Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes

Yu-Sok KIM,*†, Rogier V. IMMINK†‡, Wim J. STOK†§, John M. KAREMAKER†§, Niels H. SECHER∥¶ and Johannes J. VAN LIESHOUT*†

*Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, †Human Cardiovascular Physiology Unit, AMC Center for Heart Failure Research, University of Amsterdam, Amsterdam, The Netherlands, ‡Department of Anesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, §Department of Physiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, ∥Department of Anaesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, and ¶The Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Type 2 diabetes is associated with an increased risk of endothelial dysfunction and microvascular complications with impaired autoregulation of tissue perfusion. Both microvascular disease and cardiovascular autonomic neuropathy may affect cerebral autoregulation. In the present study, we tested the hypothesis that, in the absence of cardiovascular autonomic neuropathy, cerebral autoregulation is impaired in subjects with DM+ (Type 2 diabetes with microvascular complications) but intact in subjects with DM− (Type 2 diabetes without microvascular complications). Dynamic cerebral autoregulation and the steady-state cerebrovascular response to postural change were studied in subjects with DM+ and DM−, in the absence of cardiovascular autonomic neuropathy, and in CTRL (healthy control) subjects. The relationship between spontaneous changes in MCA Vmean (middle cerebral artery mean blood velocity) and MAP (mean arterial pressure) was evaluated using frequency domain analysis. In the low-frequency region (0.07–0.15 Hz), the phase lead of the MAP-to-MCA Vmean transfer function was 52°±10° in CTRL subjects, reduced in subjects with DM− (40°±6°; P<0.01 compared with CTRL subjects) and impaired in subjects with DM+ (30°±5°; P<0.01 compared with subjects with DM−), indicating less dampening of blood pressure oscillations by affected dynamic cerebral autoregulation. The steady-state response of MCA Vmean to postural change was comparable for all groups (−12.6±6% in CTRL subjects, −15.6±6% in subjects with DM− and −15.7±7% in subjects with DM+). HbA1c (glycated haemoglobin) and the duration of diabetes, but not blood pressure, were determinants of transfer function phase. In conclusion, dysfunction of dynamic cerebral autoregulation in subjects with Type 2 diabetes appears to be an early manifestation of microvascular disease prior to the clinical expression of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.

Key words: blood pressure, cerebrovascular circulation, diabetic complication, transcranial Doppler, Type 2 diabetes.

Abbreviations: BMI, body mass index; BP, blood pressure; ABP, arterial BP; CBF, cerebral blood flow; CBFV, CBF velocity; CTRL, healthy control; CVRi, cerebrovascular resistance index; HbA1c, glycated haemoglobin; HR, heart rate; LF, low-frequency; MAP, mean arterial pressure; MAPbrain, MAP at the brain level; MCA, middle cerebral artery; MCA Vmean, MCA mean blood velocity; Petco2, end-tidal partial pressure of carbon dioxide; DM+, Type 2 diabetes with microvascular complications; DM−, Type 2 diabetes without microvascular complications; TCD, transcranial Doppler.

Correspondence: Dr Johannes J. van Lieshout (email j.j.vanlieshout@amc.uva.nl).
INTRODUCTION

Blood flow to the brain is influenced by regional changes in neural activity and by global regulatory mechanisms, including cerebrovascular autoregulation. Maintenance of cerebral perfusion during physiological challenges is secured by both fast- and slow-acting autoregulatory mechanisms [1]. Although acute changes in ABP (arterial BP) are transmitted to the cerebral circulation, under normal conditions CBF (cerebral blood flow) tends to return to its baseline value within a few seconds [2,3]. This short-term control is usually referred to as dynamic cerebral autoregulation. Static cerebral autoregulation considers the net change in CBF resulting from a manipulated change in cerebral perfusion pressure under steady-state conditions [1–4].

In patients with moderate hypertension, cerebral autoregulation protects the brain from regional hyper-perfusion [5]. However, with severe hypertension or ischaemic stroke, impairment of cerebral autoregulation leads to a loss of control of cerebral perfusion and CBF becomes a function of arterial pressure, so-called pressure-dependency [4,6,7]. Type 2 diabetes is associated with hypertension and an increased risk of endothelial dysfunction and microvascular complications with impaired autoregulation of tissue perfusion [6,8]. In subjects with long-standing Type 1 diabetes with orthostatic hypotension due to cardiovascular autonomic neuropathy and microvascular complications, including diabetic nephropathy and retinopathy, cerebral autoregulation is impaired [6,9–11]. Impairment of cerebral autoregulation in subjects with diabetes is attributed to both cardiovascular autonomic neuropathy and microvascular endothelial dysfunction associated with cerebral small vessel disease [6,9,11–13]. Despite sympathetic innervation of cerebral arteries, the role of the autonomic nervous system in the control of CBF remains controversial.

We hypothesized that, in subjects with Type 2 diabetes who manifest microvascular complications but without symptomatic cerebrovascular disease, cerebral autoregulatory capacity may become impaired in the absence of cardiovascular autonomic neuropathy. We hypothesized further that, in subjects with Type 2 diabetes who have no signs of microvascular disease or cardiovascular autonomic neuropathy, cerebral autoregulatory capacity is maintained. To test these questions we set out to evaluate the dynamic component of cerebral autoregulatory capacity and the steady-state cerebrovascular response to a postural change in subjects with DM+ (Type 2 diabetes with microvascular complications) but without symptomatic cerebrovascular disease and cardiovascular autonomic neuropathy. Frequency domain analysis was used to evaluate the relationship between TCD (transcranial Doppler)-determined beat-to-beat changes in CBEV (CBF velocity) and spontaneous ABP oscillations [14,15]. Subjects with DM− (Type 2 diabetes without microvascular complications) and CTRL (healthy control) subjects served as reference subjects.

MATERIALS AND METHODS

Subjects and study design

A total of 30 subjects participated in the present study: ten subjects with DM+ (aged, 61 ± 8 years; six male), ten subjects with DM− (aged, 54 ± 8 years; five male) and ten age- and gender-matched CTRL subjects (aged, 61 ± 16 years; four male) were studied. Each subject received verbal and written information about the study objectives, measurement techniques and the risks and benefits associated with the investigation. All subjects gave their written informed consent as approved by the AMC Medical Ethical Committee, and experiments were performed in accordance with the Declaration of Helsinki.

Subjects with DM+ and DM− had been diagnosed with Type 2 diabetes according to the WHO (World Health Organization) criteria [16], and were receiving treatment with insulin and/or oral anti-diabetic agents. Selection criteria for the DM+ group included microvascular complications such as diabetic nephropathy [clinically defined as a persistent urinary albumin excretion rate of > 300 mg/24 h or albumin/creatinine ratio > 2.5 mg/mmol (men) or > 3.5 mg/mmol (women) in the presence of diabetic retinopathy and in the absence of clinical or laboratory evidence of other kidney or renal tract disease] [17,18], retinopathy (diagnosed by an ophthalmologist) and symptoms or signs of diabetic polyneuropathy [19,20]. Subjects without these complications were designated as DM−. Exclusion criteria included history of stroke, TIA (transient ischaemic attack), clinical manifestation of cardiovascular disease or heart failure, uncontrolled hypertension (BP > 160/100 mmHg), orthostatic hypotension, cardiovascular autonomic neuropathy, use of medication with potential influence on autonomic cardiovascular function and poor metabolic control [HbA1c (glycated haemoglobin) > 9.5 %]. Prior to inclusion in the present study, all subjects underwent cardiovascular autonomic function testing. Parasympathetic control of HR (heart rate) was evaluated by quantifying the time-course and magnitude of HR responses to active standing and the Valsalva manoeuvre [21–23]. Sympathetic cardiovascular control was assessed by the BP responses to active standing and the Valsalva manoeuvre [19,24]. The presence of two or more abnormal test results was considered to reflect the presence of cardiovascular autonomic neuropathy [19,25].

After a light breakfast, subjects reported to the laboratory at 08:00 hours and were studied in a room at 22°C. They abstained from caffeinated beverages. Subjects were placed in the supine position for instrumentation. After obtaining systemic and cerebrovascular
variables in the supine resting position, the subjects were asked to stand up for 5 min.

**ABP, CBFV and PETCO₂ (end-tidal partial pressure of carbon dioxide)**

Continuous ABP was measured non-invasively by a servo-controlled finger photoplethysmograph (Portapres; Finapres Medical Systems) with the cuff placed on the middle phalanx of the left middle finger kept at heart level. Changes in MAP (mean arterial pressure) measured by photoplethysmography are not different from intra-arterial BP measurements both at rest and during dynamic exercise [26]. An automated non-invasive BP measuring device (HEM-705CP; Omron) was used to calibrate the finger BP measurements. HR was monitored using a lead III ECG. The TCD (DWL Multidop X4)-derived CBFV was measured in the proximal segment of the right MCA (middle cerebral artery) and insonated through the posterior temporal window. TCD determinations of the MCA \( V_{\text{mean}} \) (MCA mean blood velocity) are reproducible with a difference between two measurements of less than 3% with an \( R = 0.95 \) [27]. Once the optimal signal-to-noise ratio was obtained, the probe (Marc 600; Spencer Technologies) was secured with a headband. PETCO₂ was measured by a sampling infrared capnograph (Tonocap; Datex-Ohmeda).

**Data analysis**

The signals of BP, spectral envelope of MCA velocity, ECG and PETCO₂ were analogue/digital-converted at 100 Hz and stored on a hard disk for off-line analysis. Beat-to-beat values for MCA \( V_{\text{mean}} \) and MAP were derived as the integral over one beat divided by the corresponding beat interval, and HR was the inverse of the inter-beat pressure interval. MAP at the MCA level was calculated from MAP measured at heart level and the vertical finger-to-TCD probe distance [28]. CVRi (cerebrovascular resistance index) was the ratio of MAP\(_{\text{brain}}\) (MAP at the brain level) and MCA \( V_{\text{mean}}\). The Gosling pulsatility index of the MCA was taken as an index of cerebral microangiopathy, expressed as the amplitude of CBFV divided by time-averaged CBFV [29].

**Cerebral autoregulation**

The steady-state response of MCA \( V_{\text{mean}} \) to a postural change in relation to MAP\(_{\text{brain}}\) was assessed from data sampled from 1 min before and 5 min after standing. When healthy humans stand up, the head is positioned approx. 30 cm above heart level within a few seconds, resulting in a reduction in cerebral perfusion pressure of approx. 20 mmHg [15], with a decrease in cerebral tissue oxygenation [15,28] and CBF [30] reflected by the TCD-determined MCA \( V_{\text{mean}}\) [2]. Such steady-state reductions in cerebral perfusion take place even though the cerebral perfusion pressure remains within what is considered to be its autoregulatory range. In healthy subjects, static cerebral autoregulation limits the physiological reduction in MCA \( V_{\text{mean}}\) to approx. 15% following a postural change [15,28,31,32].

Frequency domain analysis quantified the counter-regulatory capacity of dynamic cerebral autoregulation from spontaneous BP oscillations [3,7]. A 5-min tracing of beat-to-beat data of MAP and MCA \( V_{\text{mean}}\) was spline-interpolated and resampled at 4 Hz. To quantify the variability of ABP and CBFV, the power spectra of the two variables were estimated by transforming the time series of ABP and CBFV with discrete Fourier transformation to the frequency domain. From the cross spectrum, transfer function phase shift and gain were derived. According to the high-pass filter model of cerebral autoregulation, autoregulatory capacity is reflected by the positive phase relationship between oscillations of ABP (input function) and CBFV (output function) [3,33]. At high frequencies, less cerebral attenuation of MAP oscillations to MCA \( V_{\text{mean}}\) implies that the cerebral autoregulation cannot respond fast enough to rapid changes in MAP [3]. Results are expressed as the averaged integrated area for the LF (low-frequency) range (0.07–0.15 Hz). The gain, as the ratio of the amplitudes of MCA \( V_{\text{mean}}\) and MAP, is taken to reflect the effective amplitude dampening of ABP fluctuations. To examine the strength of the relationship between MAP and MCA \( V_{\text{mean}}\), coherence was used to signify that the two cardiovascular signals co-vary significantly in the LF area. As with a correlation coefficient, it varies between 0 and 1, and a coherence above 0.5 was considered to provide a reliable estimate of the transfer function variables. Phase shift was defined positive where MCA \( V_{\text{mean}}\) leads MAP. In healthy subjects, MCA \( V_{\text{mean}}\) leads MAP with 50–60° in the LF range [3,7]. To account for the inter-subject variability, the gain was normalized for MAP and MCA \( V_{\text{mean}}\), and is expressed as the percentage change in \( \text{cm} \cdot \text{s}^{-1} \) per percentage change in mmHg [3,4].

**Statistics**

Values are presented as means ± S.D. When data fitted a normal distribution, as indicated by Kolmogorov–Smirnov analysis, an unpaired Student’s \( t \) test was used, and a Mann–Whitney rank-sum test was applied when data were not normally distributed. Differences among the three groups were identified by ANOVA. A multivariate stepwise regression model was constructed with the MAP-to-MCA \( V_{\text{mean}}\) transfer function phase as the dependent variable and duration of diabetes, systolic and diastolic BP, BMI (body mass index), actual plasma glucose and HbA1c as the independent variables, with forward entry and removal. \( P < 0.05 \) was considered to indicate a statistically significant difference.
Table 1 Characteristics of the subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTRL</th>
<th>DM−</th>
<th>DM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n) (male/female)</td>
<td>6/4</td>
<td>5/5</td>
<td>4/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 16</td>
<td>54 ± 8</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 3.6</td>
<td>28.3 ± 8.1</td>
<td>29.8 ± 4.0</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133 ± 17</td>
<td>133 ± 14</td>
<td>137 ± 13</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74 ± 11</td>
<td>73 ± 11</td>
<td>76 ± 7</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>—</td>
<td>8 ± 3</td>
<td>16 ± 10</td>
</tr>
<tr>
<td>Microvascular complication (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Polyneuropathy (sensorimotor)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral hypoglycaemic agents (n)</td>
<td>0</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Insulin (n)</td>
<td>0</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>7.5 ± 1.6</td>
<td>7.5 ± 1.2</td>
<td>7.5 ± 1.2</td>
</tr>
<tr>
<td>HbA1c (% Hb)</td>
<td>7.2 ± 0.8</td>
<td>8.0 ± 1.1</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>Albumin/creatinine ratio (mg/mmol)</td>
<td>0.80 ± 0.65</td>
<td>8.38 ± 12.89</td>
<td>8.38 ± 12.89</td>
</tr>
<tr>
<td>Antihypertensive medication (n)</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Diuretic</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>AT, RA</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Statin</td>
<td>0</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

RESULTS

Subject characteristics

Results of the cardiovascular autonomic function tests were without any abnormalities in any of the subjects. None of the subjects experienced symptoms of orthostatic intolerance or other signs of cerebral hypoperfusion. There were no differences among the groups with regard to BMI, age, gender ratio, plasma glucose levels and systolic or diastolic BP (Table 1). In the subjects with DM+, duration of diabetes tended to be longer \((P = 0.14)\) and the \(\text{HbA}_1\text{c}\) value tended to be higher \((P = 0.09)\) than in the subjects with DM−.

MCA \(\text{V}_{\text{mean}}\) response to postural change

At rest prior to standing, baseline cerebro- and cardiovascular variables were comparable between the groups, whereas the pulsatility index and \(\text{PETCO}_2\) did not differ (Table 2). Upon standing, CVRi did not change, and the postural reduction in MAPbrain and MCA \(\text{V}_{\text{mean}}\) was comparable among the groups (Figure 1).

Dynamic cerebral autoregulation

Spectral analysis and MAP-to-MCA \(\text{V}_{\text{mean}}\) transfer function results are shown in Table 3. In the LF region \((0.07–0.15\ \text{Hz})\), MAP power was lower in both subjects with DM− and DM+ compared with CTRL subjects, whereas MCA \(\text{V}_{\text{mean}}\) power was comparable between groups. Coherence was >0.5 in all groups. The transfer function phase between MAP and MCA \(\text{V}_{\text{mean}}\) was 52 ± 10° in CTRL subjects, lower in subjects with DM− \((40 ± 6°; P < 0.01\) compared with CTRL subjects) and reduced further in subjects with DM+ \((30 ± 5°; P < 0.01\) compared with subjects with DM−) (Figure 2). Phase

Figure 1 MAPbrain and MCA \(\text{V}_{\text{mean}}\) responses to postural stress in CTRL subjects (○), and subjects with DM− (△) and DM+ (▲). Bar indicates standing.

Figure 2 Spectral analysis and MAP-to-MCA \(\text{V}_{\text{mean}}\) transfer function results.
Table 3 Dynamic cerebral autoregulation control
Averaged LF (0.07–0.15 Hz) transfer function gain, phase and coherence results are shown. Values are means ± S.D. for ten subjects per group. ∗ P < 0.05 and ∗∗ P < 0.01 compared with CTRL; † P < 0.01 compared with DM−.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTRL</th>
<th>DM−</th>
<th>DM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP power (mmHg² · Hz⁻¹)</td>
<td>9.7 ± 7.5</td>
<td>4.7 ± 2.9</td>
<td>3.3 ± 2.4</td>
</tr>
<tr>
<td>MCA Vmean power (cm · s⁻¹)² · Hz⁻¹</td>
<td>3.5 ± 2.5</td>
<td>3.8 ± 3.8</td>
<td>4.2 ± 0.6</td>
</tr>
<tr>
<td>Coherence (k²)</td>
<td>0.76 ± 0.11</td>
<td>0.79 ± 0.12</td>
<td>0.73 ± 0.12</td>
</tr>
<tr>
<td>Phase (°)</td>
<td>52 ± 10</td>
<td>40 ± 6°**</td>
<td>30 ± 5°**†</td>
</tr>
<tr>
<td>Normalized gain (% · %⁻¹)</td>
<td>1.21 ± 0.28</td>
<td>1.47 ± 0.73</td>
<td>1.44 ± 0.42</td>
</tr>
</tbody>
</table>

Table 4 Stepwise regression analysis of the determinant of transfer function phase in subjects with DM+ and DM−
Yes, variable is in stepwise model; No, variable is not in stepwise regression model; S.E., standard error.

<table>
<thead>
<tr>
<th>In</th>
<th>Variable</th>
<th>S.E. of estimate</th>
<th>R² increment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>HbA1c</td>
<td>5.75</td>
<td>0.47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>Duration of diabetes</td>
<td>5.09</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>BMI</td>
<td>—</td>
<td>—</td>
<td>0.396</td>
</tr>
<tr>
<td>No</td>
<td>Systolic BP</td>
<td>—</td>
<td>—</td>
<td>0.542</td>
</tr>
<tr>
<td>No</td>
<td>Diastolic BP</td>
<td>—</td>
<td>—</td>
<td>0.639</td>
</tr>
<tr>
<td>No</td>
<td>Plasma glucose</td>
<td>—</td>
<td>—</td>
<td>0.806</td>
</tr>
</tbody>
</table>

Figure 2 Group-averaged LF (0.07–0.15 Hz) transfer function phase between MAP and MCA Vmean in CTRL subjects (white bar), and subjects with DM− (grey bar) and DM+ (black bar)
Values are means ± S.D.

compared with MAP power did not correlate in the three groups. Representative examples of declining MAP-to-MCA Vmean phase leads are shown in Figure 3. The larger gain in subjects with DM− and DM+ did not reach statistical significance. Plasma HbA1c and duration of diabetes, but not BMI, plasma glucose and systolic and diastolic BP, contributed to a multiple linear regression model of the MAP-to-MCA Vmean transfer function phase (Table 4).

DISCUSSION

The present study provides novel information regarding the dynamic cerebral autoregulation in Type 2 diabetes. The major finding was a significant impairment of dynamic cerebral autoregulation in subjects with Type 2 diabetes and microvascular complications. This reduced dynamic cerebral autoregulatory capacity was present in the absence of signs or symptoms of cardiovascular autonomic neuropathy. In addition, in contrast with our hypothesis, dynamic cerebral autoregulatory efficiency was already reduced in subjects with Type 2 diabetes in the absence of the clinical expression of established indicators of microvascular damage. At the same time, the steady-state response of MCA Vmean to a postural change was unaffected in both DM− and DM+ groups. Together, these findings suggest impairment of dynamic cerebral autoregulation as an early manifestation of microvascular disease prior to cardiovascular autonomic neuropathy or clinical microvascular disease, reflected by diabetic nephropathy and retinopathy. The following discussion details the assumptions and evidence that underlie these conclusions.

There are potential limitations of the present study that need consideration. The lower age of subjects with DM− compared with DM+ questions the effect of age on cerebral autoregulation; however, in healthy subjects, aging does not affect dynamic cerebral autoregulation [34].

The MCA Vmean was chosen for the evaluation of changes in CBF assuming that changes in MCA Vmean are representative of those in CBF. TCD monitors blood velocity rather than blood flow and changes in the diameter of the insonated vessel by enhanced sympathetic activity could modulate velocity independently of flow. However, large cerebral arteries, including the MCA, are conductance, rather than resistance, vessels and moderate sympathetic activation does not modify the luminal diameter of a systemic conduit artery [35]. Thus the constancy of the MCA diameter links changes in cerebral blood velocity to changes in flow.

BP was comparable in the CTRL, DM− and DM+ groups. Although dynamic and static components of cerebral autoregulatory capacity are affected in malignant hypertension [4], cerebral autoregulation indices are unimpaired in uncomplicated hypertension in middle-aged humans, rendering an effect of the BP level itself unlikely [36]. In the DM+ and DM− groups, an effect of antihypertensive medication should be considered. However, integrity of cerebral autoregulation and preservation of CBF during treatment with β-blockade, calcium channel blocker and angiotensin-converting enzyme inhibition or AT₁-receptor (angiotensin II
type 1 receptor) antagonist are confirmed [37–42]. Thus elderly subjects with hypertension, whether controlled or uncontrolled with antihypertensive medication, retain cerebral autoregulatory capacity [43].

The impairment of dynamic cerebral autoregulation in subjects with DM+ in the present study was as severe as that found in patients with acute large MCA territory stroke [7]. In patients with unilateral ischaemic lacunar stroke, dynamic cerebral autoregulation is impaired uniformly at both the non-ischaemic and ischaemic hemisphere. This is compatible with the notion that pre-existing generalized cerebral small vessel disease may affect cerebral autoregulation [7,11]. MCA $V_{\text{mean}}$ LF power was comparable in all groups, whereas MAP LF power as input to the transfer function was lower in subjects with DM− compared with CTRL subjects, and, in subjects with DM+, the reduction reached statistical significance. This resulted in a higher gain in both subjects with DM− and DM+, reflecting proportionally less dampening of MAP oscillations compared with CTRL subjects. Given a lower amplitude of a particular oscillation, there might be more influence of background noise in the determination of oscillation parameters. However, coherence between MAP and MCA $V_{\text{mean}}$ was not statistically different for subjects with DM+ and DM− and CTRL subjects. In addition, the expected increase in variance of the extracted parameters, gain and phase, was not observed. Moreover, MAP power and phase did not correlate. Therefore we consider that the findings do not depend on signal noise, but reflect an inherent problem in subjects with DM+.

The present study indicates that dynamic cerebral autoregulation becomes affected in subjects with Type 2 diabetes prior to the occurrence of cerebral ischaemic symptoms. Impaired cerebral autoregulation is associated with cardiovascular autonomic neuropathy [11,44]. Moreover, when healthy humans are subjected to ganglion blockade with the development of arterial hypotension, cerebral autoregulation can no longer maintain MCA $V_{\text{mean}}$ [45]. This has been attributed to removal of vasomotor effects of autonomic neural activity. The present study was designed to account for the influence of cardiovascular autonomic neuropathy by excluding patients with demonstrable cardiovascular autonomic dysfunction by standardized autonomic function tests [19,23]. The mechanism underlying this early decrease in autoregulatory capacity in subjects with Type 2 diabetes cannot be determined from the present study, but dynamic cerebral autoregulatory capacity was reduced in the absence of overt cardiovascular autonomic neuropathy.

To our knowledge, this is the first study to establish a reduction in dynamic cerebral autoregulatory efficiency in subjects with Type 2 diabetes who have no clinical evidence of microvascular complications. The cerebral arterial pulsatility index is proposed as an indicator of cerebral microangiopathy in diabetes [29]. An elevated pulsatility index of the MCA in complicated compared with uncomplicated Type 2 diabetes and a close correlation with the duration of diabetes suggest that the pulsatility index reflects microangiopathic changes of cerebral vessels [29], but this was not substantiated in the present study where the pulsatility index did not differ across groups. The progressive reduction in phase lead of MCA $V_{\text{mean}}$ to MAP correlated closely with the duration of diabetes, suggesting that impairment of dynamic cerebral autoregulation is an early marker of microangiopathy in advance of established indicators for retinopathy and nephropathy.

A role for hyperglycaemia in affected cerebral autoregulation should be considered. However, in patients with diabetes, MCA $V_{\text{mean}}$ does not relate to either glucose or insulin plasma concentrations [46]. Furthermore, hyperglycaemic clamping does not affect dynamic
cerebral autoregulatory capacity both at rest and during exercise [47]. The finding that the physiological postural reduction in MCA $V_{\text{mean}}$ in both subjects with DM− and DM+ was comparable with that found in healthy subjects confirms the integrity of static cerebral autoregulation [15,32,48]. The present study reports that a reduced dynamic cerebral autoregulatory capacity does not jeopardize cerebral perfusion when exposed to orthostatic stress. The finding that dynamic cerebral autoregulation appears to be a more vulnerable component of cerebrovascular control conforms to earlier observations that progressive impairment in cerebral autoregulation first affects the latency and then the efficiency of the cerebral autoregulation response [1].

Our findings are of concern for subjects with Type 2 diabetes who have no clinical evidence of microvascular complications. Subjects with Type 2 diabetes are advised to combine aerobic and resistance training [49,50]. Similar to aerobic exercise, resistance training enhances insulin sensitivity but it also involves repeated strain-like manoeuvres with abrupt BP increments [31]. The findings of the present study indicate that transmission of BP surges to the cerebral vasculature is dampened less effectively in subjects with Type 2 diabetes. In conclusion, Type 2 diabetes is associated with early impairment of dynamic cerebral autoregulation becoming manifest prior to the occurrence of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.

ACKNOWLEDGMENTS

We thank our patients for their co-operation in this study. This study is supported by a grant from the Dutch Diabetes Foundation (grant #2004–00–001).

REFERENCES

15 Wieling, W. and Van Lieshout, J. J. (1997) Maintenance of cerebral perfusion when exposed to orthostatic stress. The finding that the physiological postural reduction in MCA $V_{\text{mean}}$ in both subjects with DM− and DM+ was comparable with that found in healthy subjects confirms the integrity of static cerebral autoregulation [15,32,48]. The present study reports that a reduced dynamic cerebral autoregulatory capacity does not jeopardize cerebral perfusion when exposed to orthostatic stress. The finding that dynamic cerebral autoregulation appears to be a more vulnerable component of cerebrovascular control conforms to earlier observations that progressive impairment in cerebral autoregulation first affects the latency and then the efficiency of the cerebral autoregulation response [1].

Our findings are of concern for subjects with Type 2 diabetes who have no clinical evidence of microvascular complications. Subjects with Type 2 diabetes are advised to combine aerobic and resistance training [49,50]. Similar to aerobic exercise, resistance training enhances insulin sensitivity but it also involves repeated strain-like manoeuvres with abrupt BP increments [31]. The findings of the present study indicate that transmission of BP surges to the cerebral vasculature is dampened less effectively in subjects with Type 2 diabetes. In conclusion, Type 2 diabetes is associated with early impairment of dynamic cerebral autoregulation becoming manifest prior to the occurrence of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.

ACKNOWLEDGMENTS

We thank our patients for their co-operation in this study. This study is supported by a grant from the Dutch Diabetes Foundation (grant #2004–00–001).

REFERENCES

15 Wieling, W. and Van Lieshout, J. J. (1997) Maintenance of cerebral perfusion when exposed to orthostatic stress. The finding that the physiological postural reduction in MCA $V_{\text{mean}}$ in both subjects with DM− and DM+ was comparable with that found in healthy subjects confirms the integrity of static cerebral autoregulation [15,32,48]. The present study reports that a reduced dynamic cerebral autoregulatory capacity does not jeopardize cerebral perfusion when exposed to orthostatic stress. The finding that dynamic cerebral autoregulation appears to be a more vulnerable component of cerebrovascular control conforms to earlier observations that progressive impairment in cerebral autoregulation first affects the latency and then the efficiency of the cerebral autoregulation response [1].

Our findings are of concern for subjects with Type 2 diabetes who have no clinical evidence of microvascular complications. Subjects with Type 2 diabetes are advised to combine aerobic and resistance training [49,50]. Similar to aerobic exercise, resistance training enhances insulin sensitivity but it also involves repeated strain-like manoeuvres with abrupt BP increments [31]. The findings of the present study indicate that transmission of BP surges to the cerebral vasculature is dampened less effectively in subjects with Type 2 diabetes. In conclusion, Type 2 diabetes is associated with early impairment of dynamic cerebral autoregulation becoming manifest prior to the occurrence of diabetic nephropathy, retinopathy or cardiovascular autonomic neuropathy.

Published as Immediate Publication 18 March 2008, doi:10.1042/CS20070458