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Cutaneous sympathetic neural responses to body cooling in type 2 diabetes mellitus

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Abstract

In humans, sympathetic vasoconstrictor nerves in the skin contribute to resting vascular tone and mediate reflex vasoconstrictor responses to body cooling. Although it is well recognized that type 2 diabetes mellitus (T2DM) is associated with peripheral neurovascular changes, it is unclear to what extent the thermal responsiveness of the cutaneous vasoconstrictor system is altered in individuals with relatively uncomplicated T2DM. We tested the hypothesis that skin sympathetic nerve activity (SSNA) is decreased at baseline and during body cooling in individuals with T2DM compared to healthy controls (C) of similar age and body size. We measured SSNA (microneurography) and skin blood flow (laser-Doppler flowmetry) in the innervated area in 8 T2DM and 12 C subjects at baseline and during 3–4 minutes of rapid whole body cooling via water-perfused suit. SSNA (total integrated activity) increased, and cutaneous vascular conductance decreased in both groups during body cooling ($P < 0.01$ for both). However, SSNA was not different between groups during either baseline or body cooling conditions ($P = \text{NS}$). The deltas in SSNA between baseline and body cooling were similar between groups: T2DM: 55 ± 27 and C: 57 ± 12 units ($P = \text{NS}$). We conclude that reflex cutaneous sympathetic and vascular responses to rapid whole body cooling are preserved in relatively healthy individuals with T2DM.

Keywords

skin sympathetic nerve activity; thermoregulation; skin blood flow; vasoconstriction

INTRODUCTION

Sympathetic neural control of skin blood flow is key to the maintenance of normal body temperature during changes in environmental exposure and/or body temperature. Cutaneous sympathetic vasoconstrictor nerves control vascular tone at rest, in thermoneutral environments, via release of norepinephrine which binds to alpha adrenergic receptors causing tonic vasoconstriction. During cold exposure, further activation of cutaneous vasoconstrictor nerves increases reflex vasoconstriction via norepinephrine and cotransmitters. This reflex vasoconstriction contributes to the maintenance of body temperature and prevention of hypothermia.

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Individuals with type 2 diabetes mellitus (T2DM) have altered thermoregulatory responses compared to controls of similar age and body size. Epidemiological data suggest that diabetes is associated with an increased risk of heat illness, including heat stroke and heat exhaustion. We have previously shown decreased reflex cutaneous vasodilation during whole body heating in T2DM, which could contribute to an impaired capacity for thermoregulation in the heat. Progressive changes in peripheral nerve function may have a role in this diminished capability for thermoregulation, since cutaneous sympathetic nerves control most of the wide range of reflex (whole-body) changes in skin blood flow that occur during exposure to heat and cold in humans. In this context, it is not known whether decreased cutaneous sympathetic neural and vasoconstrictor responses to body cooling are an aspect of impaired thermoregulation in T2DM.

Our goal in the present study was to quantify cutaneous sympathetic neural and blood flow responses during baseline thermoneutral conditions and during body cooling in individuals with T2DM and control subjects of similar age and body size. We measured skin sympathetic nerve activity (SSNA) at the peroneal nerve via microneurography, and used water-perfused suits to control body temperature. We used laser Doppler measurement of skin blood flow to quantify reflex vasoconstriction in the area innervated by the measured nerve. We tested the hypothesis that SSNA at rest and during body cooling is lower in individuals with T2DM compared to control individuals of similar age and body size, and that this would result in less vasoconstriction in the T2DM group.

METHODS

Subjects

The study group included 8 individuals with T2DM and 12 control subjects of similar age and body size. All subjects were screened via telephone to rule out any co-morbidities that could influence microvascular or thermoregulatory function. Subjects were excluded if they showed signs/symptoms of neuropathy, or had a history of cardiovascular disease. In addition, any subjects taking thiazolidinediones or first-generation sulfonylureas were excluded from participation; other anti-diabetic agents were accepted. Of the 8 women studied, 3 were post-menopausal and none of these was taking hormone replacement therapy.

Subjects reported to the Mayo Clinical Research Unit (CRU) for a screening visit and again on the day of the study. Written informed consent was obtained before any procedures began. The protocol for this experiment was approved by the Institutional Review Board at the Mayo Clinic in Rochester, MN. Any T2DM subjects taking oral anti-diabetic agents were instructed to temporarily withdraw their medication for 2 weeks prior to the study visit. Subjects kept in contact with the nurse study coordinator during those two weeks, and were requested to monitor their reflectance meter glucose values daily at home. If glucose values exceeded 300 mg/dl on more than one occasion during the two week period, they were asked to resume their anti-diabetic medications and were excluded from further participation.

Screening Visit

All subjects had a 12-lead ECG, and fasting blood samples were drawn and analyzed for glucose and hemoglobin A1c. All individuals with T2DM, and all control subjects over 55 years of age, participated in a treadmill exercise test conducted at the Mayo Cardiovascular Health Clinic using a standard Bruce protocol, to identify and exclude subjects with occult cardiovascular disease.

Study Visit

Subjects reported to the CRU at 7:00 AM. Blood glucose was measured in all T2DM subjects before any procedures began. If glucose values exceeded 300 mg/dl on the study day, we did not proceed with the experiment and the subject was instructed to resume his/her medication. Subjects changed into a two piece water-perfused suit that covered their entire body, except the head, hands, and feet. Subjects then rested supine during instrumentation. Heart rate was measured with a three-lead ECG and blood pressure was measured on a beat-to-beat basis using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands) placed on the right middle finger.

SSNA was recorded via microneurography of the peroneal nerve at the lateral aspect of the fibular head as previously described. We used the following established criteria to identify a SSNA signal: a) irregular, spontaneous bursts which were not synchronous with the cardiac cycle; b) afferent activity during stroking of the skin; and c) reflex activation in response to loud/surprising sensory stimuli (such as a sudden loud noise). The recorded signal was amplified 80,000-fold, band-pass filtered (700 to 2000 Hz), rectified and integrated (resistance-capacitance integrator circuit, time constant 0.1 sec) by a nerve-traffic analyzer.

Skin blood flow was measured as cutaneous red blood cell flux using Periflux laser-Doppler flowmetry (LDF) in the area of innervation of the recorded SSNA signal. We identified the area of innervation as the area of skin which elicited afferent activity in the recorded nerve signal when lightly stroked. One integrating LDF probe (Periflux System 5000; Perimed, Stockholm, Sweden) was attached by adhesive to this location. Most often, the location was the dorsal aspect of the foot; however on three occasions this was the medial aspect of the tibial surface of the lower leg. The probe was attached to the skin in a specialized holder that measured and controlled temperature over an area of 12 cm² (Perimed).

Experimental Protocol—A 10-minute baseline was recorded while the subject rested supine. Following baseline measurements, we perfused cool water (10–12 °C) through the water-perfused suit for 3–4 minutes, as we have used previously to assess reflex cutaneous vasoconstriction. We aimed for 4 minutes of cooling in all subjects; however, subjects were asked to report if they felt like they were about to start shivering; if this happened, we stopped the cooling early, usually around 3 minutes. At the end of each experiment, to obtain maximum cutaneous vascular conductance (CVC), local temperature at the LDF site was increased to 42 °C for 35 minutes.

Data Recording and Analysis—LDF, SSNA, ECG and beat-to-beat blood pressure data were collected at 250 Hz using the Windaq data acquisition system (Dataq Instruments, Akron, OH) and stored for offline analysis. LDF was divided by mean arterial pressure to derive an index of CVC. Baseline CVC was assessed as the average of the last 2 min during baseline, and cooling CVC as an average of the last 30 seconds during cooling. Maximal CVC was calculated as the average of the last 2 min during local warming. CVC data are expressed as a percentage of this maximum (%maxCVC) and as absolute units (au/mmHg).

SSNA

SSNA bursts are irregular in shape and do not exhibit a regular relationship to the cardiac cycle. We quantified total activity of SSNA in order to take into account bursts of varying size and shape during baseline and body cooling in both groups. To control for differences in signal quality among subjects, each SSNA signal was calibrated on a scale of 0 – 1000 arbitrary units, where 0 represented no nerve activity and 1000 represented the height of the largest SSNA burst under baseline conditions. A Matlab® algorithm was developed to calculate integrated nerve activity before and during whole body cooling (Matlab, Version

7.6.0.324, The Mathworks, Natick, MA). Each individual subject's data set was divided into two subsets: baseline and cooling. For each subset, the algorithm displayed a plot of the data and solicited the user to select a "quiet" region of nerve activity, the average of which was used as the zero level for integration. Total SSNA for each subset was then calculated as the integral of the recording above the zero level using a trapezoidal numerical integration method.

Statistics

Data are presented as mean $\pm$ SEM. Subject descriptive information was compared between T2DM and control groups using Student's t-test. Skin blood flow (CVC) and SSNA data were compared using analysis of variance with repeated measures on condition (baseline vs. cooling) and independent measures on group (control vs. T2DM). For all comparisons, $P < 0.05$ was accepted as statistically significant.

RESULTS

As shown in Table 1, individuals in the T2DM group were similar when comparing age, height, weight, body mass index (BMI), %body fat and resting heart rate ($P = \text{NS}$ between groups). As expected, individuals with T2DM had higher fasting plasma glucose values and hemoglobin A1c levels ($P < 0.001$).

SSNA increased significantly during body cooling in both groups of subjects (PANOVA < 0.001). As shown in Figure 1, total activity of SSNA was not different between the two groups during the baseline period (T2DM: 94 ± 19 vs. C: 108 ± 11 units; $P = \text{NS}$) or during body cooling (T2DM: 148 ± 35 vs. C: 165 ± 13 units, $P = \text{NS}$). As shown in Figure 2, delta values (between baseline and whole body cooling) were also similar between groups (deltas: T2DM: $+55 \pm 27$ units vs. C: $+56 \pm 12$ units; $P = \text{NS}$). Delta values were also similar between groups when expressed as % change from baseline (T2DM: 68 ± 31 vs. C: 62 ± 16 % of baseline, $P = \text{NS}$). Mean arterial pressure increased significantly in both groups of subjects, consistent with peripheral vasoconstriction (T2DM: 95 ± 3 (baseline) to 100 ± 4 mmHg (cooling), $P < 0.05$; and C: 96 ± 4 (baseline) to 111 ± 3 (cooling), $P < 0.01$). The increase in mean arterial pressure was smaller in the T2DM group (deltas: T2DM: 6 ± 3 vs. C: 14 ± 3 mmHg; $P < 0.05$).

CVC decreased significantly in both groups during whole body cooling, consistent with cold-induced reflex vasoconstriction in the area innervated by the measured nerve. Table 2 shows values for CVC at baseline and during body cooling (expressed both in terms of % of maximal CVC as well as in absolute units) as well as the absolute values for CVC during local warming. CVC was similar between groups in both thermal conditions when expressed as absolute units. When expressed as %maxCVC, CVC was higher at baseline and during cooling in the T2DM group ($P < 0.01$). Although it is more common to express CVC data as % of maximum, we report both expressions of the data since maximal CVC was on average ~24% lower in the T2DM group.

The delta in CVC (from baseline to cooling) was similar between groups, both when expressed as absolute values (T2DM: -0.10 ± 0.04 vs. C: -0.06 ± 0.02 au/mmHg; $P = \text{NS}$) and when expressed as %maxCVC (T2DM: -6 ± 2 vs. C: -3 ± 1 %CVCmax; $P = \text{NS}$).

DISCUSSION

The major novel observation in the present study was that SSNA measured in individuals with relatively uncomplicated T2DM showed similar increases during rapid whole body cooling compared to control subjects of similar age and body size. Skin blood flow

responses, measured in the area innervated by the measured nerve, were consistent with significant reflex vasoconstriction and were not different between groups. Thus our present data suggest that relatively healthy individuals with T2DM have preserved SSNA and cutaneous vascular responses to rapid whole body cooling. Individuals with less well-controlled T2DM or significant comorbid conditions may have very different responses; however, those were not the subject of the present investigation.

Evidence suggests that people with T2DM exhibit impaired thermoregulation when exposed to environmental heat stress. Furthermore, our recent data suggest that, even in relatively healthy T2DM individuals, decreases in reflex and local mechanisms of cutaneous vasodilation could contribute to an impaired ability to dissipate heat during exposure to warm or hot environments. However, it remains unclear whether people with relatively uncomplicated T2DM exhibit impaired cutaneous vasoconstrictor responses to body cooling and, if so, whether sympathetic neural mechanisms contribute to any differences. Our goal in the present study was to provide some initial insight into this question by measuring SSNA and skin blood flow during baseline and rapid body cooling in people with T2DM and healthy controls. Our observation of comparable neural and vasoconstrictor responses in the two groups suggests relatively normal cutaneous neurovascular responses to cooling in our T2DM group.

Our present findings could suggest that the potential for impaired thermoregulation in the heat in T2DM does not extend to cold environments. There are two major caveats to this conclusion: first, our study only evaluated cutaneous sympathetic and vascular responses, and, in humans, shivering is a major component of the thermoregulatory response to cold. Second, we used a rapid cooling protocol because we wanted to reproduce the sudden physiological response to entering a cold environment. By design, this protocol was brief (3–4 minutes), and we stopped cooling before shivering started. This did not allow us to observe responses to more prolonged ramp cooling protocols that have been used in previous studies, as outlined next. Therefore, we are unable to evaluate from our present data whether a slower, more prolonged cooling protocol might show differences between control and T2DM in cutaneous sympathetic neural or vascular responses to whole body cooling.

With regard to mechanisms of reflex cutaneous vasoconstriction during body cooling in humans, several studies have used prolonged ramp cooling protocols (15–45 minutes) in conjunction with pharmacological blockade to identify specific contributors and their roles in the vasoconstrictor response over a range of skin temperatures. In addition to norepinephrine-mediated vasoconstriction, Stephens et al identified a role for noradrenergic cotransmitters in young men, which was subsequently shown to be altered as a function of reproductive hormone status in women and functionally absent in older individuals. It would be of interest in future work to evaluate whether cotransmitter mechanisms of reflex vasoconstriction in the skin are altered in T2DM.

Hemodynamically, the physiological response to whole body cooling involves an increase in arterial blood pressure due to peripheral vasoconstriction. Since skin blood flow is low in normothermia (~250 ml/min), cutaneous vasoconstriction may only contribute minimally to the increase in blood pressure. Wilson et al reported that body cooling was associated with decreases in cutaneous, celiac, superior mesenteric and renal vascular conductances, suggesting that vasoconstriction in visceral vascular beds contributes importantly to the pressor response with body cooling. They observed no changes in cardiac output, stroke volume or heart rate. In the present study, we observed a smaller increase in mean arterial pressure in our T2DM subjects compared to controls during body cooling. Although we observed similar dorsal foot cutaneous vasoconstriction between groups, we can not identify

from the present results whether differences in other (possibly visceral) vasoconstrictor responses might have contributed to the smaller pressor response in the T2DM group.

Methodological considerations

As outlined clearly by Young and colleagues in a recent editorial, there are characteristics of SSNA which make it important to use caution when attempting to draw conclusions regarding the functional significance of between-group comparisons. First, the SSNA signal is made up of four distinct nerve types: vasoconstrictor, vasodilator, sudomotor and pilomotor. In multi-unit recordings such as those used in the present study, it is not possible to differentiate between these nerve types. Second, the size and shape of SSNA bursts is quite variable, unlike muscle SNA bursts which are regular in shape and therefore easier to count. Third, counting SSNA bursts does not take into account bursts of very different size (presumably representing different total amounts of SSNA), or bursts that may overlap and be difficult to distinguish as one or several overlapping bursts. Fourth, quantification of total activity (total area under bursts) is limited by the proximity of the electrode to a given nerve bundle, so a better signal in one individual will result in larger bursts than in another individual with a lower quality nerve signal.

While we recognize the importance of the limitations outlined above, we nonetheless felt it was of interest to investigate potential changes in SSNA responses to body cooling in T2DM. We agree with Young and colleagues that our results should be interpreted with full recognition of their limitations. To minimize these with regard to signal quality, we normalized each individual's nerve signal to the largest burst in that individual (giving that burst a height of 1000 units) to control for differences between and among individuals in signal quality which might contribute to burst size, as previously reported by Cui et al and others. We report normalized total activity of SSNA to avoid the potential confounds noted above associated with counting bursts (i.e., reporting bursts/minute).

Additionally, in neutral and cool environments, the primary type of skin sympathetic nerve activity is vasoconstrictor. SSNA in the present study increased from baseline to body cooling conditions, consistent with physiological responses of sympathetic vasoconstrictor nerves. Furthermore, in the present study, we present skin blood flow (cutaneous vascular conductance) data from the area of innervation of the measured nerve. The CVC data showed vasoconstriction during body cooling, consistent with increases in vasoconstrictor SSNA in the innervated area. Taken together, the data suggest that the majority of the nerve activity we present in this study represents sympathetic vasoconstrictor innervation of the skin. However, we do not rule out the possibility of minor contributions of other nerve types.

In this context, the major physiological stimulus for reflex thermoregulatory vasoconstriction in humans is mean skin temperature, and thus it is a limitation of the present study that we did not directly measure this variable. Since we used water-perfused suits (which cover most of the body surface) and administered the same protocol (i.e., 10 °C water perfused through the suit) in all subjects, it is likely that mean skin temperature responses were similar. However, we cannot say with certainty whether subtle differences in skin temperatures between groups could have been a confounding variable in the present study.

There are also potential statistical limitations to our conclusions regarding a lack of difference between groups in SSNA and skin blood flow responses to body cooling. There were more women in the control group than in the T2DM group (which, despite our best efforts, included only one woman). Any potential sex differences in these responses, or in the effect of T2DM on the responses, could therefore cloud interpretation. Furthermore, our

groups exhibited a much larger inter-individual variability, and a much smaller mean difference between groups, than that which we had anticipated. Thus, an additional ~110 subjects per group would have been required to evaluate the mean difference we observed (~15–18 SSNA units) between groups with 80% power. As with any set of “negative” results involving a large amount of inter-individual variability, we add this note of caution to our conclusions.

In summary, we report here that directly measured SSNA showed similar reflex increases during body cooling in a group of relatively healthy T2DM individuals compared to nondiabetic controls of similar age and body size. Cutaneous vascular conductance measured in the innervated area decreased during body cooling in both groups, showing similar reflex vasoconstriction. Our findings suggest preserved reflex cutaneous sympathetic and vasoconstrictor responsiveness during cold exposure in relatively healthy individuals with T2DM, unlike cutaneous vascular responses to body heating which are decreased in this subject group.

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Figure 1.

Average data for SSNA total activity in control and T2DM subjects at baseline and during body cooling. There was a significant increase in SSNA in both groups during body cooling, consistent with a reflex increase in vasoconstrictor innervation of the skin. On average, there were no differences between groups in either condition. * $P < 0.001$, baseline vs. body cooling

Figure 2. Average delta SSNA (change in total activity between baseline and body cooling conditions) for control and T2DM groups. There was no difference between the groups in this delta value.

Table 1 Baseline characteristics of control and T2DM subjects (mean $\pm$ SEM)

	<u>Control</u>	<u>T2DM</u>	<u>P value</u>
N	12 (7 F)	8 (1 F)	
Age (year)	51 $\pm$ 3	55 $\pm$ 2	NS
Height (m)	1.69 $\pm$ 0.05	1.75 $\pm$ 0.01	NS
Weight (kg)	75 $\pm$ 6	82 $\pm$ 2	NS
BMI (kg/m²)	25.8 $\pm$ 1.2	26.8 $\pm$ 0.6	NS
% fat	36.6 $\pm$ 3.2	31.7 $\pm$ 1.9	NS
Heart rate (b/min)	64 $\pm$ 1	66 $\pm$ 2	NS
Fasting glucose (mg/dl)	93 $\pm$ 3	135 $\pm$ 9	< 0.001
HbA1c (%)	5.5 $\pm$ 0.1	6.7 $\pm$ 0.3	< 0.001

Table 2

Average cutaneous vascular conductance (CVC) values at baseline and during body cooling in the two groups.

	<u>Control</u>	<u>T2DM</u>
<u>Baseline</u>		
Absolute CVC (au/mmHg)	0.32 ± 0.06	0.43 ± 0.09
%maxCVC	17 ± 2	26 ± 4
<u>Whole body cooling</u>		
Absolute CVC (au/mmHg)	0.26 ± 0.05 [*]	0.33 ± 0.06 [*]
%maxCVC	14 ± 2 [*]	20 ± 3 [*]
<u>Local warming</u>		
Absolute CVC (au/mmHg)	1.91 ± 0.18	1.46 ± 0.23 [†]

* P < 0.05 vs. baseline

[†] P = 0.06 vs. control group