001) and group (P=0.049)
344 observed for baroreflex sensitivity during recovery (Figure 5). While no differences were observed
345 between T1DM (11 ± 3 ms·mmHg$^{-1}$) and Control (12 ± 4 ms·mmHg$^{-1}$, P=0.485) at baseline, the
346 reduction in baroreflex sensitivity was exacerbated from 10 min into recovery (T1DM: 2.9 ± 0.5
347 ms·mmHg$^{-1}$; Control: 5.3 ± 1.0 ms·mmHg$^{-1}$, P=0.003) until the end of the 60 min recovery
348 (T1DM: 5.7 ± 1.0 ms·mmHg$^{-1}$; Control: 8.4 ± 1.3 ms·mmHg$^{-1}$, P=0.011).
349
350 *Blood glucose, plasma osmolality, and changes in plasma volume*.
351 The responses for blood glucose, plasma osmolality, and the changes in plasma volume are
352 presented in Table 3.We observed a main effect of time (P=0.035) and group (P=0.020) for venous
353 blood glucose throughout the experimental session such that blood glucose was increased in T1DM
354 (9.9 ± 1.0 mmol·L$^{-1}$) compared to Control (5.3 ± 0.2 mmol·L$^{-1}$, P=0.004) only at baseline. Plasma
355 osmolality and changes in plasma volume also exhibited a main effect of time (P<0.001), but not
356 group (plasma osmolality: P=0.650; plasma volume: P=0.189) throughout the experimental
357 session.
358 [*Please insert Table 3 around here*]
359

## DISCUSSION

In this study, we simultaneously assessed the thermoregulatory and cardiovascular responses during recovery from exercise in individuals with T1DM. Contrary to our hypothesis, there were no differences in the level of suppression in postexercise skin blood flow or sweating. This was paralleled by similar esophageal and mean skin temperatures between T1DM and Control, thereby indicating a similar level of heat stress. However, we show that the rate of suppression in sweating at the forearm and chest sites is greater in the Control group. The postexercise cardiovascular responses were consistent with our hypothesis such that we observed a greater attenuation in baroreflex sensitivity in individuals with T1DM relative to Control. In addition, the reduction in postexercise mean arterial pressure relative to baseline resting values was less pronounced in individuals with T1DM. Taken together, our findings indicate that individuals with T1DM do not exhibit marked differences in thermoregulatory or cardiovascular control following prolonged exercise-induced heat stress despite experiencing a greater degree of heat storage as defined by a significantly higher end-exercise rectal temperature.

### *Thermoregulatory control*

The only study to date that has examined postexercise skin blood flow in individuals with T1DM (Stapleton et al. 2013) reported no differences in skin blood flow at the forearm throughout the exercise (i.e., 60 min at 200 $W \cdot m^{-2}$or subsequent 60-minute recovery. These findings are consistent with our results at both the forearm and upper back sites such that we observed no differences between groups despite a higher exercise intensity during the final hour of exercise (i.e., $\geq$250 $W \cdot m^{-2}$) and a greater level of hyperthermia (a 0.6°C greater increase in end-exercise rectal temperature in our T1DM group) achieved in the current study. However, these observations contrast those of prior studies reporting impairments in skin vascular function associated with

T1DM as assessed through pharmacological stimuli (Katz et al. 2001; Khan et al. 2000). Thus, the altered skin blood flow response induced by the administration of exogenous vasoactive agents may not reflect changes in skin blood flow during or following exercise in the heat. Taken together, our findings indicate that the similarity in skin blood flow responses between T1DM and healthy individuals are not limited to the exercise period (Carter et al. 2014; Stapleton et al. 2013), but rather are also observed during the subsequent recovery.

Although we did not observe any differences in skin blood flow between groups, we show that the end-exercise sweating response was attenuated at the forearm and chest skin sites in our T1DM participants. Of note, however, regional differences were observed such that there was no difference in end-exercise sweat rate at the upper back. Although sweat rate was reduced at the end of exercise in the T1DM group, we observed similar tau values between groups despite a smaller amplitude of change (i.e., a smaller decrease) in sweat rate for our T1DM group at the forearm and chest sites. While this more rapid suppression of sweating could be explained by a reduced thermal load defined by a lower end-exercise rectal temperature in the Control group, the lack of a difference in esophageal and/or mean skin temperatures (i.e., thermal drive perceived at the hypothalamus) would suggest otherwise (Figure 2). On the other hand, we did not observe any differences between groups in absolute sweat rate at any of the skin sites throughout the postexercise period which parallels the findings by Stapleton and colleagues (2013) who reported no differences in whole-body heat loss for 60 min of recovery in habitually active individuals with T1DM.

In parallel with the heat loss responses during recovery, both groups showed similar time-dependent changes in esophageal and mean skin temperatures. In contrast, rectal temperature remained significantly elevated in T1DM participants relative to Controls throughout the recovery

period. It has been argued that esophageal temperature is more reflective of blood temperature, and therefore central brain temperature (Whitby & Dunkin 1971). As such, esophageal temperature is thought to be the main stimulus driving the activation of thermoeffector activity during heat stress at the level of the hypothalamus (i.e., thermal drive). On this basis, and consistent with prior findings from a whole-body calorimetric perspective (Stapleton et al. 2013), our results would indicate that individuals with T1DM experienced similar thermal drive compared to their healthy Controls and demonstrate a similar rate of heat loss throughout the postexercise period. On the other hand, it has been suggested that rectal temperature more accurately reflects the amount of whole-body heat storage (Jay et al. 2007). As noted, rectal temperature, and therefore body heat storage, was significantly greater in our T1DM group (Figure 2). These differences in rectal temperature between groups may be attributed to altered tissue perfusion [i.e., reduced muscle blood flow (Menon et al. 1992)] in our T1DM group which would ultimately influence heat transfer in the surrounding tissues (i.e., in the rectum). Irrespective of the absolute differences in rectal temperature, the level of heat loss was similar between groups. This corresponded to a similar magnitude of decrease from end-exercise levels between groups over the course of the 60 minute recovery (T1DM: ~0.8°C; Controls: ~0.7°C), thereby indicating that rectal temperature may not be the primary stimulus driving heat loss during recovery. In the context of our observations, further research is required to examine the relationship between regional changes in central and peripheral thermal input, and therefore sensor-to-effector pathways, on heat loss in individuals with diabetes.

*Cardiovascular control*

Postexercise hypotension has been shown to be largely mediated by histamine ($H_1$ and $H_2$) receptor activation causing skeletal muscle vasodilation in healthy individuals (McCord & Halliwill 2006). We did not observe any differences in absolute mean arterial pressure between groups which were paralleled by similarities in other hemodynamic measures including cardiac output, stroke volume, heart rate, and total peripheral resistance. However, it was noted that the magnitude of hypotension was blunted in our T1DM participants such that blood pressure returned to baseline levels much more quickly compared to the Controls (Figure 5). Considering postexercise hypotension is thought to be largely mediated by skeletal muscle vasodilation (Halliwill et al. 2013), our observations would be explained by previously reported reductions in muscle blood flow associated with T1DM (Menon et al. 1992). Specifically, Menon et al. (1992) observed greater reductions in postexercise muscle blood flow in individuals with T1DM relative to matched healthy adults. The mechanism(s) and potential implications for this response remain unclear. However, it has been shown that individuals with T1DM experience a state of chronic inflammation (King 2008) which may lead to differences in histamine receptor activation.

A relationship between persistent postexercise hyperthermia and postexercise hypotension has been postulated such that the postexercise attenuation in heat loss responses of skin blood flow and sweating was the result of a nonthermal baroreflex-mediated suppression (Kenny & Jay 2013). This hypothesis was supported by reports demonstrating that reversal of baroreceptor unloading (i.e., increases in blood pressure) during the postexercise period resulted in a reversal in the attenuation of heat loss responses paralleled by a more rapid decay in esophageal temperature (Jackson & Kenny 2003; McInnis et al. 2006). In the present study, absolute mean arterial pressure did not differ between groups; however, we did observe a greater reduction in the magnitude of

postexercise hypotension in participants with T1DM (Figure 5) when compared to Controls. In contrast to previous reports (Jackson & Kenny 2003), the blunted postexercise hypotension was not associated with a concomitant increase in skin blood flow or sweating. Consequently, further study is warranted to determine whether diabetes can alter the relationship between postexercise heat dissipation and blood pressure regulation.

It has also been shown that baroreflex sensitivity is reduced following exercise in healthy adults compared to baseline resting levels (Armstrong, Seely 2010). Consistent with these observations, we showed reductions in postexercise baroreflex sensitivity in both T1DM and Control groups. However, baroreflex sensitivity was impaired to a greater extent in individuals with T1DM during recovery which is consistent with findings reported under resting conditions (Weston, James 1998; Weston, Panerai 1996). Alternatively, recent reports indicate a hypoglycemic episode can be followed by decreases in baroreflex sensitivity and sympathetic activation (Adler et al. 2009; Limberg et al. 2014). Importantly, we supplemented with Gatorade when blood glucose reached <4.5 $mmol \cdot L^{-1}$, which was necessary for 75% (6 of 8) of our participants with T1DM during exercise. The consequences of hypoglycemia on cardiovascular and thermoregulatory responses are currently unknown; however, it is possible that the high incidence of lower blood glucose levels (albeit not clinical hypoglycemia) during recovery may present a confounding influence to our measurements of baroreflex sensitivity during recovery.

*Considerations*

It is important to consider that our findings may only apply to young, otherwise healthy, and active individuals with T1DM. Specifically, our participants with T1DM had good-to-moderate glycemic control ($HbA_{1c}$ <8.5%) and were habitually active. While these characteristics

were employed to ensure the safety of our participants, it is unclear how individuals with T1DM who are older, less active and with poorer blood glucose control may differ. Considering the reductions to heat loss observed in healthy older adults (Kenny & Jay 2013), and in view of the impairments to skin blood flow and sweating being exacerbated by higher $HbA_{1c}$ and the presence/severity of diabetic neuropathy (Yardley et al. 2013), it seems likely that we would observe a more pronounced impairment in these individuals.

*Perspectives*

Recent evidence indicates that T1DM is associated with regional sweating impairments at exercise-induced heat loads at ≥250 $W \cdot m^{-2}$ (i.e., ~55-65% of maximal oxygen consumption), leading to greater body heat storage (Carter et al. 2014). Thus, otherwise healthy individuals with T1DM may not be at increased risk for heat-related injury during exercise-induced heat loads below 250 $W \cdot m^{-2}$ (equivalent to ~55% of maximal oxygen consumption in our participants). However, increases in metabolic and/or environmental heat loads may present a greater risk for individuals with T1DM who would likely store more heat. In light of our observations that individuals T1DM exhibited a similar reduction in heat loss to their healthy counterparts during recovery despite greater heat storage, they would likely sustain a greater level of hyperthermia. This may have important implications in the context of intermittent work which represents the majority of daily activities. Specifically, the impairments in heat loss associated with T1DM during exercise combined with a similar level of heat loss during recovery would result in individuals with T1DM carrying over a greater level of hyperthermia into subsequent exercise bouts. Studies show that intermittent exercise corresponds to a progressive increase in body heat storage due to the fact that the heat stress is maintained via a continued rapid suppression in heat loss during

recovery (Kenny et al. 2009). The extent to which this may impact individuals with T1DM is unclear; however, given the impairments in heat loss observed during exercise, it is likely that subsequent exercise bouts would result in even greater levels of heat storage. Further research is necessary to evaluate this hypothesis in the context of athletes and workers with T1DM, and to determine the most efficacious work-rest cycles to minimize the risk for heat-related injury.

In summary, we show that there are no differences in local skin blood flow or sweating between groups for the duration of the 60-min recovery. We also observed a similar pattern in absolute hemodynamic responses; however, the magnitude of postexercise hypotension was markedly reduced in our participants with T1DM compared to Controls. In addition, a reduction in baroreflex sensitivity during recovery was demonstrated in our T1DM group; albeit this may have been confounded by the high incidence of lower levels of blood glucose during exercise. Therefore, our findings indicate that young adults with T1DM who are otherwise healthy do not appear to exhibit greater perturbations in thermal or hemodynamic responses following exercise.

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**Table 1.** Participant characteristics presented for Controls and individuals with Type 1 Diabetes (T1DM).

| | Control | T1DM |
|---|---|---|
| Age (years) | 23.5 ± 2.9 | 22.3 ± 4.7 |
| Height (cm) | 177 ± 10 | 178 ± 8 |
| Body Mass (kg) | 79.1 ± 15.6 | 81.8 ± 15.8 |
| Body surface area ($m^2$) | 1.97 ± 0.23 | 1.99 ± 0.23 |
| $VO_{2max}$ ($L \cdot min^{-1}$) | 3.4 ± 0.7 | 3.3 ± 0.7 |
| $VO_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | 45.3 ± 2.4 | 42.7 ± 6.9 |
| Baecke Score | 4.8 ± 2.4 | 4.8 ± 2.9 |
| Kohl's Score ($met \cdot hr \cdot week^{-1}$) | 60.5 ± 22.7 | 55.4 ± 38.8 |
| $HbA_{1c}$ (%) | | 8.5 ± 0.4 |
| Duration of Diabetes (years) | N/A | 8.4 ± 2.9 |

N/A, not applicable. $VO_{2max}$, maximal oxygen consumption. $HbA_{1c}$, Hemoglobin $A_{1c}$. Values are mean ± standard error. No differences were found between groups for any variables ($P>0.05$). The same participants were used as in our previous study (Carter et al. 2014).

**Table 2.** Cardiovascular responses (cardiac output, stroke volume, heart rate, total peripheral resistance, and mean arterial pressure) at baseline and at 10-minute intervals during recovery.

| | Baseline | Recovery | | | | | |
|---|---|---|---|---|---|---|---|
| | | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min |
| | | | | *Cardiac output ($L \cdot min^{-1}$)* | | | |
| T1DM | 6.4 ± 0.2 | 7.5 ± 0.4 | 7.3 ± 0.4 | 7.1 ± 0.4 | 6.9 ± 0.3 | 6.6 ± 0.3 | 6.2 ± 0.3 |
| Control | 6.8 ± 0.3 | 8.0 ± 0.4 | 7.5 ± 0.3 | 7.2 ± 0.3 | 7.3 ± 0.3 | 7.1 ± 0.3 | 6.8 ± 0.4 |
| | | | | *Stroke volume ($mL \cdot beat^{-1}$)* | | | |
| T1DM | 87 ± 6 | 71 ± 7 | 74 ± 7 | 74 ± 7 | 72 ± 5 | 69 ± 6 | 74 ± 5 |
| Control | 97 ± 5 | 81 ± 5 | 80 ± 4 | 79 ± 4 | 79 ± 5 | 78 ± 5 | 75 ± 5 |
| | | | | *Heart rate ($beats \cdot min^{-1}$)* | | | |
| T1DM | 75 ± 4 | 109 ± 6 | 102 ± 6 | 99 ± 6 | 99 ± 5 | 99 ± 6 | 98 ± 6 |
| Control | 71 ± 3 | 101 ± 5 | 95 ± 4 | 92 ± 4 | 94 ± 4 | 93 ± 4 | 92 ± 4 |
| | | | | *Total peripheral resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$)* | | | |
| T1DM | 14 ± 1 | 10 ± 1 | 11 ± 1 | 12 ± 1 | 12 ± 1 | 13 ± 1 | 14 ± 1 |
| Control | 13 ± 1 | 10 ± 1 | 10 ± 1 | 11 ± 0 | 11 ± 1 | 11 ± 1 | 12 ± 1 |
| | | | | *Mean arterial pressure (mmHg)* | | | |
| T1DM | 86 ± 1 | 77 ± 4 | 79 ± 3 | 80 ± 2 | 82 ± 2 | 83 ± 1 | 85 ± 2 |
| Control | 89 ± 3 | 79 ± 3 | 76 ± 2 | 78 ± 2 | 77 ± 2 | 80 ± 2 | 81 ± 2 |

T1DM, Type 1 Diabetes Mellitus. Values are presented as mean ± standard error. No differences were found between groups ($P>0.05$).

626 **Table 3.** Venous blood glucose concentrations, plasma osmolality, and changes in plasma
627 volume at baseline, end of exercise (End-Ex), and at minutes 30 and 60 of recovery.

| | Baseline | End-Ex | Recovery | |
|---|---|---|---|---|
| | | | 30 min | 60 min |
| | *Venous blood glucose (mmol·L$^{-1}$)* | | | |
| T1DM | 9.9 ± 1.0* | 6.1 ± 0.8 | 7.3 ± 0.9 | 7.6 ± 0.8 |
| Control | 5.3 ± 0.2 | 5.1 ± 0.2 | 5.9 ± 0.4 | 5.7 ± 0.5 |
| | *Plasma osmolality (mosmol·kg$H_2O^{-1}$)* | | | |
| T1DM | 288 ± 3 | 297 ± 2 | 293 ± 2 | 296 ± 2 |
| Control | 289 ± 1 | 300 ± 2 | 295 ± 2 | 295 ± 1 |
| | *Change in plasma volume (%)* | | | |
| T1DM | | -11 ± 2 | -3 ± 2 | -5 ± 1 |
| Control | | -12 ± 2 | -6 ± 1 | -6 ± 1 |

628 Values are mean ± standard error. *, T1DM significantly greater venous blood glucose
629 concentration at baseline compared to Control ($P<0.05$).

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## FIGURE CAPTIONS

**Figure 1.** Experimental protocol timeline. Ambient conditions were 35ºC and 20% relative humidity. Downward arrow indicates a point at which cardiac output was measured (i.e., at baseline and every 10 min during recovery). Thermoregulatory variables were measured continuously. *, data from exercise has been discussed previously in detail (Carter et al. 2014). BD, blood draws were taken at baseline, end of exercise, and at minutes 30 and 60 of recovery.

**Figure 2.** Esophageal ($T_{eso}$, panel A), mean skin ($T_{skin}$, panel B), and rectal ($T_{rec}$, panel C) temperatures at baseline (Rest), end of exercise (End-Ex), and at 10-minute intervals throughout recovery for participants with Type 1 Diabetes Mellitus (T1DM) and healthy Controls (Control). Values are mean ± standard error. *, T1DM significantly greater than Control ($P<0.05$).

**Figure 3.** Cutaneous vascular conductance (CVC) presented as percentage of maximum (% Max) at the forearm (panel A) and upper back (panel B) at baseline (Rest), end of exercise (End-Ex), and at 10-minute intervals throughout recovery for participants with Type 1 Diabetes Mellitus (T1DM) and healthy Controls (Control). Values are mean ± standard error. No differences were found between groups ($P>0.05$).

**Figure 4.** Local sweat rate (LSR) presented at the forearm (panel A), upper back (panel B), and chest (panel C) at baseline (Rest), end of exercise (End-Ex), and at 10-minute intervals throughout recovery for participants with Type 1 Diabetes Mellitus (T1DM) and healthy Controls (Control). Values are mean ± standard error. *, T1DM significantly lower than Control ($P<0.05$).

**Figure 5.** Baroreflex sensitivity (panel A) and the magnitude of hypotension (panel B) at baseline (Rest) and at 10-minute intervals throughout recovery for participants with Type 1 Diabetes Mellitus (T1DM) and healthy Controls (Control). Values are mean ± standard error. *, T1DM significantly different from Control ($P<0.05$).

**Figure 1.**

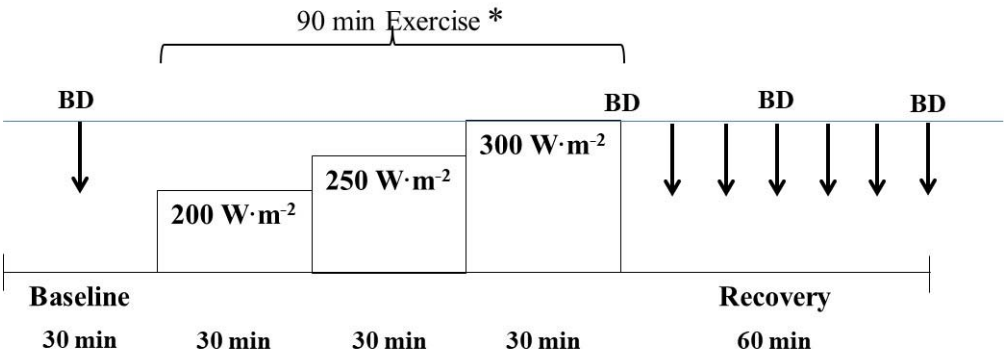

90 min Exercise *
BD
BD
BD
BD
300 W·m-2
250 W·m-2
200 W·m-2
Baseline
Recovery
30 min
30 min
30 min
30 min
60 min

**Figure 2.**

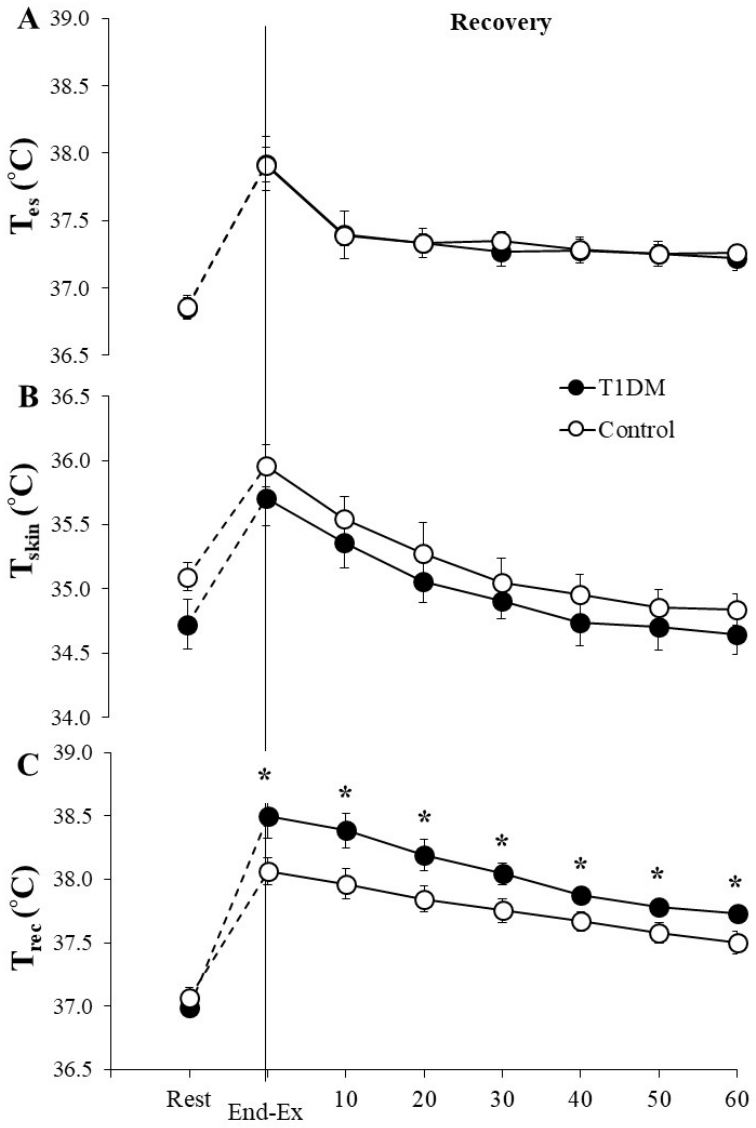
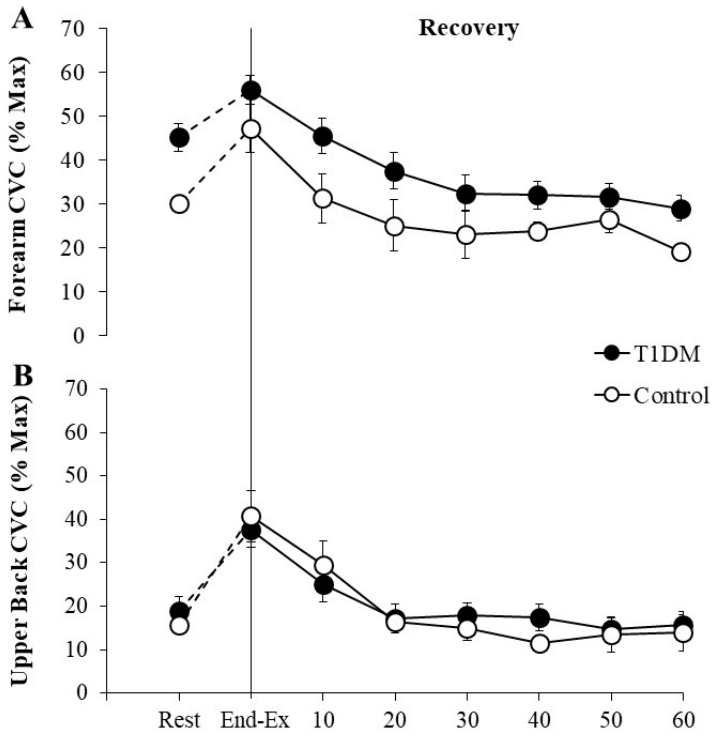

A
B
C
Recovery
T1DM
Control
$T_{es}$ (°C)
$T_{skin}$ (°C)
$T_{rec}$ (°C)
39.0
38.5
38.0
37.5
37.0
36.5
36.5
36.0
35.5
35.0
34.5
34.0
39.0
38.5
38.0
37.5
37.0
36.5
*
Rest
End-Ex
10
20
30
40
50
60

**Figure 3.**


A
Recovery
Forearm CVC (% Max)
70
60
50
40
30
20
10
0
T1DM
Control
B
Upper Back CVC (% Max)
70
60
50
40
30
20
10
0
Rest
End-Ex
10
20
30
40
50
60

677 **Figure 4.**

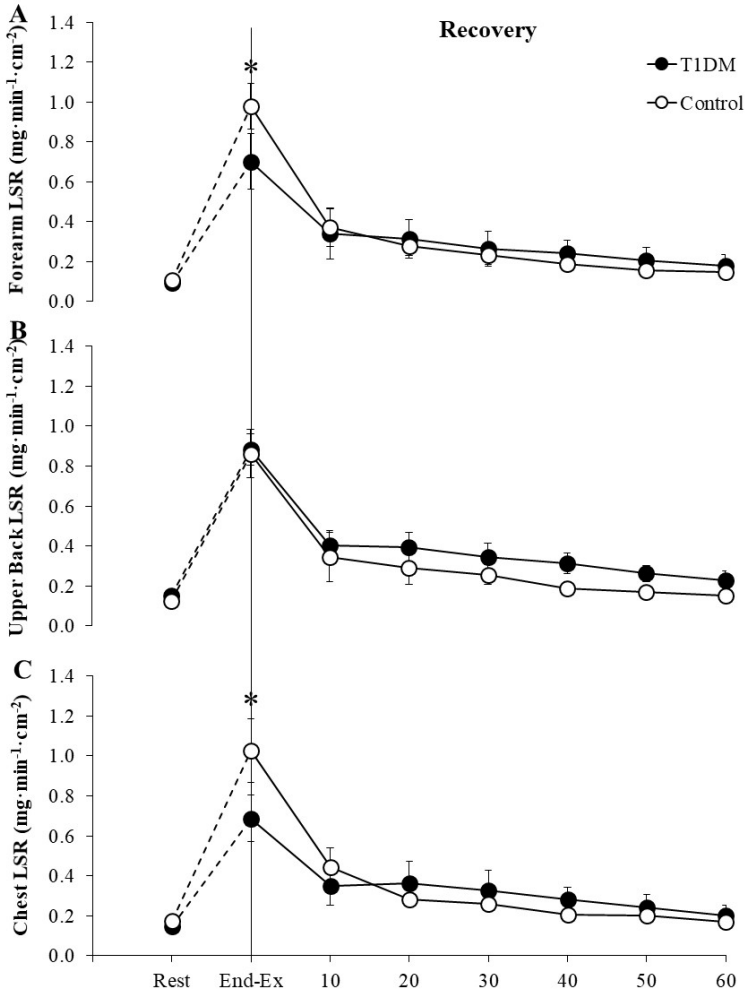



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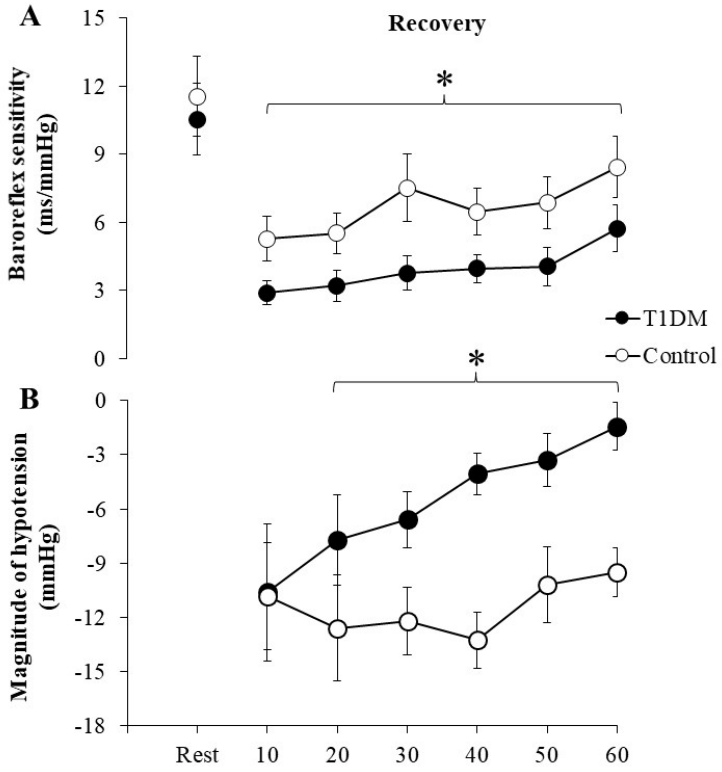
**Figure 5.**


A
Recovery
Baroreflex sensitivity (ms/mmHg)
15
12
9
6
3
0
*
T1DM
Control
B
Magnitude of hypotension (mmHg)
0
-3
-6
-9
-12
-15
-18
*
Rest
10
20
30
40
50
60