Type 1 diabetes modulates cyclooxygenase- and nitric oxide-dependent mechanisms governing sweating but not cutaneous vasodilation during exercise in the heat

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Fujii N, Dervis S, Sigal RJ, Kenny GP. Type 1 diabetes modulates cyclooxygenase- and nitric oxide-dependent mechanisms governing sweating but not cutaneous vasodilation during exercise in the heat. Am J Physiol Regul Integr Comp Physiol 311: R1076–R1084, 2016. First published October 12, 2016; doi:10.1152/ajpregu.00376.2016.—Both cyclooxygenase (COX) and nitric oxide synthase (NOS) contribute to sweating, whereas NOS alone contributes to cutaneous vasodilation during exercise in the heat. Here, we evaluated if Type 1 diabetes mellitus (T1DM) modulates these responses. Adults with (n = 11, 25 ± 5 yr) and without (n = 12, 24 ± 4 yr) T1DM performed two bouts of 30-min cycling at a fixed rate of heat production of 400 W in the heat (35°C); each followed by a 20- and 40-min recovery period, respectively. Sweat rate and cutaneous vascular conductance (CVC) were measured at four intradermal microdialysis sites treated with either 1 lactated Ringer (vehicle control site), 2 10 mM ketorolac (nonselective COX inhibitor), 3 10 mM Nω-nitro-l-arginine methyl ester (nonselective NOS inhibitor), or 4 a combination of both inhibitors. In nondiabetic adults, separate and combined inhibition of COX and NOS reduced exercise sweat rate (P ≤ 0.05), and the magnitude of reductions were similar across sites. In individuals with T1DM, inhibition of COX resulted in an increase in sweat rate of 0.10 ± 0.09 and 0.09 ± 0.08 mg min−1 cm−2 for the first and second exercise bouts, respectively, relative to vehicle control site (P ≤ 0.05), whereas NOS inhibition had no effect on sweating. In both groups, NOS inhibition reduced CVC during exercise (P ≤ 0.05), although the magnitude of reduction did not differ between the nondiabetic and T1DM groups (exercise 1: −28 ± 10 vs. −23 ± 8% max, P = 0.51; exercise 2: −31 ± 12 vs. −24 ± 10% max, P = 0.38). We show that in individuals with T1DM performing moderate intensity exercise in the heat, NOS-dependent sweating but not cutaneous vasodilation is attenuated, whereas COX inhibition increases sweating.

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Reports indicate that the risk of heat-related injuries is greater in individuals with Type 1 diabetes mellitus (T1DM) than in nondiabetic individuals (35). However, the underlying reason for this elevated risk is unclear. This is in part due to the fact that there is a paucity of information on the effects of T1DM on the body’s ability to dissipate heat. It has been shown that cutaneous vascular function (as defined by changes in cutaneous vasodilation induced by the administration of pharmacological agents) is attenuated in individuals with T1DM relative to their nondiabetic counterparts. This response is thought to be associated with a lower production of, or a lower sensitivity to, nitric oxide (NO) (17, 22). Furthermore, individuals with T1DM demonstrate impaired sweating, although regional heterogeneity has been observed (3, 25, 39). To date, however, the mechanisms underlying these T1DM-related alterations in cutaneous perfusion and sweating remain unclear.

Recent reports demonstrate that both cyclooxygenase (COX) (8) and NO synthase (NOS) (8, 38, 41) contribute to sweating, whereas NOS (8, 26, 41), but not COX (8), is involved in the regulation of cutaneous perfusion during exercise in the heat. However, the extent to which T1DM may affect the relative contributions of these important mediators in the regulation of the heat loss responses is unclear. Some insight may be gleaned from earlier studies which showed that T1DM attenuates NOS contribution (2, 7), whereas it augments COX contribution (30) to the regulation of blood flow in human conduit artery. Whether or not a similar pattern of response occurs in the regulation of sweating and cutaneous vasodilation during heat stress has not been examined.

The present study evaluated the influence of T1DM on the mechanisms underpinning heat loss responses of cutaneous vasodilation and sweating. We hypothesized that individuals with T1DM would show increased COX contribution with diminished NOS contribution to the regulation of cutaneous vasodilation and sweating during exercise in the heat in comparison with nondiabetic controls.

MATERIALS AND METHODS

Ethical approval. This study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and adhered to the guidelines set forth by the Declaration of Helsinki. Verbal and written informed consent was obtained from all volunteers before their participation.

Participants. Eleven otherwise healthy young individuals diagnosed with T1DM for >5 yr (9 males and 2 females) and 12 healthy young counterparts (Control group, 10 males and 2 females) participated in this study. All participants were free of respiratory disease, heart disease, uncontrolled hypertension, cardiac abnormalities, neuropathy, vasoactive medications, and cigarette smoking. All females were tested during their early follicular phase (within 6 days from the beginning of menstruation) or during placebo pill phase if taking contraceptives. Participant characteristics are described in Table 1.

Experimental design. All participants completed one preliminary and one experimental session (two separate visits). Before participating in both sessions, all participants were asked to refrain from

consuming alcohol, caffeine, and partaking in heavy exercise (>12 h before). They also refrained from taking any supplement and over-the-counter medications 48 h before. During the preliminary session, body mass, height, body surface area, body fat, and peak oxygen uptake were measured. Body height was measured using a stadiometer (model 2391, Detecto Scale, Webb City, MO), and body mass was measured using a digital weight scale platform (model CBU150X, Mettler Toledo, Mississauga, ON, Canada). Body surface area was calculated using body mass and height (5). Hydrostatic weighing was used to estimate body fat percentage (36). Peak oxygen uptake on a semirecumbent cycle ergometer (Corival Recumbent, Lode B.V., Groningen, The Netherlands) was evaluated using an automated gas analyzer (Medgraphics Ultima, Medical Graphics, St. Paul, MN) as reported elsewhere (9).

On the day of the experimental session, participants changed into shorts and running shoes (sports bra for females) and provided a urine sample, which was analyzed to assess urine specific gravity using a hand-held total solids refractometer (model TS400, Reichert, Depew, NY). The measured urine specific gravity was 1.015 ± 0.002 in the control group and 1.010 ± 0.002 in the T1DM group (P = 0.10 for between-group comparison), indicating euhydration based on a criterion (34). Thereafter, participants were moved to a thermoneutral room (~23°C) where they were seated in a semirecumbent position and were instrumented with four microdialysis fibers (MD2000, Bioanalytical Systems, West Lafayette, IN) in the dermal layer of the skin on the dorsal side of the left forearm. This fiber has a semipermeable membrane (30 kDa cutoff, 10 mm), through which pharmacological agents were started through four intradermal microdialysis sites (~20 min after the fiber insertion). The four sites were continuously perfused in a counterbalanced manner with either 1) lactated Ringer (Baxter, Deerfield, IL) (vehicle control), 2) 10 mM ketorolac (Sigma-Aldrich, St. Louis, MO) (nonselective COX inhibitor), 3) 10 mM N^2-nitro-l-arginine methyl ester (Sigma-Aldrich) (nonselective NOS inhibitor), or 4) a combination of both inhibitors (i.e., simultaneous administration of 10 mM ketorolac and 10 mM N^2-nitro-l-arginine methyl ester). The concentrations of ketorolac and N^2-nitro-l-arginine methyl ester were determined from previous studies in which intradermal microdialysis was used in human skin (14, 18, 29).

A microinfusion pump (model 400, CMA Microdialysis, Solna, Sweden) was used to perfuse each drug at a constant rate of 4.0 μL/min for at least 75 min before data collection to ensure sufficient inhibition of COX and NOS. Since this drug infusion was performed in the heat (35°C), the participants were preexposed to a prolonged ambient heat stress before data collection.

After a 75-min drug infusion period, a 10-min baseline resting measurement was continued in the heat (35°C). Thereafter, the participants completed two 30-min bouts of cycling at a fixed rate of metabolic heat production (400 W). A fixed heat load was employed to ensure a similar thermal drive and therefore stimulus for sweating, between individuals (11). This exercise condition was equivalent to a relative exercise intensity of ~45% of the individual’s predetermined peak oxygen uptake (i.e., Control vs. T1DM group: 45 ± 7 vs. 43 ± 6% peak oxygen uptake, P = 0.71). The first and second bouts of exercise were followed by 20- and 40-min recovery periods, respectively. Given that the activation of the sweating response is enhanced in a second exercise bout [i.e., priming effect (12)], a second exercise bout was used to verify that the relative contributions of COX and NOS remained intact. After the second 40-min recovery period, 50 mM sodium nitroprusside (Sigma-Aldrich) was administered at a rate of 6.0 μL/min for 20–30 min to induce endothelium-independent cutaneous vasodilation.

**Measurements.** We employed the ventilated sweat capsule method to measure local forearm sweat rate. Local sweat rate is estimated based on sweat production evaluated under the sweat capsules, which were positioned over the center of each microdialysis membrane and were affixed to the skin with adhesive rings and topical skin glue (Collodion HV, Mavidon Medical Products, Lake Worth, FL). To evaporate all sweat produced under the capsule, dry compressed air from gas tanks located in the thermal chamber was supplied to each capsule at a constant rate. The water content of the effluent air was measured with a capacitance hygrometer (model HMT333, Vaisala, Helsinki, Finland). Local forearm sweat rate was calculated every 5 s using the difference in humidity between influent and effluent air, multiplied by the flow rate, and normalized for the skin surface area under the capsule (mg/m^2·min)^−1.

Cutaneous red blood cell flux, expressed in perfusion units (index of cutaneous blood flow), was locally measured at a sampling rate of 32 Hz with laser-Doppler flowmetry (PeriFlux System 5000, Perimed, Stockholm, Sweden). An integrated laser-Doppler flowmetry probe with a 7-laser array (model 413, Perimed) was placed in the center of each sweat capsule directly over each microdialysis fiber. One trained experimenter measured systolic and diastolic blood pressures through-out the experiment by manual auscultation using a validated mercury column sphygmomanometer (Baumanometer Standby model, WA Baum, Copiague, NY). Blood pressures were obtained twice during the 10-min baseline resting period; thereafter they were measured once every 5 min. Mean arterial pressure was calculated as diastolic arterial pressure plus one-third the difference between systolic and diastolic pressures (i.e., pulse pressure). Cutaneous vascular conductance (CVC) was calculated as cutaneous red blood cell flux divided by mean arterial pressure. CVC data were normalized within each site as percentage of maximum (expressed as %max) using the highest CVC value obtained throughout the experiment. The highest CVC was typically observed during the administration of sodium nitroprusside at the end of the experiment. However, on occasion, the highest CVC was measured during exercise at the vehicle control and COX inhibition sites. Heart rate was recorded every 5 min using a heart rate monitor (RS400, Polar Electro, Kempele, Finland).

Body core temperature was measured using either a thermocouple or a temperature sensor (Braun ThermoScan PRO 6000, Welch Allyn, Skaneateles Falls, NY) in-
sented in the aural canal. Both measurement sites have been shown to track brain temperature similarly (40). Skin temperature was measured using thermocouples (Concept Engineering, Old Saybrook, CT) attached to the skin with adhesive rings and surgical tape. Mean skin temperature was estimated as an unweighted mean value using local skin temperatures measured at four sites (chest, biceps, quadriceps, and calf). Esophageal and skin temperature data were sampled at 15-s intervals (with exception of aural canal temperature that was measured every 5 min) using a data acquisition module (model 34970A; Agilent Technologies Canada, Mississauga, ON, Canada) and simultaneously displayed and recorded in spreadsheet format on a personal computer with LabVIEW software (version 7.0, National Instruments, Austin, TX).

Metabolic rate was determined using indirect calorimetry (MOXUS system, Applied Electrochemistry, Pittsburgh, PA) where expired gas was analyzed for oxygen (error of ± 0.01%) and carbon dioxide (error of ± 0.02%) concentrations. Approximately 20 min before the start of baseline data collection, gas mixtures of known concentrations were used to calibrate gas analyzers and a 3-liter syringe was used to calibrate the turbine ventilometer. The subjects wore full face masks (model 7600 V2; Hans-Rudolph, Kansas City, MO) attached to a two-way T-shape nonrebreathing valve (model 2700, Hans-Rudolph). Oxygen uptake and respiratory exchange ratio were obtained every 30 s and were used to calculate metabolic rate (20, 31). Metabolic heat load was estimated as metabolic rate minus the external work (i.e., work rate during cycling).

For the safety of participants, plasma glucose level in the T1DM group was monitored every 20–30 min using a blood glucose meter (Contour Next, Bayer, Leverkusen, Germany). When necessary, glucose tablets (Dex4, AMG Medical, Dalton, Quebec, Canada) were given to avoid low glucose levels (<5.0 mmol/L).

Data analysis. All data used for data analysis were obtained by averaging values over the last 5 min of each period, with the exception of absolute CVC (perfusion units/mmHg) obtained during sodium nitroprusside administration. Peak values averaged over 2 min. The contribution of NOS to the sweating response during the last 5 min of each exercise bout was evaluated as the difference (Δ) in sweat rate between the vehicle control and NOS inhibition sites. Similarly, the COX contribution and COX + NOS contribution to the sweating response was evaluated as Δ sweat rate between the vehicle control vs. COX inhibition sites and between the vehicle control vs. NOS + COX inhibition sites, respectively. The same evaluation was conducted for CVC to assess NOS and/or COX contribution to cutaneous vasodilation. Absolute CVC obtained during sodium nitroprusside administration did not differ across four sites (see Results). Accordingly, they were averaged for each participant and used for data analysis. Averaging data over four sites minimizes between-site regional variation in the absolute CVC during sodium nitroprusside administration. Because of technical difficulties, mean skin temperature could not be determined for three participants in the T1DM group.

Statistical analysis. Local forearm sweat rate and CVC were analyzed using a three-way mixed-design analysis of variance with factors of treatment site (vehicle control, COX inhibition, NOS inhibition, COX + NOS inhibition), time, and group. Mean skin temperature and cardiovascular variables (blood pressure and heart rate) were analyzed using a two-way mixed-design analysis of variance with factors of time and group. Body core temperature was analyzed using a one-way repeated-measures analysis of variance with a factor of time within each group. As body core temperature measurement differed between some subjects (i.e., esophageal vs. aural canal temperature), to eliminate the potential misinterpretation of results, we elected not to statistically compare body core temperature response between groups. Absolute CVC (expressed in perfusion units/mmHg) attained during sodium nitroprusside infusion was analyzed using a two-way mixed-design analysis of variance with factors of treatment site and group. When a significant main effect or an interaction was observed, post hoc multiple comparison was conducted with Student’s pairwise or nonpairwise t-test. P values for the multiple comparison were adjusted using the modified Bonferroni procedures [i.e., Hochberg procedure (13) or Holm procedure]. Student’s nonpairwise t-test was employed to assess between-group difference where appropriate. The level of significance for all analyses was set at P ≤ 0.05, and all values are reported as means ± 95% confidence interval otherwise indicated.

RESULTS

Sweat rate. Sweat rate during each exercise was attenuated by the separate and combined inhibition of COX and NOS in the Control group (Fig. 1A, all P ≤ 0.05), and the magnitude of reductions were similar for all three treatment sites (Fig. 2A, all P > 0.52). A lower sweat rate with NOS inhibition alone was also observed during each recovery period in the Control group (Table 2). In the T1DM group, COX inhibition resulted in a higher sweat rate relative to the vehicle control site during

![Fig. 1. Sweat rate evaluated at the last 5 min of first (Ex 1) and second (Ex 2; 30-min exercise in individuals with Type 1 diabetes mellitus (T1DM, B) and the nondiabetic control group (Control, A). Sweat rate was evaluated at four skin sites treated with either 1) lactated Ringer (vehicle control site), 2) cyclooxygenase (COX) inhibition, 3) nitric oxide synthase (NOS) inhibition, or 4) COX + NOS inhibition. Data are expressed as means ± 95% confidence interval. *Significantly different vs. vehicle control (P ≤ 0.05). No between-group difference in sweat rate was detected for all values presented (all P > 0.20).](http://ajpregu.physiology.org/)
baseline resting, each exercise bout, and both postexercise recovery periods (Fig. 1B; Table 2, all $P \leq 0.05$). There was no between-group difference in sweat rate at any time point (Fig. 1 and Table 2, all $P > 0.08$). The percent reduction in body weight following the experiment was similar between the Control and T1DM groups ($1.6 \pm 0.2\%$ vs. $1.8 \pm 0.1\%$, $P = 0.33$), inferring that whole body sweating relative to body mass was not different between groups.

**Cutaneous vascular conductance.** NOS inhibition alone and in combination with COX inhibition reduced CVC during each exercise relative to the vehicle control site in both groups (Fig. 3, all $P \leq 0.05$), and the magnitude of reduction did not differ between groups (Fig. 4, all $P > 0.38$). A lower CVC associated with NOS inhibition alone was also observed at baseline rest and during recovery periods (all $P \leq 0.05$) (Table 3). CVC during exercise (Fig. 3) and baseline rest and recovery periods (Table 3) were not different between groups (all $P > 0.14$). CVC during sodium nitroprusside administration (i.e., endothelin-independent vasodilation) was lower in the T1DM versus the Control groups (Fig. 5, $P = 0.02$).

**Cardiovascular and thermal responses.** During exercise, heart rate, mean arterial pressure, and body (core and skin) temperatures were higher relative to baseline rest in both groups (all $P \leq 0.05$) with the exception that no significant increases in mean blood pressure were measured in the Control group (all $P > 0.99$) (Table 4). There was no between-group difference in any cardiovascular and body temperature variables (all $P > 0.11$) albeit a lower mean skin temperature was measured in the participants with T1DM relative to the Control group during and following each exercise cycle (all $P \leq 0.05$) (Table 4).

**Blood glucose.** Blood glucose in the T1DM group at baseline rest was $11.2 \pm 1.8$ mmol/l, which gradually decreased toward the end of second recovery ($8.3 \pm 1.0$ mmol/l).

### DISCUSSION

We are the first to evaluate the relative contributions of COX- and NOS-dependent mechanisms in the regulation of sweating and cutaneous vasodilation in patients with T1DM exercising in the heat. We showed that the separate and combined inhibition of COX and NOS reduced sweat rate similarly during exercise in the heat in healthy young adults. In contrast, individuals with T1DM showed augmented sweating with COX inhibition, whereas inhibition of NOS alone or combined with COX inhibition did not affect sweating. Inhi-

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**Table 2. Sweat rate measured during baseline rest (before exercise) and postexercise recovery periods**

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<tr>
<th></th>
<th>Control group</th>
<th>T1DM group</th>
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<tr>
<td></td>
<td>Sweat Rate, mg·min⁻¹·cm⁻²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline rest</td>
<td>Rec 1 at 20 min</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>0.25 ± 0.06</td>
<td>0.41 ± 0.12</td>
</tr>
<tr>
<td>COX inhibition</td>
<td>0.21 ± 0.08</td>
<td>0.33 ± 0.12‡</td>
</tr>
<tr>
<td>NOS inhibition</td>
<td>0.21 ± 0.05</td>
<td>0.31 ± 0.10*</td>
</tr>
<tr>
<td>COX + NOS inhibition</td>
<td>0.24 ± 0.06</td>
<td>0.36 ± 0.12</td>
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</table>

All values are expressed as means ± 95% confidence interval. Data were obtained by averaging values over the last 5 min at each time period. Rec, recovery; T1DM, Type 1 diabetes mellitus; COX, cyclooxygenase; NOS, nitric oxide synthase. *Significantly different vs. vehicle control ($P \leq 0.05$); †significantly different vs. vehicle control ($P \leq 0.10$). Each value did not differ between groups (all $P > 0.08$).
bition of NOS irrespective of the presence or absence of COX inhibition attenuated cutaneous vasodilation in both groups with no between-group differences observed in the magnitude of reduction. We show that relative to healthy controls, the contribution of NOS in mediating sweating was diminished, whereas NOS contributed similarly to the regulation of cutaneous vasodilation in individuals with T1DM exercising in the heat. We also show that COX inhibition increases exercise sweating in individuals with T1DM.

Sweating response. As we reported previously (8), we showed that both COX and NOS contribute to sweating response (i.e., a contribution of ~20% for both COX and NOS, respectively) during exercise in healthy young adults (Fig. 1A), but these contributions are not additive (Fig. 2A). It is plausible that COX and NOS work in a tandem manner to mediate the sweating response. Indeed, studies show that COX and NOS have an interactive influence that may occur through different pathways (33). A key discovery of our study is our observation that NOS-dependent sweating is diminished in young individuals with T1DM during exercise in the heat compared with young healthy adults (Fig. 1); a response that is interestingly similar to our previous findings in older healthy adults (9, 10, 38). In context of these observations, it appears that young individuals with T1DM demonstrate an aging-like effect on NOS-dependent sweating during exercise in the heat.

In addition to NOS-dependent sweating, our results suggest that T1DM also modulates COX-dependent sweating. Specifically, we showed that COX inhibition resulted in an increase in sweat production during exercise in individuals with T1DM (~10% increase, Fig. 1B); a response contrasting with our observation in healthy controls (Fig. 1A). Thus it appears that COX attenuates sweating in individuals with T1DM. From the fact that the influence of COX inhibition was not detected when NOS was simultaneously inhibited (Fig. 1B), it can be concluded that the COX-mediated suppression of sweating during exercise in the heat likely occurs via the attenuation of...
NOS-dependent sweating. Whereas the mechanisms underpinning this response cannot be fully elucidated from the present findings, it is possible that COX may increase superoxide from COX itself (6) or by activating NADPH oxidase (44). These increases in superoxide can reduce NO bioavailability, as superoxide is known to bind with NO (32).

Although we do not know why COX differentially modulates the sweating response between young adults with and without T1DM, this may be in part associated with lower mean skin temperature in individuals with T1DM (Table 4). This lower mean skin temperature does not seem to be attributed to greater whole body sweating, as percent reduction in body weight occurring during the experiment did not differ between groups (1.6 ± 0.2% vs. 1.8 ± 0.1%, P = 0.33). It is important to note, however, that we only employed a four-point measurement for the estimation of mean skin temperature. As such, it is possible that regional differences in skin temperature may in part explain the slightly lower mean skin temperature (~0.4–0.5°C) response measured in the T1DM group during exercise in the heat. It should be noted that a previous study by Carter et al. (3) showed a comparably lower (~0.3–0.4°C) mean skin temperature response in individuals with T1DM performing a similar intensity exercise, although differences were not significantly different. Future studies should be conducted using more skin measurement sites to reduce the potential influence of regional variations. Finally, further study is warranted to delineate what causes differential influence of COX on sweating during exercise in the heat in young nondiabetic and T1DM individuals.

Noteworthy, we also observed an augmentation of sweating with COX inhibition during baseline resting and both exercise recovery periods in the individuals with T1DM (Table 2). In our healthy Control group, we observed an effect of NOS inhibition on sweating during these same periods (Table 2), a response that parallels exercise (Fig. 1A). Taken together, our findings demonstrate that the effect of COX and/or NOS on sweating can remain intact irrespective of levels of sweat rate (Fig. 1, Table 2) and body temperature (Table 4) that normally occur with the transitions from a resting state to that associated with successive exercise/recovery cycles.

**Cutaneous vascular response.** In keeping with previous reports (24, 26, 27, 41), we showed that NOS contributes to cutaneous vasodilatation during exercise in the heat in healthy young adults (Fig. 3A). However, for the first time, we demonstrated that NOS also contributes to cutaneous vasodilatation during exercise in the heat in individuals with T1DM (Fig. 3B). When comparing the magnitude of the contribution of NOS to cutaneous vasodilatation (as defined by the magnitude of change from the vehicle control site), there was no between-group difference (i.e., a ~30–40% contribution of NOS in both groups, Figs. 3 and 4). These results indicate that T1DM has no effect on NOS-dependent cutaneous vasodilatation during exercise in the heat. Similarly, no effect of T1DM on COX-dependent cutaneous vasodilatation is suggested because COX did not affect cutaneous vasodilatation in the T1DM group (Fig. 3B), a response that is similar to that observed in the Control group (Fig. 3A). Our results are consistent with those responses measured in human forearm artery wherein no influence of T1DM on COX- and/or NOS-dependent vasodilatation was reported (4, 43), though a T1DM-mediated decrease of NOS-dependent vasodilatation (2, 7) or increase of COX-dependent vasodilatation (30) was also reported in some studies. While we showed that T1DM does not modulate COX- and NOS-depen-

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**Table 3. Cutaneous vascular conductance measured during baseline rest (before exercise) and postexercise recovery periods as well as that evaluated during sodium nitroprusside administration**

<table>
<thead>
<tr>
<th>Cutaneous Vascular Conductance, % max</th>
<th>Control group</th>
<th>T1DM group</th>
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<tbody>
<tr>
<td><strong>Vehicle control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline rest</td>
<td>39 ± 9</td>
<td>48 ± 7</td>
</tr>
<tr>
<td>Rec 1 at 20 min</td>
<td>44 ± 9</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>Rec 2 at 20 min</td>
<td>47 ± 11</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>Sodium Nitroprusside Administration</td>
<td></td>
<td>1.52 ± 0.30</td>
</tr>
<tr>
<td>Administration, perfusion units/mmHg</td>
<td></td>
<td>50 ± 8</td>
</tr>
<tr>
<td><strong>COX inhibition</strong></td>
<td>36 ± 11</td>
<td>48 ± 11</td>
</tr>
<tr>
<td><strong>NOS inhibition</strong></td>
<td>21 ± 5*</td>
<td>20 ± 10</td>
</tr>
<tr>
<td><strong>COX + NOS inhibition</strong></td>
<td>29 ± 8**</td>
<td>34 ± 8**</td>
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All values are expressed as means ± 95% confidence interval. Data were obtained by averaging values over the last 5 min at each time period. *Significantly different vs. vehicle control (P ≤ 0.05); †significantly different vs. Control group (P ≤ 0.05); ‡significantly different vs. vehicle control (P ≤ 0.10).

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**Fig. 5. Cutaneous vascular conductance evaluated during sodium nitroprusside administration in individuals with T1DM and the nondiabetic control group (Control).** Cutaneous vascular conductance averaged over four skin sites was used for data analysis to minimize between-site variations. Data are expressed as means ± 95% confidence interval.
gent mechanisms for cutaneous vasodilation (Figs. 3 and 4), it does mediate changes in COX- and NOS-dependent sweating as discussed above (Figs. 1 and 2). Further studies are required to ascertain how this T1DM-mediated response influences the end-organ itself (i.e., sweat glands, cutaneous vessels).

We observed that individuals with T1DM exhibited less cutaneous vasodilation in response to sodium nitroprusside during exposure to the hot ambient conditions (i.e., 35°C) relative to their healthy counterparts (Fig. 5). This finding suggests that endothelium-independent cutaneous vasodilation is impaired in resting individuals with T1DM who are exposed to a heat-stress condition. This result is in accordance with previous reports where sodium nitroprusside was administered iontophoretically under normothermic conditions (17, 22), although one study showed intact endothelium-independent cutaneous vasodilation in T1DM patients with no peripheral neuropathy (42). Previous studies assessing the effect of T1DM on endothelium-independent vasodilation in humans forearm artery show mixed results (1, 2, 7, 16, 23, 37). Irrespective of these disparate findings, it is important to note that despite the fact that the cutaneous vascular response to sodium nitroprusside (NO donor) was impaired in our individuals with T1DM (Fig. 5), NOS-dependent cutaneous vasodilation during exercise was not (Fig. 4). It may be that NO production from NOS in the cutaneous vessels is augmented in individuals with T1DM to compensate for the impaired responsiveness of cutaneous vessels to NO. Further study is warranted to directly delineate this possibility.

During baseline resting and postexercise recovery periods, NOS, but not COX, was shown to play an important role in the regulation of cutaneous blood flow in both groups (Table 3). These responses paralleled those observed during exercise in the heat (Fig. 3). There were no between-group differences in CVC at each of the skin sites (Table 3). Therefore, it appears that T1DM does not modulate mechanisms underpinning cutaneous vascular control during a passive or exercise-induced heat stress.

Considerations. Consistent with our previous work examining thermoregulatory responses in young physically active adults with well-controlled T1DM during exercise in the heat (3, 39), we showed no differences in core temperature between groups (Table 4). This was also paralleled by similar exercise-induced increases in CVC and sweating between groups (Figs. 1 and 3). Taken together, these findings demonstrate T1DM does not impair the body’s ability to dissipate heat in otherwise healthy young individuals with well-controlled T1DM during low-to-moderate intensity exercise (i.e., equivalent workload of <50% peak oxygen uptake). While our findings would seem to contradict reports that indicate that individuals with T1DM have a reduced tolerance to heat (35), it is important to reemphasize that our subjects were young, physically active with well-controlled T1DM and no presence of neuropathy. It may be that impairments in heat loss would manifest in individuals with T1DM with reduced physical fitness or physical inactivity, poor glucose regulation, and/or presence of neuropathy. Indeed, studies show that diabetic patients with poor glucose control and/or peripheral neuropathy may experience a deterioration in thermoregulatory function as evidenced by an attenuation of cutaneous perfusion and sweating during a thermal challenge (21). Moreover, this degree of impairment would likely be worsened in older adults with T1DM, as aging impairs heat loss responses (15, 19).

Noteworthy, we assessed heat loss responses of cutaneous blood flow and sweating in the forearm. Regional variations in heat loss responses have been well documented (20). Recently, Carter et al. (3) showed no differences in sweating between young physically active adults with and without T1DM at low-to-moderate exercise intensities (i.e., ≤50% peak oxygen uptake) and the pattern of response was similar across all three measured skin sites: chest, upper back, and forearm. However, differences were observed at moderate-to-high intensity exercise (i.e., >50% peak oxygen uptake) eliciting higher rates of heat production such that T1DM was associated with a reduced sweating response at the forearm and chest. No differences were observed in the upper back. Furthermore, with respect to cutaneous blood flow, responses in the forearm and upper back were similar across all exercise intensities. As such, it is possible that our results pertaining to the sweating response may have differed had we employed higher exercise intensity.
Perspectives and Significance

Nonsteroidal anti-inflammatory drugs (NSAIDs), which typically block the action of COX, are widely used for several purposes (e.g., analgesic effect). Aspirin, one of the NSAIDs, is widely prescribed to manage and/or prevent cardiovascular events in several populations. Since we show that COX inhibition augmented sweating response in individuals with T1DM during heat stress (Fig. 1B, Table 2), the prescription of aspirin for example may help enhance heat dissipation via an increase in sweat production. This in turn may help prevent dangerous increases in body core temperature in individuals with T1DM whom are known to be at greater risks to heat-related injuries (35). Alternatively, prescription of aspirin may cause increases in sweating, which could increase the risk of hypohydration. Further studies are required to evaluate if prescribing NSAIDs influences the sweating response in individuals with T1DM.

In conclusion, we show that in exercising individuals with T1DM, NOS contribution to sweating is diminished, whereas NOS contributes similarly to the regulation in cutaneous vasodilation relative to young healthy adults. We also show that COX inhibition increases sweating during exercise in the heat in T1DM patients.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

N.F. and G.P.K. conception and design of research; N.F. and S.M.D. performed experiments; N.F. analyzed data; R.J.S., and G.P.K. interpreted results of experiments; N.F. drafted manuscript; N.F. prepared figures; N.F. drafted manuscript; N.F. prepared figures; N.F. performed experiments; N.F. analyzed data; N.F., R.J.S., and G.P.K. interpreted results of experiments; N.F., S.M.D., R.J.S., and G.P.K. edited and revised manuscript; N.F., S.M.D., R.J.S., and G.P.K. approved final version of manuscript.

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