Elevation in blood flow and shear rate prevents hyperglycemia-induced endothelial dysfunction in healthy subjects and those with type 2 diabetes

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Greyling A, Schreuder TH, Landman T, Draijer R, Verheggen RJ, Hopman MT, Thijsen DH. Elevation in blood flow and shear rate prevents hyperglycemia-induced endothelial dysfunction in healthy subjects and those with type 2 diabetes. J Appl Physiol 118: 579–585, 2015. First published January 15, 2015; doi:10.1152/japplphysiol.00936.2014.—Hyperglycemia, commonly present after a meal, causes transient impairment in endothelial function. We examined whether increases in blood flow (BF) protect against the hyperglycemia-mediated decrease in endothelial function in healthy subjects and patients with type 2 diabetes mellitus (T2DM). Ten healthy subjects and 10 age- and sex-matched patients with T2DM underwent simultaneous bilateral assessment of brachial artery endothelial function by means of flow-mediated dilation (FMD) using high-resolution echo-Doppler. FMD was examined before and 60, 120, and 150 min after a 75-g oral glucose challenge. We unilaterally manipulated BF by heating one arm between minute 30 and minute 60. Oral glucose administration caused a statistically significant, transient increase in blood glucose in both groups (P < 0.001). Forearm skin temperature, brachial artery BF, and shear rate significantly increased in the heated arm (P < 0.001), and to a greater extent compared with the nonheated arm in both groups (interaction effect P < 0.001). The glucose load caused a transient decrease in FMD% (P < 0.05), whereas heating significantly prevented the decline (interaction effect P < 0.01). Also, when correcting for changes in diameter and shear rate, we found that the hyperglycemia-induced decrease in FMD can be prevented by local heating (P < 0.05). These effects on FMD were observed in both groups. Our data indicate that nonmetabolically driven elevation in BF and shear rate can similarly prevent the hyperglycemia-induced decline in conduit artery endothelial function in healthy volunteers and in patients with type 2 diabetes. Additional research is warranted to confirm that other interventions that increase BF and shear rate equally protect the endothelium when challenged by hyperglycemia.

METHODS

Elevation in blood flow and shear rate prevents hyperglycemia-induced endothelial dysfunction in healthy subjects and those with type 2 diabetes

Participants

Ten male subjects with T2DM (age 63 ± 6 yr) and 10 age-matched healthy male controls (57 ± 9 yr) were included in our study. Individuals were excluded if they smoked, or had past or present cardiovascular disease, hypercholesterolemia, or hypertension (>160 mmHg systolic and/or >90 mmHg diastolic blood pressure). The subjects in the T2DM group had to be diagnosed with T2DM at least 2 yr ago. Subjects in this group were excluded if they had vascular complications due to T2DM (e.g., diabetic foot ulcer). All participants provided written informed consent before participation. The study procedures were approved by the medical ethics committee of the Arnhem-Nijmegen region of The Netherlands and adhered to the
measurements were performed following a simultaneous assessment of brachial artery FMD was repeated at 60, 120, and 150 min after heating. A 10-MHz multifrequency linear array handheld probe, attached to a high-resolution ultrasound machine (T3000; Terson, Burlington, MA), was then used to image the brachial artery in the distal one-third of the upper arm. When an optimal image was obtained, the probe was held stable and the ultrasound parameters were set to optimize the longitudinal, B-mode image of the lumen-arterial wall interface. Settings were identical between all assessments of the FMD. Continuous Doppler velocity assessments were also obtained using the ultrasound and were collected using the lowest possible insonation angle (always <60°). Baseline images were recorded for 1 min after which the forearm cuff was inflated (>200 mmHg) for 5 min. Diameter and flow recordings resumed 30 s prior to cuff deflation and continued for 3 min thereafter, in accordance with recent technical specifications (47).

Forearm skin temperature. During the complete protocol, forearm skin temperature of both forearms was measured using iButtons (Maxim Integrated, San Jose, CA). These data were transferred to a computer and analyzed afterward. Furthermore, forearm skin temperature was also measured manually using a standard auriicle thermometer before every FMD and every 5 min during the heating process so that the researcher had a direct indication of the heating progress.

Venous blood. In all individuals, a routine hematocrit was checked by performing standard methods before testing. A venous blood sample was taken at baseline for assessment of fasting blood lipids, glucose, and insulin levels. The subjects’ degree of insulin resistance was assessed by calculating the homeostasis model assessment of insulin resistance (HOMA-IR) index from fasting glucose and insulin levels. Furthermore, venous blood was repeatedly drawn to assess blood glucose levels at 60, 120, and 150 min after glucose ingestion.

Brachial Artery Diameter and Blood Flow Analysis

Analysis of brachial artery diameter was performed using custom-designed edge-detection and wall-tracking software, which is independent of investigator bias. Previous papers contain detailed descriptions of our analysis approach (47). From synchronized diameter and velocity data, blood flow (the product of arterial lumen cross-sectional area and Doppler velocity) were calculated at 30 Hz. Pulse rate (an estimate of shear stress without viscosity) was calculated as 4 × mean blood velocity/vessel diameter. Reproducibility of diameter measurements using this semiautomated software is significantly better than manual methods and significantly reduces observer error (47).

Baseline diameter and shear rate were calculated as the mean of data acquired across the 1 min preceding the cuff inflation period. Following cuff deflation, peak diameter following cuff deflation was automatically detected according to an algorithm that identified the maximum bracket of data subsequent to performance of a moving window smoothing function. This smoothing routine calculates the median value from 100 consecutive samples before the window shifts to the next bracket of data.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls*</th>
<th>T2DM*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 9</td>
<td>63 ± 6</td>
<td>0.14</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178 ± 6</td>
<td>176 ± 7</td>
<td>0.43</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85 ± 10</td>
<td>90 ± 13</td>
<td>0.85</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>26.7 ± 3.6</td>
<td>29.0 ± 3.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>132.4 ± 14</td>
<td>138.2 ± 17.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>79.0 ± 6.2</td>
<td>79.9 ± 6.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Total cholesterol, mmol/liter</td>
<td>6.2 ± 1.1</td>
<td>4.7 ± 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High-density lipoproteins, mmol/liter</td>
<td>1.5 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Low-density lipoproteins, mmol/liter</td>
<td>4.0 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/liter</td>
<td>1.9 ± 0.9</td>
<td>2.0 ± 0.8</td>
<td>0.85</td>
</tr>
<tr>
<td>Insulin, mmol/liter‡</td>
<td>6.0 ± 6.1</td>
<td>10.3 ± 5.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Glucose, mmol/liter</td>
<td>4.9 ± 0.5</td>
<td>7.1 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR‡</td>
<td>1.4 ± 1.6</td>
<td>3.3 ± 1.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

T2DM, type 2 diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance. *Values are means ± SD; n = 10 per group. †Calculated via unpaired Student’s t-test. ‡One erroneous measurement from the control group was excluded.

Declaration of Helsinki (2000). This study is registered at the Netherlands Trial Registry as NTR4631.

Experimental Design

In this study, both groups reported to our laboratory once for assessment of glucose homeostasis and brachial artery endothelial function. First, we performed simultaneous, bilateral assessment of brachial artery FMD, immediately followed by the ingestion of 75 g of glucose dissolved in 200 ml of water. Thirty minutes after ingestion, we unilaterally heated one forearm for 30 min. Heating of the arm was randomized between subjects. Subsequently, bilateral simultaneous assessment of brachial artery FMD was repeated at 60, 120, and 150 min after ingestion of the glucose load.

Experimental Measures

Ultrasound assessments were performed in a quiet, temperature-controlled room (22°C). Measurements of a single arm were always performed by the same sonographer for each individual subject. All measurements were performed following a ≥6 h fast, ≥18 h abstinence from coffee (and other products containing caffeine, including energy drinks), alcohol, vitamin supplements, products with high levels of vitamin C, polyphenol-rich foods, and at least 24 h after strenuous physical activity. All glucose-lowering and vasoactive medications were also withheld on the morning of the measurement (40). We performed all tests between 8:00 A.M. and 4:00 P.M. to control for variation in FMD between subjects (4, 14, 15, 38).

Brachial artery FMD. Measurements were performed by two well-experienced sonographers following a resting period of at least 20 min in the supine position. We simultaneously measured FMD in the right and left brachial arteries according to recent guidelines for assessment of FMD as previously described by Thijssen et al. (40). For this purpose, both arms were extended and positioned at an angle of ~80° from the torso. A rapid inflation and deflation pneumatic cuff (D.E. Hokanson, Bellevue, WA) was positioned on the forearm immediately distal to the olecranon process to provide a stimulus to forearm ischemia. A 10-MHz multifrequency linear array handheld probe, attached to a high-resolution ultrasound machine (T3000; Terson, Burlington, MA), was then used to image the brachial artery in the distal one-third of the upper arm. When an optimal image was obtained, the probe was held stable and the ultrasound parameters were set to optimize the longitudinal, B-mode image of the lumen-arterial wall interface. Settings were identical between all assessments of the FMD. Continuous Doppler velocity assessments were also obtained using the ultrasound and were collected using the lowest possible insonation angle (always <60°). Baseline images were recorded for 1 min after which the forearm cuff was inflated (>200 mmHg) for 5 min. Diameter and flow recordings resumed 30 s prior to cuff deflation and continued for 3 min thereafter, in accordance with recent technical specifications (47).

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Baseline diameter and shear rate were calculated as the mean of data acquired across the 1 min preceding the cuff inflation period. Following cuff deflation, peak diameter following cuff deflation was automatically detected according to an algorithm that identified the maximum bracket of data subsequent to performance of a moving window smoothing function. This smoothing routine calculates the median value from 100 consecutive samples before the window shifts to the next bracket of data.

Fig. 1. Blood glucose levels before (0) and after (60, 120, and 150 min) administration of 75 g of oral glucose in patients with type 2 diabetes (T2DM, n = 10, ●) and healthy, age-matched controls (n = 10, ○). P values refer to a two-way ANOVA with group (diabetic vs. control) and time (0, 60, 120, and 150 min) as fixed effects and subject as random effect. Data are presented as LSmeans ± SE corrected for baseline. *Post hoc significantly different from baseline at P < 0.05. †Post hoc significantly different from control group at P < 0.05.

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that shares 20% overlap with the preceding bracket. The maximum value of all the calculated median values is then automatically detected and chosen to represent the peak of the diameter curve.

FMD was calculated as the percentage rise of this peak diameter from the preceding baseline diameter. Calculation of FMD was therefore observer-independent and based on standardized algorithms applied to data that had undergone automated edge-detection and wall-tracking. The postdeflation shear rate data, derived from simultaneously acquired velocity and diameter measures at 30 Hz, were used to calculate the area under the shear rate curve (SRAU(C)) for data up to the point of maximal postdeflation diameter (FMD) for each individual. In addition, we calculated the peak blood flow across a 10-s period after cuff release. Reproducibility of the brachial artery FMD using this semiautomated software possesses a CV of 6.7–10.5%.

**Statistical Analysis**

Statistical analyses were performed using SPSS 21.0 software (SPSS, Chicago, IL). Descriptive statistics are presented as means and standard deviation (SD). All data are reported as LSmeans (95%CI) unless reported otherwise and were considered statistically significant at \( P < 0.05 \). Baseline differences between both arms were examined using a paired Student’s \( t \)-test. A two-way repeated-measures ANOVA was used to assess difference in blood glucose levels after intervention (both time effect, \( P < 0.001 \), Fig. 1). The increase in blood glucose was significantly larger in patients with T2DM compared with controls (time*group interaction effect \( P = 0.002 \), Fig. 1). Forearm skin temperature significantly increased in the heated arm during the experiment (time effect \( P < 0.001 \), Table 2) and to a greater extent compared with the nonheated arm (time*arm interaction effect \( P < 0.001 \)). Patients with T2DM and controls demonstrated a comparable change in skin temperature across time in both arms (time*arm*group interaction effect \( P = 0.09 \)).

In both groups, ingestion of 75 g of glucose resulted in a significant increase in blood glucose levels at 60 min, which returned toward baseline levels within 150 min (time effect \( P < 0.001 \), Fig. 1). The increase in blood glucose was significantly larger in patients with T2DM compared with controls (time*group interaction effect \( P = 0.002 \), Fig. 1). Forearm skin temperature significantly increased in the heated arm during the experiment (time effect \( P < 0.001 \), Table 2) and to a greater extent compared with the nonheated arm (time*arm interaction effect \( P < 0.001 \)). Patients with T2DM and controls demonstrated a comparable change in blood flow and shear rate across time in both arms (time*arm*group interaction effect \( P = 0.15 \) and 0.25, respectively). In both groups, post hoc analyses indicated a significant increase in blood flow and shear rate at 60 min in the heated arm, which returned to baseline within 150 min. The increase in blood flow and shear rate at 60 min was significantly greater in controls compared with the patients with T2DM (both \( P < 0.05 \)). Baseline brachial artery diameter did not change during the experiment and differed neither between arms nor between healthy controls and patients with T2DM (Table 2).

**Effect of Hyperglycemia and Heating On Blood Flow, Diameter, and Glucose**

In both groups, ingestion of 75 g of glucose resulted in a significant increase in blood glucose levels at 60 min, which returned toward baseline levels within 150 min (time effect \( P < 0.001 \), Fig. 1). The increase in blood glucose was significantly larger in patients with T2DM compared with controls (time*group interaction effect \( P = 0.002 \), Fig. 1). Forearm skin temperature significantly increased in the heated arm during the experiment (time effect \( P < 0.001 \), Table 2) and to a greater extent compared with the nonheated arm (time*arm interaction effect \( P < 0.001 \)). Patients with T2DM and controls demonstrated a comparable change in skin temperature across time in both arms (time*arm*group interaction effect \( P = 0.09 \)).

Similar to skin temperature, brachial artery blood flow and shear rate significantly increased in the heated arm during the experiment (both time effect \( P < 0.001 \); Fig. 2, A and B) and to a greater extent compared with the nonheated arm (both time*arm interaction effect \( P < 0.001 \). Patients with T2DM and controls demonstrated a comparable change in blood flow and shear rate across time in both arms (time*arm*group interaction effect \( P = 0.15 \) and 0.25, respectively). In both groups, post hoc analyses indicated a significant increase in blood flow and shear rate at 60 min in the heated arm, which returned to baseline within 150 min. The increase in blood flow and shear rate at 60 min was significantly greater in controls compared with the patients with T2DM (both \( P < 0.05 \)). Baseline brachial artery diameter did not change during the experiment and differed neither between arms nor between healthy controls and patients with T2DM (Table 2).

**Effect of Hyperglycemia and Heating On Brachial Artery FMD**

A significant time*arm-interaction was found (\( P = 0.01 \)). Post hoc analyses indicated that hyperglycemia induced a significant decrease in FMD in the nonheated arm of 1.4% at 10.5%.

**RESULTS**

Baseline characteristics are described in Table 1. Patients with T2DM had significantly higher glucose and HOMA-IR indices compared with controls, whereas the control group had significantly higher total and LDL cholesterol concentrations.

**Table 2. Brachial artery diameter and skin temperature before (0) and 60, 120, and 150 min after administration of 75 g of oral glucose load in the nonheated control arm and the heated arm**

<table>
<thead>
<tr>
<th>Time</th>
<th>Baseline diameter, mm</th>
<th>Linear Mixed Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Heated Controls</td>
<td>4.3 (4.2; 4.5)</td>
<td>4.6 (4.4; 4.7)</td>
</tr>
<tr>
<td>Nonheated Controls</td>
<td>4.3 (4.2; 4.5)</td>
<td>4.5 (4.3; 4.6)</td>
</tr>
<tr>
<td>T2DM Heated</td>
<td>4.3 (4.2; 4.5)</td>
<td>4.3 (4.2; 4.5)</td>
</tr>
<tr>
<td>Nonheated T2DM</td>
<td>4.4 (4.2; 4.5)</td>
<td>4.4 (4.2; 4.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>Controls</th>
<th>Linear Mixed Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heated Controls</td>
<td>31.8 (31.0; 32.5)</td>
<td>31.3 (31.0; 32.5)</td>
</tr>
<tr>
<td>Nonheated Controls</td>
<td>31.6 (30.9; 32.4)</td>
<td>31.2 (30.9; 32.4)</td>
</tr>
<tr>
<td>T2DM Heated</td>
<td>31.9 (31.2; 32.6)</td>
<td>31.9 (31.2; 32.6)</td>
</tr>
<tr>
<td>Nonheated T2DM</td>
<td>31.8 (31.1; 32.5)</td>
<td>31.8 (31.1; 32.5)</td>
</tr>
</tbody>
</table>

Data are presented as LSmeans (95% CI) corrected for baseline (time = 0). *Post hoc significantly different from baseline at \( P < 0.05 \) (paired \( t \)-test). †Post hoc significantly different from nonheated arm at \( P < 0.05 \) (unpaired \( t \)-test).
In contrast, the heated arm demonstrated an increase in FMD of 1.5% and 1.3% at 60 and 150 min, respectively, despite the presence of hyperglycemia (P < 0.05). The difference in FMD between the heated and nonheated arms was statistically significant at 60, 120, and 150 min (P < 0.05, Fig. 3). When comparing the responses between controls and patients with T2DM, we found no time*arm*group interaction effect (Fig. 3). These outcomes were reinforced when we repeated our analyses using the absolute (millimeters) or allometrically scaled FMD (Table 3). No changes across time or differences between arms or groups were evident for baseline diameter (Table 2) or shear rate area-under-the-curve (Table 3).

**DISCUSSION**

The aim of this study was to examine whether nonmetabolically driven increases in blood flow and shear rate (through heating of the skin) protects against the hyperglycemia-mediated decrease in endothelial function in healthy subjects and patients with T2DM. For this purpose, we performed bilateral assessment of brachial artery endothelial function, which enabled us to simultaneously study the effects of both a systemic challenge (i.e., hyperglycemia) and a local intervention (i.e., increased blood flow through unilateral heating). This provides a number of observations. First, we confirmed previous observations (1, 16, 17, 33, 43, 46) that hyperglycemia, induced by a 75 g glucose load, leads to a transient decline in brachial artery endothelial function. Second, local heating of a forearm leads to a marked increase in blood flow and shear rate, which effectively prevented the hyperglycemia-induced decline in brachial artery endothelial function. Third, the ability of increases in blood flow and shear rate to prevent brachial artery endothelial dysfunction after hyperglycemia is similarly present in healthy middle-aged controls and patients with T2DM. Taken together, these data suggest that elevation in blood flow or shear rate can prevent the hyperglycemia-induced decline in conduit artery endothelial function that typically occurs after a meal.

Hyperglycemia may affect endothelial function via different pathways. Nitric oxide (NO) bioavailability is decreased through inhibition of endothelial NO synthase (eNOS) and increased production of reactive oxygen species. Moreover, hyperglycemia may increase production of vasoconstrictor prostanoids such as prostaglandin H₂ and thromboxane A₂ (3, 36). Transient damage to the endothelial glyocalyx may also occur. This luminal surface layer serves as a mechanosensor of shear stress to mediate shear-induced release of NO (17, 29). Consequently, a decline in (partly NO-mediated) endothelial function is observed after a meal or glucose load in healthy volunteers (1, 26, 43), with some suggestion of an exaggerated impairment in patients with T2DM (6, 16).

Mechanistic research from Hambrecht and coworkers revealed that increases in shear stress, for example through exercise (11), can improve NO-mediated vasodilator function, increases eNOS expression, and endothelial content of phospho-eNOSSer1177, Akt, and phospho-Akt. Other mechanistic research has demonstrated that elevation in shear also downregulates expression of vasoconstrictors, adhesion molecules,
and coagulation factors (12). On the basis of this mechanistic research, we hypothesized that elevation in shear may attenuate or prevent the hyperglycemia-induced decrease in FMD. After successfully increasing blood flow and shear rate in the heated arm, we confirmed our hypothesis that FMD in the heated arm showed no decrease. In fact, a significant increase was observed, which may be explained by the marked increases in blood flow during the heating intervention. Previous studies also found that (local) heating can acutely and chronically increase brachial artery FMD% (27, 42). In addition to the effects of shear rate, sympathetic and sensory nerve activity play a major role in vasodilatory responses to local heat in the skin (7, 13). We cannot exclude that these responses in the skin could also have affected our observations in the brachial artery. Taken together, our observations suggest that local heat-induced increases in shear stress protect the endothelial function under hyperglycemic conditions.

Our study also allowed a comparison between healthy volunteers and patients with T2DM. The significantly larger increase in blood glucose levels after administration of 75 g of glucose fits with the presence of insulin resistance in patients with diabetes. Despite a substantially larger increase in glucose blood in the patients with T2DM, the attenuation in FMD in the nonheated arm was similar to that in the healthy controls. We also found no correlation between changes in blood glucose and FMD (data not shown), which is in agreement with two earlier studies in healthy subjects (1, 43). Kawano et al. did, however, report a significant negative correlation between plasma glucose and FMD, which may be due to the larger sample size and the inclusion of patients with T2DM who had been untreated (16).

Additionally, heating resulted in comparable increases in FMD between the two groups. Therefore, our results suggest that the ability of increases in shear to prevent hyperglycemia-induced endothelial dysfunction is similarly present in patients with T2DM and healthy, age-matched controls. It is, however, interesting to note that the change in blood flow in response to heating was less pronounced in our group of patients with diabetes compared with the healthy controls. This could indicate that decreased reactivity of resistance vessels and skin microcirculation is already present in patients with T2DM before overt changes in conduit artery endothelial function occur. This observation however, should be interpreted with caution because a statistically significant group effect was not evident in our main analysis. A subsequent subgroup analysis on data from the heated arm did, however, indicate a significant time*group interaction at time = 60 min for both blood flow and shear rate (P = 0.05 and 0.03, respectively, data not shown). This finding is also supported by data from other groups of researchers who have demonstrated that people with diabetes have impaired skin blood flow responses to both local (30, 31) and whole body heating (37). Moreover, impaired muscle blood flow responses to exercise stimuli in people with diabetes compared with healthy controls have also been demonstrated in a number of studies (5, 18, 21).

An unexpected finding in our study is that control subjects and patients with T2DM reveal no difference in baseline brachial artery FMD. Although it is generally accepted that patients with T2DM demonstrate lower FMD compared with healthy peers (24, 25), this is not a universal finding (34, 35). One potential explanation for our finding is that patients with T2DM received optimal pharmacological therapy, including statins (60%) and metformin (80%). These drugs are associated with improvements in brachial artery FMD (32, 49) and may, therefore, contribute to the lack of difference in FMD between groups, despite all medication being withheld on the morning of the measurement. Nonetheless, it is important to emphasize

<table>
<thead>
<tr>
<th>FMD, mm</th>
<th>Time</th>
<th>Controls</th>
<th>Nonheated</th>
<th>Heated</th>
<th>T2DM</th>
<th>Nonheated</th>
<th>Heated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.20 (0.14; 0.25)</td>
<td>0.19 (0.14; 0.25)</td>
<td>0.25 (0.20; 0.31)*</td>
<td>0.18 (0.12; 0.24)</td>
<td>0.22 (0.16; 0.28)</td>
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<td>0.26 (0.20; 0.31)</td>
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<td>60</td>
<td>0.24 (0.18; 0.30)</td>
<td>0.16 (0.10; 0.22)</td>
<td>0.26 (0.20; 0.32)*</td>
<td>0.26 (0.20; 0.31)</td>
<td>0.15 (0.09; 0.21)*</td>
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<td>120</td>
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<td>0.16 (0.10; 0.22)</td>
<td>0.23 (0.17; 0.29)</td>
<td>0.26 (0.20; 0.31)</td>
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<table>
<thead>
<tr>
<th>Scaled FMD, %</th>
<th>Time</th>
<th>Controls</th>
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<th>Heated</th>
<th>T2DM</th>
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<tr>
<td>0</td>
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<td>3.9 (2.6; 5.3)</td>
<td>5.4 (4.0; 6.7)*</td>
<td>4.3 (2.9; 5.7)</td>
<td>4.1 (2.8; 5.4)</td>
<td>4.0 (2.6; 5.3)</td>
<td>5.1 (3.8; 6.4)</td>
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<tr>
<td>120</td>
<td>5.4 (4.0; 6.7)</td>
<td>3.9 (2.6; 5.3)</td>
<td>6.1 (4.8; 7.4)*</td>
<td>5.5 (4.1; 6.8)</td>
<td>4.3 (2.9; 5.7)</td>
<td>4.0 (2.6; 5.3)</td>
<td>5.6 (4.3; 6.9)*</td>
</tr>
<tr>
<td>150</td>
<td>27.7 (22.6; 32.9)</td>
<td>25.8 (20.7; 30.9)</td>
<td>30.0 (24.9; 35.1)</td>
<td>26.3 (21.1; 31.4)</td>
<td>27.7 (22.6; 32.8)</td>
<td>26.3 (21.1; 31.4)</td>
<td>27.7 (22.6; 32.8)</td>
</tr>
</tbody>
</table>

Table 3. Brachial artery flow-mediated dilation before (0) and after (60, 120, and 150 min) administration of 75 g of oral glucose in the nonheated control arm and the heated arm

FMD, flow-mediated dilation; SRAUC, shear rate area under the curve. Data are presented as LSmeans (95% CI) corrected for baseline (time = 0). *Post hoc significantly different from baseline at P < 0.05 (paired t-test). †Post hoc significantly different from nonheated arm at P < 0.05 (unpaired t-test).
that both groups demonstrated distinct responses to the heat stimulus.

Limitations

A potential limitation of our study is that we did not examine endothelium-independent vasodilation. Due to the prolonged effects of glyceryl trinitrate (unpublished data), including repeated measurements of endothelium-independent dilation would have importantly compromised our study design and outcomes. However, previous studies have found no indication that acute heating or hyperglycemia directly affect vascular smooth muscle cell reactivity (16, 19, 27, 46). Our study setup did not allow us to explore specific mechanisms such as the evaluation of NO metabolites to better understand the underlying mechanisms of our findings. Another potential limitation relates to our method of heating. We employed a simple setup involving directed hot air. This inadvertently caused a small increase in ambient and skin temperature of the control arm (Table 2). As a result, small (nonsignificant) increases in blood flow and shear rate were evident in the nonheated arm (Fig. 2). Therefore, although a reduction in FMD was still evident in the nonheated arm, it may have been attenuated to a small extent.

Clinical Relevance

A potential clinical relevance of our findings relates to the suggestion that (repeated) exposure to transient periods of endothelial dysfunction contributes to the development of atherosclerosis. Although this is speculative, prevention or attenuation of endothelial dysfunction during hyperglycemia seems to be a potential target. Our observations suggest that nonmetabolically driven elevations in shear may be of use to prevent the presence to endothelial dysfunction. Similarly, exercise (particularly high-intensity exercise) is demonstrated to prevent the postprandial decrease in endothelial function (45). Because exercise is a strong stimulus for elevation in blood flow (41), our observations warrant future studies to explore whether the immediate benefits of physical activity or exercise to prevent postprandial endothelial dysfunction relate to shear-stress-mediated mechanisms and may contribute to preservation of endothelial function in patients with diabetes.

In conclusion, postprandial hyperglycemia resulted in a transient impairment in brachial artery FMD in healthy subjects and those with T2DM, whereas a heating-induced increase in brachial artery blood flow and shear rate countered the impairment in FMD. Therefore, our data suggest that interventions that are aimed at elevating blood flow or shear rate can prevent the hyperglycemia-induced decline in conduit artery endothelial function that typically occurs after a meal.

GRANTS

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES


