Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients

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1Faculty of Physical Education, University of Brasília, DF, Brazil; 2Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri; 3Dalton Cardiovascular Research Center, University of Missouri, Columbia, Missouri; and 4Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, Nebraska

Submitted 20 May 2014; accepted in final form 15 January 2015

Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. Am J Physiol Heart Circ Physiol 308: H681–H687, 2015. First published January 16, 2015; doi:10.1152/ajpheart.00343.2014.—Type 2 diabetes mellitus patients (T2D) have elevated risk of stroke, suggesting that cerebrovascular function is impaired. Herein, we examined dynamic cerebral autoregulation (CA) at rest and during exercise in T2D patients and determined whether underlying systemic oxidative stress is associated with impairments in CA. Middle cerebral artery blood velocity and arterial blood pressure (BP) were measured at rest and during 2-min bouts of low- and high-intensity isometric handgrip performed at 20% and 40% maximum voluntary contraction, respectively, in seven normotensive and eight hypertensive T2D patients and eight healthy controls. Dynamic CA was estimated using the rate of regulation (RoR). Total reactive oxygen species (ROS) and superoxide levels were measured at rest. There were no differences in RoR at rest or during exercise between normotensive and hypertensive T2D patients. However, when compared with controls, T2D patients exhibited lower RoR at rest and during low-intensity handgrip indicating impaired dynamic CA. Moreover, the RoR was further reduced by 29 ± 4% during high-intensity handgrip in T2D patients (P = 0.012/s rest vs. 0.220 ± 0.014/s high intensity; P < 0.01), although well maintained in controls. T2D patients demonstrated greater baseline total ROS and superoxide compared with controls, both of which were negatively related to RoR during handgrip (e.g., total ROS: r = 0.71, P < 0.05; 40% maximum voluntary contraction). Collectively, these data demonstrate impaired dynamic CA at rest and during isometric handgrip in T2D patients, which may be, in part, related to greater underlying systemic oxidative stress. Additionally, dynamic CA is blunted further with high intensity isometric contractions potentially placing T2D patients at greater risk for cerebral events during such activities.

Voxel-based analysis showed that patients with T2D had greater cerebral blood flow reductions in the left parietal, right precuneus, and right parietal regions compared with controls during high-intensity activity. Thus, the present study supports the notion that impaired dynamic CA in T2D patients may be due, at least in part, to greater underlying systemic oxidative stress. Isometric exercise presents a challenge to CA, not only due to rapid and robust elevations in BP but also due to increases in sympathetic nerve activity (10) and cerebral metabolism (43, 52, 54). However, it is unknown how T2D influences the regulation of cerebral blood flow during exercise. This is important considering T2D-related impairments in peripheral vascular control have been reported at rest (32) and during exercise (46). Indeed, exaggerated sympathetic vasoconstritor tone and blunted vasodilator responsiveness have been demonstrated in exercising skeletal muscle of T2D patients (15, 25, 46, 47). Whether these peripheral vascular abnormalities seen in T2D patients are manifest in the cerebral circulation and alter dynamic CA during exercise remains unknown.

Herein, we tested the hypothesis that patients with T2D would have an impaired dynamic CA during graded intensities of isometric handgrip exercise compared with healthy age, sex, and body-weight matched controls. Because hypertension is a common comorbidity in T2D patients (27, 45), we also studied a group of T2D patients with diagnosed hypertension. Furthermore, given recent evidence from rodent and human studies suggesting that an elevation in oxidative stress may impair cerebrovascular function (3, 9, 38), a second goal of the present study was to examine whether underlying oxidative stress is associated with impairments in dynamic CA at rest or during isometric exercise.
METHODS

Subjects. A total of 23 subjects participated in the present study: seven normotensive patients with T2D (reported duration of disease: 4 ± 1 years), eight hypertensive patients with T2D (reported duration of disease: 6 ± 1 years), and eight normotensive controls with no family history of T2D and matched to T2D patients for age, sex, and body weight. Characteristics of the T2D patients and healthy control subjects are provided in Table 1. None of the T2D patients were being treated for or had symptoms of peripheral neuropathy. All experimental procedures and protocols conform to the Declaration of Helsinki and were approved by the University of Missouri Health Sciences Institutional Review Board. Each subject received a verbal and written explanation of the study objectives, measurement techniques, and risks and benefits associated with the investigation. Before participation, each subject provided written informed consent and completed a medical health history questionnaire and a 12-h fasting blood chemistry screening including a lipid panel, metabolic panel, and Hba1c measurement.

Cardiovascular measurements. Heart rate (HR) was continuously monitored using a standard lead II surface electrocardiogram (ECG; Quinton Q710 Foremost Equipment, Rochester, NY). BP was measured on a beat-to-beat basis using servo-controlled finger photoplethysmography (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands) placed on the middle finger of the left hand and supported on a bedside table positioned at the level of the heart. The changes in arterial pressure measured by photoplethysmography have been shown to provide an accurate estimate of directly measured intra-arterial BP both at bedside and during exercise (13, 44). In addition, an automated sphygmomanometer (Welch Allyn, Skaneateles Falls, NY) recorded resting BP every minute by the auscultation of the brachial artery of the right arm to estimate resting dynamic CA for each subject (37).

Experimental protocols. Before the actual experimental day, each subject was familiarized with the equipment and the study protocol including inflation of bilateral thigh cuffs for dynamic CA measurements (1, 48), as described in detail below. On the experimental day, T2D patients were instructed to refrain from medication use. Although medications being withheld on the morning of the study would not completely eliminate the impact medications may be having on experimental measures, because of the high risk in this patient group it would neither be safe nor ethical to completely discontinue medications for an extended period of time. Moreover, we would suggest that the clinical applicability of our results is enhanced by the patients being on their existing medications as this addresses the true clinical picture of T2D patients. All subjects arrived at the laboratory a minimum of 2 h after a light meal. Subjects were also asked to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 24 h before experimental sessions. All experiments were performed at an ambient room temperature of 22°–24°C with external stimuli minimized. The procedures listed below were performed.

Total reactive oxygen species and superoxide. After resting quietly for a minimum of 15 min, blood samples were obtained from the antecubital vein for the determination of total reactive oxygen species (ROS) and superoxide using electron paramagnetic resonance (EPR) spectroscopy (8). These measures were only obtained at rest because isometric handgrip does not increase systemic oxidative stress even when performed to fatigue at high intensities (2). Samples contained 3.5 mM of deferoxamine methanesulfonate salt (DF; Noxygen Science Transfer & Diagnostics GmbH, Elzach, Germany) and 9.08 mM of diethylidithiocarbamic acid sodium (DTC). Initially, samples were signed for the measurements of total ROS and superoxide were incubated with Krebs-HEPES buffer solution at 37°C for 15 min. Subsequently, both samples were incubated with methoxy carbonyl-2,2,5,5-tetramethylpyrrolidine (CMH) spin probe at 37°C for 15 min. After complete mixing, 50 μL of each sample were loaded into a 1-cm syringe and flash frozen between buffer solutions to form a continuous frozen plug using liquid nitrogen. Samples were then stored at −80°C and shipped to the University of Nebraska Medical Center for analyses. Total ROS was measured directly using the CMH probe, while superoxide was calculated indirectly by subtracting superoxide dismutase-treated samples from total ROS.

Dynamic cerebral autoregulation at rest. Subjects were seated in a semi-recumbent position on a medical examination table and instrumented for measures of HR, BP, respiration, MCAV, and PETCO2. After instrumentation, cuffs (SC12; 13 × 85 cm; Hokanson) were placed around both thighs for the assessment of dynamic CA (1, 48). Subjects then rested quietly for 10 min followed by a 3-min baseline data collection period, and bilateral inflation of the thigh cuffs to suprasystolic pressure (220 mmHg) for 3 min, after which the thigh cuffs were deflated and continuous data collection occurred for an additional 3 min. Cuffs were always deflated at end expiration, observed from the respiratory band, to eliminate potential respiratory influences. This protocol was performed twice with the trials separated by a minimum of 20 min, and the average of the trials was used to estimate resting dynamic CA for each subject (37).

Dynamic cerebral autoregulation during exercise. Subjects had both arms supported on adjustable bedside tables with a handgrip dynamometer held in the dominant hand (model 78010; Lafayette Instruments, Bella Vista, NSW, Australia), sampled at frequencies of 1,000 Hz, and stored on a personal computer for offline analysis.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>T2D Patients</th>
<th>T2D + HTN Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>6/2</td>
<td>4/3</td>
<td>5/3</td>
</tr>
<tr>
<td>Age, years</td>
<td>55 ± 3</td>
<td>49 ± 3</td>
<td>55 ± 3</td>
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<tr>
<td>Weight, kg</td>
<td>91 ± 7.4</td>
<td>103 ± 8.1</td>
<td>90 ± 8.0</td>
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<tr>
<td>Height, cm</td>
<td>173 ± 2.6</td>
<td>169 ± 1.9</td>
<td>167 ± 3.4</td>
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<td>Body mass index, kg/m²</td>
<td>30 ± 2.3</td>
<td>36 ± 2.7</td>
<td>32 ± 1.9</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>96 ± 5.3</td>
<td>164 ± 31*</td>
<td>156 ± 25*</td>
</tr>
<tr>
<td>Hba1c, %</td>
<td>5.5 ± 0.1</td>
<td>7.5 ± 0.1*</td>
<td>7.5 ± 0.4*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>154 ± 42</td>
<td>155 ± 26</td>
<td>177 ± 23</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120 ± 9</td>
<td>110 ± 10</td>
<td>110 ± 11</td>
</tr>
<tr>
<td>Hypoglycemic medications</td>
<td></td>
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</tr>
<tr>
<td>Insulin</td>
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<td>1</td>
</tr>
<tr>
<td>Biguanides</td>
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<td>7</td>
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<tr>
<td>Sulfonylureas</td>
<td>—</td>
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<td>2</td>
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<tr>
<td>Combination</td>
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<td>2</td>
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<tr>
<td>Cardiovascular medications</td>
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<td>ACE inhibitors</td>
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<td>Angiotensin receptor blocker</td>
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<tr>
<td>Statin</td>
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<tr>
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<tr>
<td>β-Blocker</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are means ± SE. T2D, type 2 diabetes mellitus; HTN, hypertensive. *Represents P < 0.05 vs. controls.
Condition

Table 2. Physiological measurements at baseline and during low and high intensity isometric handgrip exercise

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mmHg</th>
<th>Middle Cerebral Artery Mean Blood Velocity, cm/s</th>
<th>Cerebrovascular Conductance Index, cm/s/mmHg</th>
<th>PETCO₂, mmHg</th>
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<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>69 ± 3</td>
<td>91 ± 3</td>
<td>52 ± 3</td>
<td>0.58 ± 0.03</td>
<td>42 ± 1</td>
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<tr>
<td>T2D patients</td>
<td>68 ± 5</td>
<td>94 ± 2</td>
<td>50 ± 4</td>
<td>0.53 ± 0.04</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>T2D + HTN patients</td>
<td>77 ± 4</td>
<td>96 ± 3</td>
<td>45 ± 3</td>
<td>0.47 ± 0.04</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>20% Handgrip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>71 ± 3</td>
<td>104 ± 3</td>
<td>53 ± 3</td>
<td>0.51 ± 0.04</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>T2D patients</td>
<td>74 ± 3</td>
<td>111 ± 1</td>
<td>48 ± 4</td>
<td>0.44 ± 0.04</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>T2D HTN patients</td>
<td>81 ± 5</td>
<td>111 ± 4</td>
<td>46 ± 3</td>
<td>0.42 ± 0.03</td>
<td>41 ± 1</td>
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<tr>
<td>40% Handgrip</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>79 ± 4</td>
<td>121 ± 5</td>
<td>56 ± 4</td>
<td>0.46 ± 0.04</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>T2D patients</td>
<td>84 ± 3</td>
<td>127 ± 2</td>
<td>52 ± 4</td>
<td>0.41 ± 0.03</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>T2D + HTN patients</td>
<td>87 ± 5</td>
<td>127 ± 8</td>
<td>48 ± 3</td>
<td>0.39 ± 0.03</td>
<td>41 ± 2</td>
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<tr>
<td>Interaction</td>
<td>0.527</td>
<td>0.767</td>
<td>0.803</td>
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<td>0.636</td>
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<tr>
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<td>0.621</td>
<td>0.360</td>
<td></td>
<td>0.472</td>
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<tr>
<td>Interaction</td>
<td></td>
<td></td>
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</tbody>
</table>

Values are means ± SE.

Instrument, Lafayette, IN) and beat-to-beat Finometer BP measures made on the opposite hand. Maximum voluntary contraction (MVC) was calculated as the highest force produced during 3 to 5 maximal efforts, each separated by at least 1 min. To estimate dynamic CA during exercise, 1.5 min after the handgrips were inflated, subjects initiated isometric handgrip exercise at either low (20% MVC) or high (40% MVC) intensity for 2 min and cuffs were then deflated at 1.5 min of exercise at end expiration, as previously described (37). Exercise bouts were performed in random order with two bouts performed at each intensity. The exercise bouts were separated by a minimum of 20 min, and the average of the trials for each intensity was used to estimate dynamic CA during exercise for each subject.

Data analyses. Resting baseline values for HR, MAP, MCAV mean, and PETCO₂ were calculated as mean values over a 1-min steady-state period at rest before bilateral cuff inflation and exercising values were calculated as mean values over the last 30 s of handgrip bouts before bilateral cuff release. For dynamic CA measures, control values of MAP, MCAV mean, and calculated CVCi (MCAV mean/MAP) were taken as 4-s averages immediately before thigh-cuff release. Changes in MAP, MCAV mean, and CVCi during cuff release were then determined relative to these control values and calculated from nadir values at the time of 1–3.5 s from cuff release. The rate of regulation (RoR) was then calculated as an index of dynamic CA (1, 34, 48): RoR = (Δrelative CVCi/ΔT)/relative MAP, where (Δ relative CVCi/ΔT) is the slope of the linear regression between relative CVCi and time (T), and Δrelative MAP, the magnitude of the transient fall in MAP, which was calculated by subtracting control MAP from averaged MAP during the interval from 1.0 to 3.5 s (1). The rate of change in CVCi between 1.0 and 3.5 s from cuff release has been shown to be directly related to dynamic CA (1, 34, 48).

Statistical analysis. All data are reported as means ± SE. Comparisons of baseline subject characteristics, total ROS, and superoxide between groups were made using a single ANOVA followed by a multiple comparison test when appropriate. Statistical comparisons of physiological variables were made using repeated-measures two-way ANOVA with the Greenhouse-Geisser correction, in which condition (i.e., baseline, 20% handgrip and 40% handgrip) and group [controls, T2D patients, T2D + hypertensive (HTN) patients] were the main factors. A Bonferroni test was used post hoc to investigate significant main effects and interactions when present. Statistical significance was set at P < 0.05. The relationships of baseline and exercise RoR with total ROS, superoxide, fasting glucose, and Hba1c were examined with Pearson correlations. Because there were no differences in RoR between normotensive and hypertensive T2D patients, these groups were combined for all correlation analyses. Relationships were also evaluated by using a partial correlation approach to account for the potential confounding influences of lipids, body mass index, age, duration of the disease, fasting glucose, and Hba1c. All statistical analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

RESULTS

Resting HR, MAP, MCAV mean, CVCi, and PETCO₂ were not significantly different between any of the subject groups (P > 0.05; Table 2). Likewise, PETCO₂, cerebral and cardiovascular responses to both low- and high-intensity handgrip were similar between groups.

The RoR was attenuated in both T2D and T2D + HTN patients compared with healthy controls at baseline, indicating an impaired dynamic CA (P < 0.05; Fig. 1). During low-intensity handgrip, the RoR was not significantly different from baseline in controls or T2D patients and thus remained lower in the T2D and T2D + HTN patients. Although RoR was well maintained in controls during high-intensity handgrip, it was reduced by 28 ± 5% from baseline in normotensive T2D patients and by 30 ± 4% in T2D + HTN patients (Fig. 1).

Peak decreases in MAP and MCAV mean to release of the thigh cuffs were similar between controls and T2D patients at rest and...
during handgrip exercise (Fig. 2). Likewise, the reflex tachycardia to the acute hypotension induced by cuff release was not statistically different between controls (+9 ± 2, +10 ± 2, +9 ± 3 beats/min during baseline, 20% and 40% MVC handgrip, respectively), T2D patients (+8 ± 2, +7 ± 2, +7 ± 2 beats/min during baseline, 20% and 40% MVC handgrip, respectively), and T2D + HTN patients (+7 ± 3, +8 ± 2, +8 ± 3 beats/min during baseline, 20% and 40% MVC handgrip, respectively).

Normotensive T2D patients and T2D + HTN patients demonstrated greater resting total ROS (P < 0.05; Fig. 3A) and superoxide (2.9 ± 0.7 × 10⁶ normotensive T2D patients and 1.7 ± 0.5 × 10⁶ T2D + HTN patients; EPR; arbitrary units) compared with controls (0.3 ± 0.1 × 10⁶; EPR; arbitrary units; P < 0.05). Baseline total ROS and superoxide did not demonstrate any significant relationships with resting dynamic CA measures in healthy controls or T2D patients (Table 3). However, for T2D
patients, baseline total ROS (Fig. 3, B and C) and superoxide (Table 3) demonstrated significant inverse relationships with dynamic CA obtained during low- and high-intensity handgrip after adjusting for other potential contributing variables including fasting glucose and HbA1C with partial correlation analysis. For healthy controls, an inverse relationship between dynamic CA and total ROS and superoxide was found only for high-intensity handgrip (Table 3). Notably, no relationships were found between fasting glucose or HbA1C and dynamic CA obtained at rest or during isometric exercise. This premise was based on recent studies suggesting that an elevation in oxidative stress may contribute to the impairment in dynamic CA at rest. Interestingly, despite the additional cardiovascular burden of hypertension, we did not find a difference in dynamic CA at rest or during handgrip exercise between the hypertensive and normotensive T2D patients. This potentially could be a consequence of their BP being well controlled.

Several mechanisms likely contribute to the impaired dynamic CA observed at rest and during isometric exercise in patients with T2D. The presence of vascular abnormalities in diabetes is well established and is characterized by increased vascular permeability (22), endothelial dysfunction (33), and capillary basement membrane thickening (19). In addition, autonomic dysfunction has also been reported in T2D patients and may contribute (15, 42). Nevertheless, a secondary aim of the present study was to examine whether underlying oxidative stress would be associated with impairments in dynamic CA at rest or during isometric exercise. This premise was based on recent studies suggesting that an elevation in oxidative stress may impair cerebrovascular function (3, 9, 38). Investigations have indicated that ROS reduces endothelial function by scavenging nitric oxide and generating highly reactive peroxynitrite (4, 9). In addition, chronic increases in oxidative stress promote vascular smooth muscle hypertrophy and remodeling that in turn alters the structural properties of the vessel wall to respond to rapid hemodynamic changes (18). However, in the present study, systemic ROS and superoxide were only inversely associated with the RoR obtained during low- and high-intensity handgrip. These data suggest that the deleterious impact of elevated ROS and superoxide on CA may not become manifest until the system is stressed. In other words, it is plausible that the challenges to dynamic CA mediated by handgrip exercise (e.g., BP elevation) cannot be adequately regulated due to the elevations in oxidative stress that are present in T2D patients. Additional studies are warranted. Also, the lack of a relationship between baseline RoR and oxidative stress measures does not definitively rule out underlying oxidative stress in contributing to the impairments in dynamic CA at rest. Overall, further investigations are needed.
to establish any causality between elevated oxidative stress and RoR at rest and during exercise in T2D patients.

Other mechanisms aside from oxidative stress need to be considered in mediating the greater impairment seen during high intensity handgrip in T2D patients since further increases in oxidative stress would not be expected during or following a 2-min isometric exercise bout even when performed at high intensity to fatigue (2). One possibility is the augmented sympatho-excitation evoked by high intensity handgrip (10). Indeed, although the increase in sympathetic nerve activity would be minimal during 2 min of 20% MVC handgrip, a robust increase would be expected during 40% MVC handgrip (29, 36, 55). Although somewhat controversial, several studies have demonstrated a role for the sympathetic nervous system in the control of the cerebral vasculature (20, 34, 55a). Moreover, patients with T2D have been reported to have an increased α-adrenergic responsiveness (14). Thus the robust sympatho-excitation during high intensity handgrip may lead to a greater vasoconstrictor tone in T2D patients, thereby contributing to a reduced ability to rapidly restore cerebral blood flow in face of changes in BP. In support of this idea, Jordan et al. (20) demonstrated that sympathetic overactivity contributes to impairments in cerebrovascular vasodilation in patients with idio-pathic orthostatic intolerance. In addition, this impairment was partially restored by blocking the vascular α-adrenergic receptors (20).

Perspectives. We demonstrate that dynamic CA is impaired at rest and during low-intensity handgrip in T2D patients with further impairments observed during high intensity handgrip. Such impairments in dynamic CA manifest with T2D were not different between normotensive and hypertensive T2D patients. Collectively, our results suggest that the cerebral vasculature of T2D patients is at a greater risk to fluctuations in BP, particularly during activities encompassing isometric contractions. These findings are of particular importance given the number of common daily activities that require an isometric muscle contraction (e.g., carrying groceries, lifting a child). Moreover, combined aerobic and resistance training has emerged as ideal to account for both vascular and nonvascular complications in T2D (31). Similar to aerobic exercise, resistance training has been shown to improve whole-body glucose utilization (31) but it also involves repeated straining like maneuvers with rapid and robust swings in BP (28, 37, 54). Hence, the integrity of the autoregulatory mechanisms protecting the brain becomes quite important under these conditions. The findings of the present study, however, indicate that transmission of BP surges to the cerebral circulation is dampened less effectively in patients with T2D, in particular during high-intensity handgrip. In this sense, lower resistance exercise intensities may be more appropriate for exercise prescription in T2D patients. Interestingly, in the T2D patient cohort studied, we did not find any relationships between fasting glucose or HbA1C and impaired dynamic CA obtained at rest or during low- and high-intensity handgrip. However, systemic ROS was inversely associated with dynamic CA during isometric handgrip, suggesting that greater underlying oxidative stress may contribute to exercise-induced impairments in dynamic CA in T2D. Given this, elevated oxidative stress may represent a potential therapeutic target for improving cerebral vascular responses during stressors in T2D patients (3, 9, 38).

In summary, our findings demonstrate that T2D impairs dynamic CA at rest and during isometric handgrip, which may be, in part, related to greater underlying systemic oxidative stress.

ACKNOWLEDGMENTS

The time and effort expended by all the volunteer subjects is greatly appreciated.

GRANTS

This work was partially supported by an American Physiological Society Arthur C. Guyton Awards for Excellence in Integrative Physiology (to P. J. Fadel). The EPR spectroscopy studies were performed in the EPR Core Facility at the University of Nebraska Medical Center, which is supported by National Institute of General Medical Sciences Grant 1P50GM10335 awarded to the University of Nebraska’s Redox Biology Center.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES

CEREBROVASCULAR REGULATION IN T2D


