Impairments in Local Heat Loss in Type 1 Diabetes during Exercise in the Heat

MIKE R. CARTER[1], RYAN MCGINN[1], JULIANA BARRERA-RAMIREZ[1], RONALD J. SIGAL[2], and GLEN P. KENNY[1]

[1]Human and Environmental Physiology Research Unit, University of Ottawa, Ottawa, Ontario, CANADA; and [2]Departments of Medicine, Cardiac Sciences, and Community Health Sciences, Faculties of Medicine and Kinesiology, University of Calgary, Calgary, Alberta, CANADA

ABSTRACT

CARTER, M. R., R. MCGINN, J. BARRERA-RAMIREZ, R. J. SIGAL, and G. P. KENNY. Impairments in Local Heat Loss in Type 1 Diabetes during Exercise in the Heat. *Med. Sci. Sports Exerc.*, Vol. 46, No. 12, pp. 2224–2233, 2014. Studies show that vasomotor and sudomotor activities are compromised in individuals with Type 1 diabetes mellitus (T1DM), which could lead to impaired skin blood flow (SkBF) and sweating during heat stress. However, recent work suggests the impairments may only be evidenced beyond a certain level of heat stress. **Purpose**: We examined T1DM-related differences in heat loss responses of SkBF and sweating during exercise performed at progressive increases in the requirement for heat loss. **Methods**: Sixteen adults (10 males and six females) with (T1DM, $n = 8$) and without T1DM (control, $n = 8$) matched for age, sex, body surface area, and fitness cycled at fixed rates of metabolic heat production of 200, 250, and 300 $W \cdot m^{-2}$ in the heat (35°C and 20% relative humidity). Each rate was performed sequentially for 30 min. Local sweat rate (LSR, ventilated capsule), sweat gland activation (modified iodine paper technique), and sweat gland output were measured on the forearm, upper back, and chest, whereas SkBF (laser Doppler) was measured on the forearm and upper back. **Results**: Despite a similar requirement for heat loss, LSR was lower in T1DM on the forearm and chest relative to that in the control. Reductions were measured in the second (forearm: 0.68 ± 0.14 vs 0.85 ± 0.11 $mg \cdot min^{-1} \cdot cm^{-2}$, $P = 0.004$; chest: 0.58 ± 0.08 vs 0.82 ± 0.12 $mg \cdot min^{-1} \cdot cm^{-2}$, $P = 0.046$) and third exercise bouts (forearm: 0.75 ± 0.11 vs 0.98 ± 0.12 $mg \cdot min^{-1} \cdot cm^{-2}$, $P = 0.005$; chest: 0.66 ± 0.1 vs 1.02 ± 0.16 $mg \cdot min^{-1} \cdot cm^{-2}$, $P = 0.032$). Differences in forearm LSR were the result of a reduction in sweat gland output, whereas the decrease in chest LSR was due to lower sweat gland activation. SkBF did not differ between groups. **Conclusions**: We show that T1DM is associated with impairments in heat dissipation during exercise in the heat, as evidenced by attenuated LSR. However, these differences are only shown beyond a certain requirement for heat loss. **Key Words:** SWEATING, SKIN BLOOD FLOW, CORE TEMPERATURE, THERMOSENSITIVITY, CHRONIC DISEASE

Exercise is considered to be an important part of the management and overall well-being for patients with Type 1 diabetes mellitus (T1DM), as engaging in regular exercise is associated with reductions in mortality and cardiovascular disease risk (4). During exercise, however, the increase in metabolic rate above resting levels increases the rate at which heat must be dissipated to the environment to prevent a dangerous rise in core temperature. When exercise is performed in the heat and skin temperature is lower than ambient air temperature, the body begins to gain heat via dry heat exchange (8). This further exacerbates the requirements for increases in skin blood flow (SkBF) and sweating, the latter representing the major avenue of heat dissipation, to achieve a rate of heat loss that will maintain heat balance (21). Studies suggest that otherwise healthy individuals with T1DM may have a reduced capacity to dissipate heat, as evidenced by reductions in SkBF (13,18,19,33,34) and attenuated sweat production (7,17,20) as measured in response to local heating and/or pharmacological stimulus. Less well understood are the consequences of T1DM on heat dissipation during exercise in the heat.

The limited studies examining SkBF in T1DM show that microvascular reactivity of the skin in individuals with T1DM is impaired, leading to lower maximal levels of SkBF (34). This is thought to result from impairments to both endothelium-dependent and endothelium-independent vasodilation (14,19,24). These impairments have been observed in

Address for correspondence: Glen P. Kenny, Ph.D., Human and Environmental Physiology Research Unit, University of Ottawa, 125 University Private, Room 367, Montpetit Hall, Ottawa, Ontario K1N 6N5, Canada; E-mail: gkenny@uottawa.ca.
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both the upper and lower body of individuals with T1DM (24,34,38). Conversely, studies examining the sudomotor response in individuals with T1DM have been limited to the evaluation of the sweating response as an indicator of autonomic neuropathy. These studies show that sweating abnormalities in T1DM include regional hypohidrosis and early hyperhidrosis (17), with complete anhydrosis in extreme situations (7,20), which can lead to global anhydrosis (15). The level of impairment in both SkBF and sweating function is exacerbated in individuals with longer duration of diabetes (18,24), poor glucose control (15,18,34) and greater degree of neuropathy (38).

To date, there remains a lack of information regarding the consequences of the T1DM-related impairments on the body's physiological capacity to dissipate heat during exercise. A recent study by Stapleton et al. (35) reported no differences in whole-body heat dissipation between young (34 ± 4 yr), otherwise healthy, subjects with T1DM and nondiabetic controls during moderate-intensity exercise (approximately 42% of maximal oxygen consumption ($\dot{V}O_{2max}$)) performed at a fixed rate of heat production (approximately 200 $W \cdot m^{-2}$). However, whole-body heat loss responses were only measured during a single heat load. It is therefore possible that the heat load used was insufficient to exceed the individual's/group's ability to achieve heat balance. The level of whole-body heat loss required to achieve heat balance during exercise, particularly in the heat, is determined by the sum of metabolic and environmental heat load (dry heat gain from the environment) (8). Thus, a greater heat load requires a greater rate of whole-body heat loss to maintain heat balance (and therefore a stable core temperature) (22). As such, it remains unclear if T1DM-related differences in heat dissipation may only be evidenced above a certain heat load and therefore requirement for heat loss.

The following study was conducted to evaluate if T1DM-related differences in local heat loss responses of SkBF and sweating are only evidenced above a certain requirement for heat loss during exercise in the heat (35°C, 20% relative humidity). Specifically, we evaluated the hypothesis that T1DM-related impairments in SkBF and sweating would only be evidenced beyond a certain level of heat stress as compared with responses measured in healthy individuals matched for physical characteristics.

METHODS

Ethical approval. The experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board in accordance with the Declaration of Helsinki. A written informed consent was obtained from all volunteers before their participation in the study.

Participants. Eight participants with T1DM (five males and three females) were matched for sex, height, body mass, body surface area, body composition, physical fitness ($\dot{V}O_{2max}$), and training status with eight healthy control participants. Participant characteristics are presented in Table 1. Hemoglobin A_{1c} (HbA_{1c}) for the group with diabetes was 8.5% ± 0.4% and ranged from 6.6% to 9.8%, whereas the duration of diabetes was 8.4 ± 2.9 yr. All participants with T1DM who experienced episodes of severe hypoglycemia (requiring assistance of another person to treat it) within the previous year and/or were clinically diagnosed with peripheral or autonomic neuropathy were excluded from the study. We cannot rule out the possibility that some participants may have had more subtle neuropathies that were undetected in clinical screening tests. To minimize the influence of differences in hormonal status across the menstrual cycle, female participants performed each experimental session within the first and fifth day after the onset of their self-reported menses. On the day of the experiment, a venous blood sample was obtained from female participants to confirm that the session occurred during the follicular phase of the menstrual cycle. Hormonal status was confirmed by taking a venous blood sample on the day of the experimental session. Blood samples were collected into an SST Vacutainer (BD Vacutainer; BD, Franklin Lakes, NJ) for the determination of plasma 17β-estradiol and progesterone. Plasma concentrations of each hormone were quantified by an independent external laboratory (Gamma-Dynacare Medical Laboratories, Ottawa, Ontario, Canada). None of the experimental sessions for female participants had to be repeated on the basis of blood sample results. Two T1DM participants (one male and one female) were taking levothyroxine (0.125 and 0.1 $mg \cdot d^{-1}$) for hypothyroidism. The female participant was also taking metformin (500 $mg \cdot d^{-1}$) for polycystic ovarian syndrome. Neither of these drugs have been reported to alter SkBF or sweating responses. All other T1DM and control participants were nonsmoking and free of any cardiovascular, respiratory, and other metabolic diseases.

TABLE 1. Mean ± SE for characteristics of participants with T1DM and without T1DM (control).

	T1DM	Control
Age (yr)	22.3 ± 4.7	23.5 ± 2.9
Height (cm)	178 ± 8	177 ± 10
Body mass (kg)	81.2 ± 15.8	79.1 ± 15.6
A_D (m^2)	1.99 ± 0.23	1.97 ± 0.23
Body fat (%)	21.9 ± 0.9	21.7 ± 1.8
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	3.3 ± 0.7	3.4 ± 0.7
$\dot{V}O_{2max}$ ($mL\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	42.7 ± 6.9	45.3 ± 4.7
Baecke sport score	4.8 ± 2.9	4.8 ± 2.4
Physical activity ($MET \cdot h \cdot wk^{-1}$)	55.4 ± 38.8	60.5 ± 22.7
HbA_{1c} (%)	8.5 ± 0.4	N/A
Duration of diabetes (yr)	8.4 ± 2.9	N/A

A_D, body surface area; N/A, not applicable.

Experimental design. All participants volunteered for one preliminary and one experimental session. During the preliminary session, training status, body height, mass, density, and $\dot{V}O_{2max}$ were determined. Training status was evaluated by having participants complete both the Kohl fitness questionnaire and the Baecke sport index questionnaire (1,25). Body height was determined using a stadiometer (Detecto model 2391; Detecto, Webb City, MO), whereas body mass was measured using a digital high-performance weighing terminal (model CBU150X; Mettler Toledo, Mississauga, Ontario, Canada). Body surface area was calculated from

body height and mass (6). Body density was measured using the hydrostatic weighing technique and used to calculate body fat percentage (32). $\dot{V}O_{2max}$ was determined by indirect calorimetry (MOXUS system; Applied Electrochemistry, Pittsburgh, PA) during a progressive incremental exercise protocol performed on a constant-load cycle ergometer (Corival; Lode BV, Groningen, the Netherlands) in an upright seated position.

For each experimental session, participants reported to the laboratory between 7:00 and 11:00 a.m. The participants were asked to drink 500 mL of water the night before and in the morning of the experimental session and to refrain from alcohol, caffeine, and exercise 24 h before experimentation. Participants were instructed to take their normal bolus of insulin adjusted for exercise and eat their usual breakfast before arriving at the laboratory.

On arrival at the laboratory, participants provided a urine sample, weighed themselves nude, and changed into shorts, sandals, and a sports bra for female participants. Participants subsequently sat upright for a 60-min instrumentation period at an ambient room temperature of 24°C. After instrumentation, participants entered an environmental chamber regulated to an ambient air temperature of 35°C and a relative humidity of 20% where they remained resting in the upright seated posture for 30 min. Thereafter, participants performed 90 min of continuous semirecumbent cycling exercise. The exercise was performed at fixed rates of heat production equal to 200, 250, and 300 $W \cdot m^{-2}$ of body surface area, with each level being 30 min in duration. Blood samples were taken from an indwelling catheter at the end of baseline and at the start of recovery to evaluate changes in plasma volume and osmolality during the exercise bout. At the end of the exercise bout, participants underwent a 45-min local heating, during which maximum SkBF at the forearm (midanterior) and upper back (superior trapezius) was determined by increasing the temperature of the heater housing the laser Doppler probes to 42°C for 15 min and then 44°C for 30 min. Participants were then weighed nude, and a urine sample was collected.

Measurements. Esophageal temperature was measured using thermocouple probes (Mallinckrodt Pharmaceuticals, Inc., St. Louis, MO) inserted 40 cm past the nostril while the participant sipped water through a straw. Rectal temperature was measured using a thermocouple temperature sensor (Mallinckrodt Pharmaceuticals, Inc., St. Louis, MO) inserted 12 cm past the anal sphincter. Skin temperature was measured at four sites using thermocouples (Concept Engineering, Old Saybrook, CT) attached to the skin with surgical tape. Mean skin temperature was subsequently calculated using a four-point weighting of the regional proportions determined by Ramanathan (28), as follows: chest (30%), arm (30%), calf (20%), and quadriceps (20%). All temperature data were collected using an HP Agilent data acquisition module (model 3497A) every 15 s. Data were simultaneously displayed and recorded in spreadsheet format on a personal computer with the LabVIEW software (version 7.0; National Instruments, Austin, TX).

The ventilated capsule technique was used to measure local sweating. Sweat production on the forearm (midanterior), upper back (superior trapezius), and chest (medial to the left nipple) was measured from 3.8-cm^2 plastic capsules attached to the skin with adhesive rings and topical skin glue (Collodion HV; Mavidon Medical Products, Lake Worth, FL). Anhydrous compressed air was passed through each capsule at a rate of 1 $L \cdot min^{-1}$. Water content of the effluent air was measured using high-precision dew point mirrors (model 473; RH Systems, Albuquerque, NM). Local sweat rate (LSR) was calculated using the difference in water content between effluent and influent air multiplied by the flow rate and normalized for the skin surface area under the capsule.

The number of heat-activated sweat glands was measured on the forearm, upper back, and chest adjacent to each affixed sweat capsule at 30, 60, and 90 min of exercise using the modified iodine paper technique with computer-assisted analysis (9). The number of glands determined by computer analysis was subsequently divided by the surface area of the paper to give a value of active sweat glands per square centimeter (9). The sweat output per gland was calculated by dividing the sweat rate at the corresponding measurement period by the number of heat-activated sweat glands.

Local SkBF at the midanterior forearm and upper back adjacent to the sweat capsules was estimated using laser Doppler velocimetry (PeriFlux System 5000; Perimed AB, Stockholm, Sweden). Before the start of the experimental trial, laser Doppler flow probes (integrating probe 413; Perimed AB, Stockholm, Sweden) were affixed with an adhesive ring to the forearm and upper back at a site that demonstrated cardio-synchronous pulsatile activity. SkBF response was expressed as a percentage of maximum, as determined during local heating performed at the end of the 90 min exercise bout.

Indirect calorimetry was used for the measurement of metabolic energy expenditure (27). Expired gas was analyzed for oxygen (error of ± 0.01%) and carbon dioxide concentrations (error of ± 0.02%) using electrochemical gas analyzers (AMETEK model S-3A/1 and CD 3A; Applied Electrochemistry, Pittsburgh, PA). Before each session, gas mixtures of known concentrations were used to calibrate the gas analyzers and a 3-L syringe was used to calibrate the turbine ventilometer. HR was measured continuously by a Polar coded WearLink™ and transmitter, Polar RS400 interface, and Polar ProTrainer 5 software (Polar Electro Oy, Finland).

Changes in plasma volume and plasma osmolality were determined using venous blood samples drawn from an indwelling venous catheter at the left antecubital vein. Blood was collected at the end of the 30-min baseline resting period and again at the end of the 90-min exercise period. Both during the baseline resting period and at end-exercise, blood draws were performed while seated on the exercise bike in an upright seated position. The catheter was inserted and secured in place with a film dressing 6 × 7 cm (Tegaderm Film; 3M Health Care, St. Paul, MN). The

catheter was connected to a luer lock extension (Microbore Extension, Clave™, locking spin collar, non-DEHP). Venous blood (approximately 10 mL) was collected into K2 EDTA™ and Serum™ vacutainers (BD Vacutainer; BD, Franklin Lakes, NJ) for hematology and plasma osmolality analysis. Blood samples in the K2 EDTA™ vacutainer were immediately analyzed for Hb concentration and hematocrit ratio (Coulter Ac·T diff 2 analyzer; Beckman Coulter, Miami, FL). Changes in hemoglobin and hematocrit concentration from baseline to the end of exercise were used to calculate changes in plasma volume (5). Plasma aliquots were analyzed upon separation to determine osmolality using the freezing point method (osmometer; Advance Instruments). In addition, the change in body mass and urine specific gravity was assessed before and after exercise. Body mass was measured using a digital high-performance weighing terminal (model CBU150X; Mettler Toledo, Mississauga, Ontario, Canada). Urine specific gravity was determined in duplicate pre- and postexercise using a handheld refractometer (TS400; Reichter, Depew, NY).

Glucose/insulin adjustments for exercise. Participants with T1DM adjusted their insulin according to their regular preexercise routine. Blood glucose levels ≥5 mM were required before the start of exercise. T1DM participants measured capillary glucose using personal handheld glucose meters 15 min into baseline and at 5, 10, 15, 30, 45, 60, and 75 min of exercise. Blood glucose was also measured from blood drawn from an indwelling catheter for both the T1DM and controls at the start of exercise and during the final minute of the 90-min incremental exercise. Gatorade was available throughout the session if necessary to increase blood glucose in the event of low blood sugars in T1DM participants. To ensure that potential differences in fluid balance at the end of exercise were caused by differences in sweating and not by differences in fluid intake, participants with T1DM completed the experimental session before the matched control to ensure that similar volumes of Gatorade were provided to the matched control participant and at the same time point during the session.

Data analysis. All measurements were calculated into minute averages, and the final minute of each workload was used to carry out statistical analyses on all variables. Because of volitional fatigue, one T1DM participant was unable to complete the full 30 min of the third and final exercise intensity (exercise load 3, 300 $W \cdot m^{-2}$). As such, end-exercise core temperature was assessed for seven matched pairs only. Because of technical problems, LSR of the upper back for one of the T1DM participants was not collected and, therefore, the data for the matched pair was not included in the analysis. Mean body temperature was calculated as 0.9 × esophageal temperature + 0.1 × mean skin temperature (30). Group differences in the onset threshold and thermosensitivity of the local sweating response during each exercise period were determined using the linear portion of the response plotted against mean body temperature and analyzed using segmental linear regression (3). Because SkBF did not increase after the first exercise intensity, the onset threshold and thermosensitivity of the response were determined only for the first exercise bout (10). As a result of technical problems with the measurement of esophageal temperature in one of the diabetic participants, it was not possible to calculate thermosensitivities for one matched pair.

Statistical analysis. All dependent variables were compared between groups (T1DM vs control). Paired-sample *t*-tests were used for comparisons between matched groups for physical characteristics, training status, and maximal aerobic capacity. Minute averages were calculated for all continuous variables (esophageal, rectal, and mean skin temperatures, local SkBF (two sites: forearm and upper back), and LSR (three sites: forearm, upper back, and chest)). A two-way mixed-model ANOVA was performed using the repeated factor of time (four levels: 0, 30, 60, and 90 min of exercise) and the nonrepeated factor of group (two levels: T1DM and control). When a significant main effect was observed, *post hoc* comparisons were carried out using paired-sample *t*-tests. The level of significance for all analyses was set at an alpha level of $P \leq 0.05$. Statistical analyses were carried out using SPSS 21.0 for Windows, (IBM SPSS Statistics for Windows version 21.0; IBM, Armonk, NY), and segmented linear regression analysis was performed using GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA) (3). All variables are reported as means ± SE, unless otherwise indicated.

RESULTS

Experimental session. No differences were observed between T1DM and control for sweat rate or SkBF as well as core and mean skin temperatures during baseline resting. By design, the rate of metabolic heat production was the same for both groups across all three exercise intensities ($P = 0.257$). Workloads represented a similar percentage of $\dot{V}O_{2max}$ for T1DM and control participants (200 $W \cdot m^{-2}$, 44.5% ± 2.6% vs 41.8% ± 1.9%; 250 $W \cdot m^{-2}$, 54.7% ± 3.1% vs 51.7% ± 2.1%; 300 $W \cdot m^{-2}$, 66.2% ± 3.5% vs 62.8% ± 2.7%, respectively; $P = 0.849$). CHO supplementation was required during exercise for six T1DM participants (21.9 ± 0.01 g of CHO).

Sweat rate. Despite exercise being performed at fixed requirements for heat loss, sweat rate was reduced over time in T1DM compared with that in control at the forearm ($P = 0.050$) and chest ($P = 0.013$); however, no differences were measured on the upper back ($P = 0.654$) (Fig. 1). Forearm and chest sweat rates did not differ between T1DM and control at the end of the first exercise period (forearm, $P = 0.174$; chest, $P = 0.150$) (Fig. 1). In contrast, LSR was reduced in T1DM relative to that in control at the forearm and chest measurement sites during the second (forearm, $P = 0.004$; chest, $P = 0.046$) and third exercise periods (forearm, $P = 0.005$; chest, $P = 0.032$) (Fig. 1). These responses were not paralleled by differences in the onset threshold for sweating at any of the sites measured ($P > 0.1$)

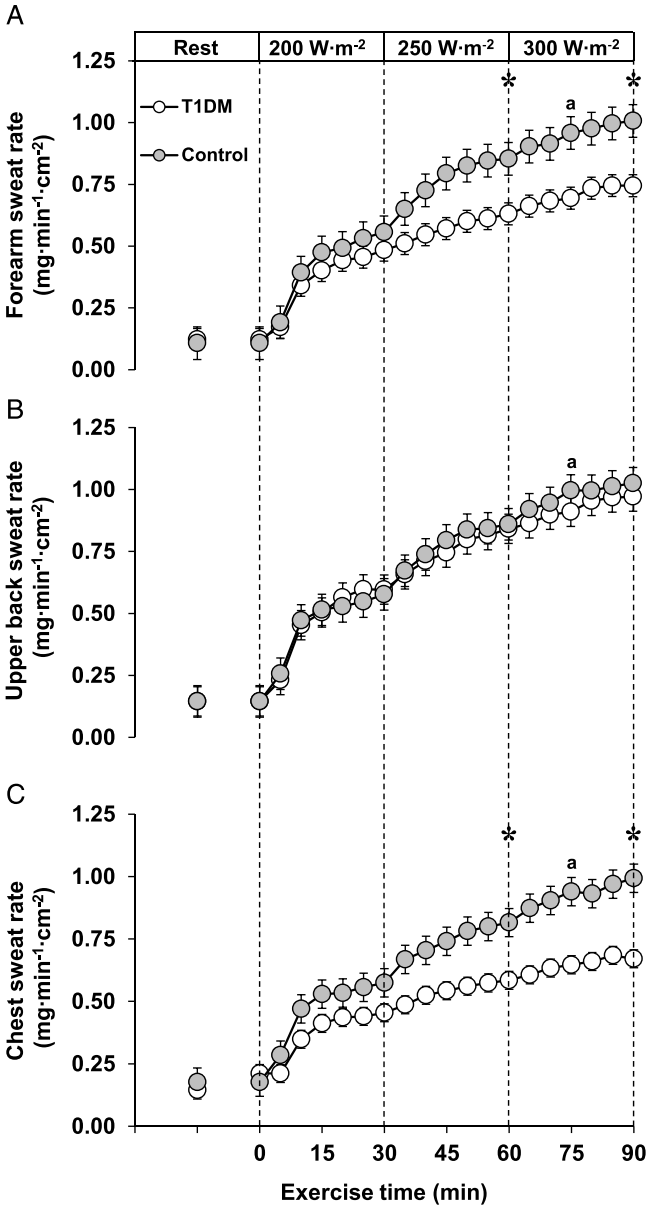

FIGURE 1—Local sweat rate at the forearm (A), upper back (B), and chest (C) at baseline (rest) and during exercise at fixed rates of metabolic heat production of 200, 250, and 300 W·m^{-2} for participants with T1DM (*white circle*) and without T1DM (control) (*gray circle*). One matched pair ended exercise after 78 min (a). For upper back (B), n = 7. Values are presented as mean ± SE. *Dashed lines* indicate the start and/or end of an exercise period. *Significance between groups at the forearm and chest sites measured at the end of the exercise period ($P \leq 0.05$).

(Table 2). In contrast, differences were observed in the thermosensitivity of the sweating response, although it should be noted that the response was heterogeneous in that the reductions in thermosensitivity in T1DM were not apparent at all heat loads at all sites. No differences were observed for thermosensitivity during the first or second exercise periods at the forearm (200 W·m^{-2}, $P = 0.576$; 250 W·m^{-2}, $P = 0.426$) or upper back (200 W·m^{-2}, $P = 0.108$; 250 W·m^{-2}, $P = 0.215$) (Table 2), whereas a greater thermosensitivity in control participants was measured at the chest site (200 W·m^{-2}, $P = 0.030$; 250 W·m^{-2}, $P = 0.017$) for those exercise periods. In contrast, T1DM had a reduced thermosensitivity during the final exercise period at all measured sites relative to that of their healthy counterparts (forearm, $P = 0.046$; upper back, $P = 0.044$; chest, $P = 0.005$) (Table 2).

Lower sweat gland activation (SGA) and output were found in T1DM relative to those in control; however, as in the case of LSR, responses vary as function of measurement site. The number of heat-activated sweat glands did not differ between groups throughout the exercise period at the forearm ($P = 0.176$) or the upper back ($P = 0.809$). However, SGA was lower in T1DM at the chest during the final exercise period only ($P = 0.049$) (Table 3). No differences between groups for sweat gland output (SGO) were observed at the upper back ($P = 0.994$) or chest skin sites ($P = 0.351$) (Table 3). In contrast, SGO was significantly lower for T1DM compared with that for control at the forearm, but only during the second ($P = 0.004$) and third ($P = 0.012$) exercise periods. Therefore, the attenuated sweat rate in T1DM at the chest was primarily driven by a reduction in SGA, whereas the lower sweat rate at the forearm was primarily driven by a reduction in SGO. Furthermore, and consistent with the attenuated LSR measured at the forearm and chest in the T1DM group, a lower change in body mass was measured in T1DM (−1.86% ± 0.09%) relative to that in control (−2.10% ± 0.14%, $P = 0.049$).

SkBF. SkBF at both the forearm and upper back sites increased significantly from baseline rest to end of the first exercise bout ($P < 0.001$) (Fig. 2). However, no further increase in SkBF was measured with the subsequent exercise bouts (forearm, $P = 0.480$; upper back, $P = 0.426$). SkBF responses over time did not differ between groups (forearm, $P = 0.660$; upper back, $P = 0.126$). Similarly, no differences between groups were observed in the onset threshold for SkBF (forearm, $P = 0.302$; upper back, $P = 0.828$). In contrast, a reduction in thermosensitivity of SkBF response was measured in the T1DM group at both the forearm ($P = 0.001$) and upper back ($P = 0.005$) during the first exercise period (Table 2).

Core and mean skin temperatures. Esophageal temperature during the three exercise periods did not significantly differ between groups ($P = 0.344$) (Fig. 3A). However, compared with that in control, T1DM had a significantly greater increase in rectal temperature over the 90-min exercise period ($P = 0.005$). Baseline rectal temperatures were similar between T1DM and control (37.00°C ± 0.05°C vs 36.95°C ± 0.09°C, $P = 0.455$), and no differences in rectal temperature were found between groups at the end of the first ($P = 0.197$) and second exercise periods ($P = 0.073$). However, end-exercise rectal temperature was significantly greater in T1DM (38.46°C ± 0.16°C) relative to that in control (38.07°C ± 0.11°C, $P = 0.048$) (Fig. 3B). No differences between groups in mean skin temperature were observed throughout the experiment ($P = 0.951$) (Fig. 3C).

TABLE 2. Mean ± SE for the onset threshold and thermosensitivity of skin blood flow and sweating for individuals with T1DM and without T1DM (control).

	200 W·m^{-2}		250 W·m^{-2}		300 W·m^{-2}	
	T1DM	Control	T1DM	Control	T1DM	Control
Skin blood flow						
Onset threshold (Δ°C)						
Forearm	0.16 ± 0.08	0.00 ± 0.01	N/A	N/A	N/A	N/A
Upper back	0.09 ± 0.03	0.03 ± 0.03	N/A	N/A	N/A	N/A
Thermosensitivity (% max·°C^{-1})						
Forearm	23.8 ± 5.9*	68.9 ± 9.8	N/A	N/A	N/A	N/A
Upper back	25.6 ± 5.6*	65.5 ± 8.8	N/A	N/A	N/A	N/A
Sweating						
Onset threshold (Δ°C)						
Forearm	0.01 ± 0.02	0.05 ± 0.02	0.01 ± 0.02	0.02 ± 0.01	0.00 ± 0.02	0.03 ± 0.02
Upper back	0.01 ± 0.01	0.02 ± 0.02	0.03 ± 0.03	0.01 ± 0.01	0.04 ± 0.05	0.01 ± 0.03
Chest	0.02 ± 0.01	0.03 ± 0.03	0.00 ± 0.01	0.01 ± 0.01	0.01 ± 0.02	0.06 ± 0.05
Thermosensitivity (mg·min^{-1}·cm^{-2}·°C^{-1})						
Forearm	1.40 ± 0.51	1.55 ± 0.18	0.93 ± 0.21	1.18 ± 0.19	0.21 ± 0.09*	0.58 ± 0.16
Upper back	0.92 ± 0.17	1.48 ± 0.28	0.91 ± 0.23	1.09 ± 0.28	0.24 ± 0.09*	0.80 ± 0.16
Chest	0.76 ± 0.09*	1.58 ± 0.26	0.53 ± 0.10*	0.99 ± 0.16	0.18 ± 0.06*	0.89 ± 0.11

*T1DM is significantly different from control ($P \leq 0.05$).
N/A, not applicable because the thermosensitivity of the skin blood flow response was measured in the first exercise only.

HR, hydration status, and blood glucose. No differences in HR were found during baseline (T1DM, 75 ± 4 bpm, vs control, 71 ± 3 bpm) and throughout the exercise period between T1DM and control (200 W·m^{-2}, 123 ± 5 vs 117 ± 6 bpm; 250 W·m^{-2}, 145 ± 8 vs 137 ± 5 bpm; 300 W·m^{-2}, 155 ± 6 vs 154 ± 5 bpm, respectively; $P = 0.532$). No differences in urine specific gravity were measured between groups before the start (T1DM, 1.02 ± 0.00, vs control, 1.01 ± 0.00; $P = 0.40$) or at the end of the experimental session (T1DM, 1.02 ± 0.00, vs control, 1.02 ± 0.00; $P = 0.18$). Plasma volume decreased during the exercise period ($P = 0.001$); however, no significant differences from baseline were found between T1DM (−10.9% ± 1.7%) and control (−10.7% ± 1.9%, $P = 0.920$). In contrast, plasma osmolality increased during exercise ($P < 0.001$), although there were no differences between groups at baseline (T1DM, 287 ± 3 mOsm·kg^{-1} H_2O, vs control, 289 ± 1 mOsm·kg^{-1} H_2O) or at the end of the 90-min exercise bout (T1DM, 295 ± 2 mOsm·kg^{-1} H_2O, vs control, 299 ± 2 mOsm·kg^{-1} H_2O). During the exercise period, the change in blood glucose concentrations differed between groups ($P = 0.027$). At baseline, individuals with T1DM had higher blood glucose concentrations (T1DM, 9.98 ± 1.03 mM, vs control, 5.26 ± 0.17 mM; $P = 0.004$); however, both groups had similar venous blood glucose concentrations by the end of exercise (T1DM, 4.57 ± 0.99 mM, vs control, 5.17 ± 0.27 mM; $P = 0.223$).

DISCUSSION

We show for the first time that individuals with T1DM demonstrate a reduction in local sweating response during exercise in the heat, as measured at the chest and forearm skin sites. However, these differences were only evidenced when the exercise heat load was ≥250 W·m^{-2}. In parallel, while the response varied as a function of site of measurement and heat load, a decrease in thermosensitivity of the sweating response was measured at all skin sites. Furthermore, we show that the underlying mechanisms associated with the lower sweat rate measured in T1DM also differed between sites, such that the decrease in sweat rate at the forearm site was attributed to a lower sweat gland output whereas a reduction in the number of heat-activated sweat glands accounted for the lower sweat rate measured at the chest. Although reductions in thermosensitivity for SkBF were measured in the T1DM group at both the forearm and upper back, this was limited to the first exercise heat load. The attenuation in heat dissipation was paralleled by a greater increase in rectal temperature measured at the end

TABLE 3. Mean ± SE for number of heat-activated active sweat glands and the sweat output per gland during exercise performed at increasing rates of metabolic heat production for individuals with T1DM and without T1DM (control).

	200 W·m^{-2}		250 W·m^{-2}		300 W·m^{-2}	
	T1DM	Control	T1DM	Control	T1DM	Control
No. of heat-activated active glands per square centimeter						
Forearm	40.8 ± 5.7	49.5 ± 6.4	79.3 ± 9.2	72.9 ± 9.7	89.6 ± 11.2	70.4 ± 12.3
Upper back	44.2 ± 7.0	53.0 ± 10.2	58.4 ± 7.7	62.7 ± 6.1	59.6 ± 5.0	70.3 ± 4.3
Chest	34.1 ± 7.4	45.7 ± 7.0	44.4 ± 5.7	60.2 ± 10.0	52.1 ± 4.0*	71.7 ± 7.2
Sweat gland output (μg per gland)						
Forearm	13.6 ± 3.2	13.1 ± 3.6	9.6 ± 3.2*	13.3 ± 2.7	8.9 ± 2.3*	15.7 ± 3.3
Upper back	13.0 ± 3.1	13.5 ± 4.3	12.9 ± 2.0	13.9 ± 2.2	14.1 ± 2.1	13.2 ± 1.9
Chest	17.3 ± 4.1	15.1 ± 2.8	15.8 ± 3.0	19.1 ± 3.6	14.8 ± 2.2	15.4 ± 3.5

*T1DM is significantly different from control ($P \leq 0.05$).

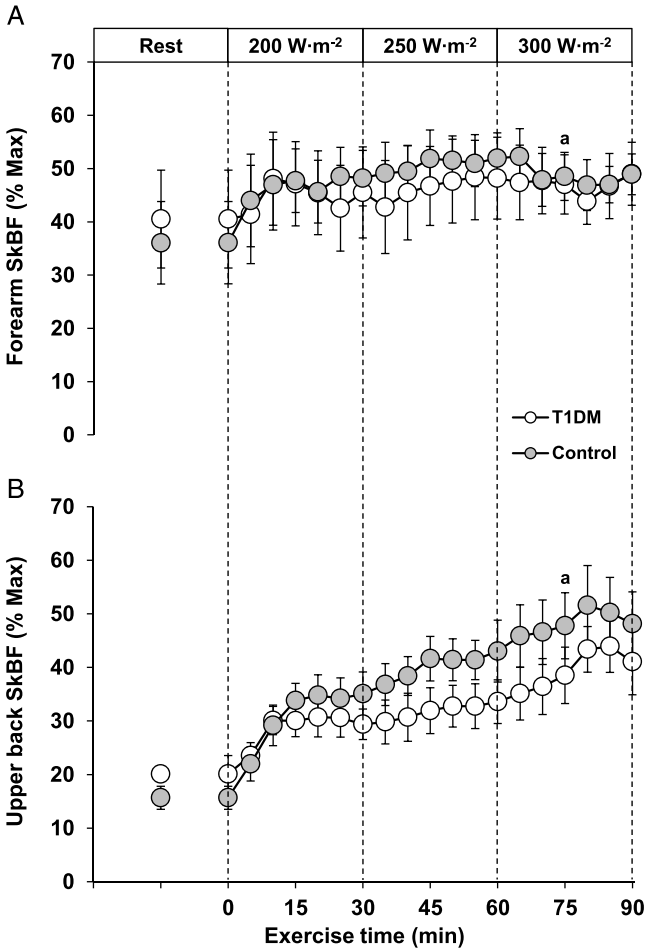

FIGURE 2—Local skin blood flow (SkBF) at the forearm (A) and upper back (B) at baseline (rest) and during exercise at fixed rates of metabolic heat production of 200, 250, and 300 W·m^{-2} for participants with T1DM (*white circle*) and without T1DM (control) (*gray circle*). One matched pair ended exercise after 78 min (a). Values are presented as mean ± SE. *Dashed lines* indicate the start and/or end of an exercise period.

of the 90-min exercise bout, albeit this was not paralleled by similar differences in esophageal temperature. Noteworthy, one participant with T1DM was unable to fully complete the final exercise load.

To date, little is known about the consequences of diabetes-related impairments in microvascular reactivity of the skin on SkBF response during exercise. Consistent with findings from the study by Stapleton et al. (35), we show that SkBF reached similar levels in both groups at a moderate exercise-induced heat load (i.e., 200 W·m^{-2}). However, in contrast to Stapleton et al. (35), thermosensitivity of the SkBF response was reduced in our T1DM participants relative to that in control at the forearm and upper back sites. The disparity in findings between the two studies may be the result of differences in glucoregulation and/or fitness. In the present study, our participants had a higher HbA_{1c} as compared with that in the participants in the study by Stapleton et al. (35) (8.5% ± 0.4% vs 7.7% ± 0.3%, respectively). A higher HbA_{1c} in individuals with T1DM has been shown to induce endothelial damage and the formation of advanced glycosylated end products, leading to a decrease in the bioavailability of nitric oxide, a potent vasodilator (2). Consequently, poor glycemic control in T1DM may lead to impairments in reflex cutaneous vasodilation (34). The greater HbA_{1c} in the current study is paralleled by a 12% lower level of fitness (i.e., $\dot{V}O_{2max}$) measured in our participants. Although a higher level of fitness or exercise training has been associated with higher SkBF during exercise (36,37), further studies are required to examine this relationship in individuals with T1DM.

There also remains a paucity of information about the consequences of diabetes on the sweating response during exercise-induced heat stress. Much of our understanding of

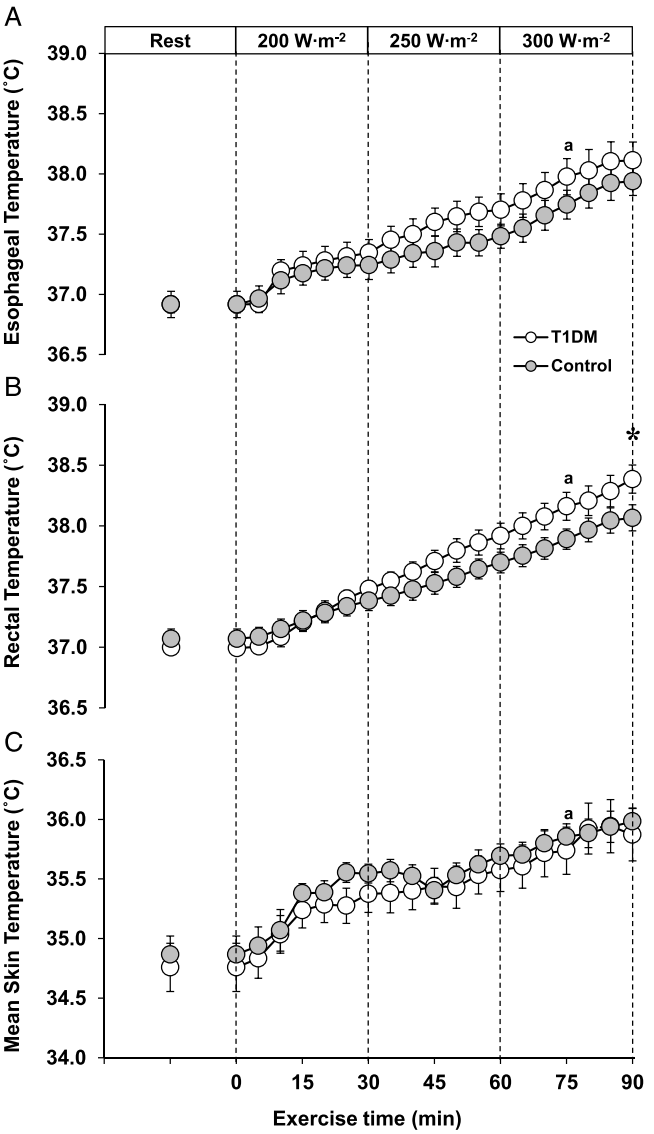

FIGURE 3—Esophageal (A), rectal (B), and mean skin (C) temperatures at baseline (rest) and during exercise at fixed rates of metabolic heat production of 200, 250, and 300 W·m^{-2} for participants with T1DM (*white circle*) and without T1DM (control) (*gray circle*). One matched pair ended exercise at 78 min (a). Values are presented as mean ± SE. *Dashed lines* indicate the start and/or end of an exercise period. *Significance between groups for rectal temperature measured the end of the exercise period ($P \leq 0.05$).

the effects of T1DM on the sweating response has been limited to studies involving a passive exposure to heat (7,20). Studies have focused on the sweating response in the hands and feet, providing limited information about the consequences of T1DM on the body's physiological capacity to dissipate heat during exercise. However, it seems that sweating abnormalities in T1DM populations may be related to blood glucose control (17). Stapleton et al. (35) showed that young adults with well-controlled T1DM and no overt neuropathies do not demonstrate reductions in whole-body evaporative heat loss during a single 60-min exercise bout performed at a fixed rate of heat production of 200 $W \cdot m^{-2}$. This was paralleled by similar responses in local sweat rate measured only at the upper back. Despite regional differences, however, our findings demonstrate that the degree of impairment in sweating is dependent on the level of heat stress.

The level of whole-body heat loss achieved during exercise in the heat is dependent upon the required evaporation for heat balance, which is defined as the sum of metabolic and environmental heat load (dry heat gain from the environment) (8). When the combined environmental and metabolic heat load exceeds the individual's ability to achieve heat balance, the level of sweating achieved is driven by the individual's maximum sweating capacity (21). As such, the thermal challenge (i.e., environmental plus metabolic heat load) presented in the study by Stapleton et al. (35) may be insufficient to exceed the T1DM group's physiological capacity to dissipate heat. Our results support this possibility, given that we only showed a marked attenuation in sweating at both the forearm and chest skin sites at a requirement for heat loss exceeding 200 $W \cdot m^{-2}$. This response was paralleled by a lower thermosensitivity measured at all heat loads for chest sweat rate and for all skin sites at the highest heat load used (300 $W \cdot m^{-2}$). The net consequence of these changes (i.e., thermosensitivity and level of sweating achieved during exercise) is a pronounced reduction in the rate of whole-body evaporative heat loss (a major avenue of heat dissipation during exercise in the heat), leading to a greater increase in body heat storage (22). Although we did not directly measure whole-body evaporative heat loss, we observed a significantly lower percent change in body mass. Given that exercise was performed under conditions that permit full evaporation, we can conclude that the observed reductions in local sweating were likely paralleled by marked reductions in whole-body evaporative heat loss (as determined by the lower change in body mass and, therefore, fluid loss) in individuals with T1DM.

In parallel to the observed attenuation in heat dissipation in the individuals with T1DM, we observed an approximately 0.4°C greater increase in rectal temperature measured at the end of the 90-min incremental exercise bout. In contrast, no differences in esophageal temperature were observed. The disparity between body core temperature measurement sites likely reflects regional variations in tissue heat exchange and, therefore, temperature gradients. Although it is not possible to determine whether diabetes-related impairments and/or abnormalities in skin perfusion (i.e., vascular responsiveness, changes in structure and quality of blood vessels, etc.) may also translate to altered blood flow response in other vascular beds, this possibility cannot be discounted. Menon et al. (26) reported that abnormalities in muscle blood flow in response to exercise (as defined by a greater reduction in postexercise muscle blood in T1DM relative to that in control) can be observed in individuals with diabetes, and this occurs even in the absence of clinical diabetic neuropathy. Regional tissue temperature at any time point is the result of regional differences in metabolic rate, conductive heat loss to adjacent tissue, and deep and peripheral convective blood flow (21). As such, the resulting differences in tissue heat distribution and/or exchange could explain the intersite temperature variations.

Some insight into the mechanism(s) governing the diabetes-related impairment in local heat loss responses of SkBF and sweating may be gleaned from our measurements of the onsets and sensitivities of the thermoeffector response. Because the interpretation of thermoefferent activity, namely skin sympathetic nerve activity, is problematic between individuals or groups (39), the onset threshold and the thermosensitivity of thermoeffector responses represent the only viable means by which we can assess the effects of nonthermal factors such as T1DM on thermoregulatory control. Although both variables can represent a central and/or peripheral modulation of temperature regulation (16), it has been suggested that a parallel shift in the onset threshold of all effector responses must occur to be representative of a central modulation (12). As such, changes in the thermosensitivity of an effector response, without parallel changes in the onset threshold, likely imply a peripheral modulation. We observed a lower thermosensitivity of the SkBF (i.e., measured at both sites for the first exercise heat load) and sweating (i.e., at all heat loads for chest and at the highest heat load for all skin sites) response. This was not paralleled by differences in the onset threshold for either the SkBF or sweating response at any skin site. Taken together, our findings suggest that the T1DM-associated impairments in SkBF and sweating are of a peripheral origin.

In the present study, we show regional differences in the underlying mechanism for the reduction in sweating. Specifically, we show that the reduction in sweat rate at the chest was mediated by a reduction in the number of heat-activated sweat glands whereas the attenuated forearm sweat rate was the result of a lower sweat output per gland. Our participants did not have clinically diagnosed peripheral or autonomic neuropathies; however, the presence of undetected neuropathy in the current study group cannot be ruled out. In addition, although other factors such as reduced sensitivity to acetylcholine may be involved, further studies are clearly warranted to determine the mechanism(s) underlying this peripherally mediated modulation of the sweating response. Furthermore, we did not observe any differences in the sweat rate achieved at the upper back skin site despite noting an impaired thermosensitivity during the final exercise bout.

Although the similarity of the sweating response at the upper back is consistent with findings by Stapleton et al. (35), more studies are required to further characterize regional differences in sweating associated with T1DM. Irrespective of the underlying cause, differences in the number of heat-activated sweat glands or sweat output per gland may be the result of changes in thermoefferent neural activity or of changes in the physical properties of the sweat glands themselves (29). This is in part supported by a recent study demonstrating that individuals with T1DM have lower density of sweat gland nerve fibers and potentially lower sudomotor activity (11).

Perspectives. Recently published guidelines by the Canadian Diabetes Association (31) have recommended that individuals with diabetes who opt to perform exercise in the heat should do so with caution. However, these recommendations were based primarily on epidemiological data showing that individuals with diabetes face a greater risk of hospitalization and/or death during prolonged heat events (23) and physiological studies, which demonstrate that impairments in SkBF and sweating are present in individuals with T1DM in response to local heating and/or pharmacological stimulus (13,15,18,19,24,33,34). Our findings demonstrate for the first time that T1DM can result in impairments in sweating, which may lead to a reduction in the body's ability to dissipate heat during exercise in the heat. Given that the consequences of these changes on deep body tissue temperature response differed on the basis of the measurement site (i.e., elevated rectal temperature with no change in esophageal temperature), further studies are required to examine the consequences of these T1DM-related impairments in local heat loss responses on body heat storage. It is important to note that the T1DM participants evaluated in this study were young, moderately active, nonneuropathic individuals with good blood glucose control. Because impairments in SkBF and sweating have been shown to be exacerbated by levels of blood glucose control and the presence/severity of diabetic neuropathy, it is plausible to suggest that a greater attenuation in heat dissipation and, therefore, level of thermal strain would be observed in those individuals with less well-controlled diabetes and/or advanced age.

In addition to the complications that exercise in the heat may present to these individuals, glucoregulation may be negatively affected by exercise in the heat. In the present study, 75% of our T1DM participants required exogenous glucose and, of the six participants requiring CHO supplementation, one participant was unable to finish the full 30 min of the third and final exercise periods. Although our study findings provide important and novel information about the consequences of diabetes on the body's physiological capacity to dissipate heat during an exercise-induced heat load, more research is needed to generate the knowledge necessary for the earlier prediction of the onset of heat-related injury and illness in this potentially vulnerable population group.

In summary, we showed that young people with generally well-controlled T1DM and without clinically diagnosed neuropathies had a reduced sweating response during exercise in the heat and regional differences were evident. Specifically, we showed that the reductions in forearm and chest sweating occurred when the rate of heat production/gain exceeded 200 $W \cdot m^{-2}$. In parallel, we observed reductions in thermosensitivity of the SkBF and sweating response, with no differences in the onset threshold, although it should be noted that responses varied as a function of the measurement site and heat load. Although a greater increase in rectal temperature was observed in the individuals with T1DM, this was not paralleled by a similar increase in esophageal temperature. Taken together, these results provide important new evidence demonstrating that T1DM-related impairments in thermoeffector activity are evident during exercise in the heat and may be mediated peripherally.

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