Intensive Blood Pressure Control Affects Cerebral Blood Flow in Type 2 Diabetes Mellitus Patients

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Abstract—Type 2 diabetes mellitus is associated with microvascular complications, hypertension, and impaired dynamic cerebral autoregulation. Intensive blood pressure (BP) control in hypertensive type 2 diabetic patients reduces their risk of stroke but may affect cerebral perfusion. Systemic hemodynamic variables and transcranial Doppler-determined cerebral blood flow velocity (CBFV), cerebral CO_2 responsiveness, and cognitive function were determined after 3 and 6 months of intensive BP control in 17 type 2 diabetic patients with microvascular complications (T2DM+), in 18 diabetic patients without (T2DM−) microvascular complications, and in 16 nondiabetic hypertensive patients. Cerebrovascular reserve capacity was lower in T2DM+ versus T2DM− and nondiabetic hypertensive patients (4.6±1.1 versus 6.0±1.6 [$P<0.05$] and 6.6±1.7 [$P<0.01$], Δ% mean CBFV/mm Hg). After 6 months, the attained BP was comparable among the 3 groups. However, in contrast to nondiabetic hypertensive patients, intensive BP control reduced CBFV in T2DM− (58±9 to 54±12 cm · s^{-1}) and T2DM+ (57±13 to 52±11 cm · s^{-1}) at 3 months, but CBFV returned to baseline at 6 months only in T2DM−, whereas the reduction in CBFV progressed in T2DM+ (to 48±8 cm · s^{-1}). Cognitive function did not change during the 6 months. Static cerebrovascular autoregulation appears to be impaired in type 2 diabetes mellitus, with a transient reduction in CBFV in uncomplicated diabetic patients on tight BP control, but with a progressive reduction in CBFV in diabetic patients with microvascular complications, indicating that maintenance of cerebral perfusion during BP treatment depends on the progression of microvascular disease. We suggest that BP treatment should be individualized, aiming at a balance between BP reduction and maintenance of CBFV. **(*Hypertension*. 2011;57:738-745.) • Online Data Supplement**

Key Words: autonomic function ■ blood pressure ■ cerebrovascular circulation ■ diabetes mellitus ■ hypertension ■ microvascular complication

Hypertension is a common comorbidity in patients with type 2 diabetes mellitus (T2DM), and both diabetes mellitus and hypertension are risk factors for stroke.[1] In patients with T2DM and hypertension, blood pressure (BP) control reduces the risk of complications and death related to T2DM.[2] Specifically, in T2DM, tight BP control reduces the risk of ischemic stroke significantly.[3]

Cerebrovascular autoregulation (CA) refers to the ability to maintain cerebral blood flow (CBF) constant despite changes in the cerebral perfusion pressure[4] and involves both fast and slow regulatory components.[5,6] The fast component of the cerebral vasoregulatory system can be expressed as the dynamic CA, whereas static CA reports the long-term efficacy of the system.[7,8] In patients with moderate hypertension, CA protects the brain from hyperperfusion[9,10] and equally from hypoperfusion during antihypertensive therapy.[11] However, with severe hypertension, both dynamic and static CA are impaired. During acute antihypertensive treatment of these patients, CBF decreases together with BP, that is, CBF becomes pressure dependent.[12]

In T2DM patients with microvascular complications, dynamic CA is impaired,[13,14] and this study tested the hypothesis that intensive control of BP in patients with complicated T2DM and hypertension may affect cerebral perfusion, whereas in patients with T2DM and hypertension without signs of microvascular disease, cerebral perfusion is maintained when BP is tightly controlled. We further questioned whether in these patients improved BP control restitutes

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dynamic CA capacity. To that purpose the effects of antihypertensive treatment on cerebral perfusion, static and dynamic CA, cerebrovascular reserve capacity, and cognitive function were followed in patients with complicated and uncomplicated T2DM with hypertension and in hypertensive patients without diabetes mellitus.

Methods

Subjects and Study Design

Twenty-two hypertensive patients with complicated T2DM (T2DM+) were consecutively recruited from the outpatient clinic. Patients with uncomplicated T2DM (T2DM−) and patients with hypertension without diabetes (HT) matched for age, sex, and ethnicity served as references. Each subject received verbal and written information about the study objectives, measurement techniques, and the risks and benefits associated with the investigation. All of the subjects gave their written informed consent as approved by the Academic Medical Center Medical Ethical Committee, and experiments were performed in accordance with the Declaration of Helsinki. At baseline, 11 T2DM−, 15 T2DM+, and 7 HT patients received antihypertensive treatment. T2DM+ and T2DM− patients had been diagnosed according to the World Health Organization criteria[15] and were receiving treatment with oral antidiabetic agents and/or insulin. Selection criteria for T2DM+ included microvascular complications including microalbuminuria (urinary albumin excretion rate of 30 to 300 mg/24 hours and albumin/creatinine ratio >2.5 mg/mmol for men or >3.5 mg/mmol for women), retinopathy (classified as mild, moderate, or severe nonproliferative diabetic retinopathy, respectively, and early or high-risk proliferative diabetic retinopathy), and/or sensorimotor neuropathy. Patients without these complications were designated as T2DM−. Before inclusion in the study, a 24-hour ambulatory BP measurement was obtained in all of the patients (Mobilograph, APC Cardiovascular). Selection of hypertensive patients was based on the average of daytime 24-hour BP (>130/80 mm Hg for T2DM patients and >140/90 mm Hg for HT patients). Exclusion criteria included clinical manifestation of cardiovascular disease (stroke, transient ischemic attacks, and heart failure), cardiovascular sympathetic autonomic dysfunction, and poor metabolic control.

Study Protocol

The studies were performed in morning sessions at 22°C after an overnight fast, and the patients abstained from caffeinated beverages for ≥12 hours. After instrumentation and 20 minutes of supine rest, cardiac output was measured, and baseline systemic and cerebrovascular variables were recorded. Cardiovascular autonomic function and the cerebrovascular CO_2 responsiveness were assessed at baseline. After baseline hemodynamic measurements (t=0), hypertension was treated using a stepped care approach, starting with an angiotensin-converting enzyme inhibitor, followed by increasing the dosage until maximum effect and addition of a diuretic or a calcium channel blocking agent if the targeted BP was not reached. BP treatment was checked monthly and continued for 6 months, aiming at a daytime 24-hour BP of <130/80 mm Hg for T2DM patients and <140/90 mm Hg for HT patients. At baseline, at 3 months, and after 6 months, 24-hour ambulatory BP was measured to evaluate whether the targeted BP was reached and cerebrovascular variables were determined.

Instrumentation

Continuous BP was measured noninvasively by finger photoplethysmography (Portapres, Finapres Medical Systems) and calibrated by an automated noninvasive BP measuring device (HEM-7000-E, Omron). Cardiac output was determined by foreign gas rebreathing (Innocor, Innovision).[16] Heart rate was monitored by ECG. The transcranial Doppler (TCD; DWL Multidop X4)-derived CBF velocity (CBFV) was measured in the proximal segment of the right middle cerebral artery (MCA) insonated through the posterior temporal ultrasound window, with the TCD probe secured (Marc 600, Spencer Technologies). TCD determination of MCA blood mean velocity (V_{mean}) is reproducible with a difference of <3% and an R value of 0.95 between 2 measurements.[17] End-tidal CO_2 tension (P_{ETCO_2}) was measured by an infrared capnograph (Tonocap, Datex-Ohmeda). BP, spectral envelope of MCA blood velocity, ECG, and P_{ETCO_2} signals were converted at 100 Hz. Stroke volume was the ratio of cardiac output/heart rate, cerebrovascular resistance index (CVRi) the ratio of mean arterial pressure (MAP)/MCA V_{mean}, cerebrovascular conductance index the ratio of MCA V_{mean}/MAP, and systemic vascular resistance the ratio of MAP/cardiac output. Steady-state systemic and cerebral hemodynamic data were expressed as averages of 3-minute time frames. For cerebrovascular CO_2 responsiveness, cardiovascular autonomic function, and cognitive function, please see the online Data Supplement (available at http://hyper.ahajournals.org).

Cerebrovascular Autoregulatory Capacity

Static CA relates resting supine CBF to BP and was considered intact when MCA V_{mean} was maintained with reduced BP. Dynamic CA was quantified as the counterregulatory capacity to maintain CBFV during spontaneous changes in BP. Beat-to-beat MAP and MCA V_{mean} of 5-minute episodes were spline interpolated and resampled at 4 Hz. Variability of MAP and MCA V_{mean} was estimated with discrete Fourier transformation, and from the cross-spectrum, the phase shift of the MAP to MCA V_{mean} transfer function and its gain were derived. The gain was the ratio of the amplitudes of MCA V_{mean} and MAP, reflecting the effective dampening expressed as the percentage of change in centimeters · second^{-1} per percentage of change in millimeters of mercury in the low-frequency range (0.07 to 0.15 Hz).[7] Coherence examined the strength of the relationship between MAP and MCA V_{mean}.[12] Dynamic CA capacity was measured at onset of the study and after 3 and 6 months.

Statistical Analysis

Two-way repeated-measures ANOVA identified differences and interactions between the groups of patients and the effects of antihypertensive treatment on the cerebrovascular and cardiovascular variables. The Holm-Sidak method was used for post hoc multiple comparisons if significant group and/or interaction effects were detected. Data are presented as mean±SD, and a $P<0.05$ was considered to indicate a statistically significant difference.

Results

Group Characteristics and Baseline Data

Two HT patients, 4 T2DM− patients, and 5 T2DM+ patients were lost to follow-up and were not included in the final data analysis (Table 1). As intended, there were no differences in sex, age, body mass index, or cholesterol levels among patient groups, whereas plasma glucose and hemoglobin A1c levels were higher in T2DM patients ($P<0.01$). Known duration of diabetes mellitus and the urine albumin/creatinine ratio were larger in T2DM+ versus T2DM− subjects ($P<0.01$). Among the T2DM+ patients, 5 had mild and 2 had moderate nonproliferative diabetic retinopathy. Four of the 11 T2DM+ patients underwent nerve conduction tests confirming the diagnosis of polyneuropathy, whereas in other patients sensorimotor polyneuropathy was clinically diagnosed ranging from tingling toes to neuropathic pain, for which 1 patient received medication. The cerebral CO_2 responsiveness was lower in the T2DM+ group (4.6±1.1 versus 6.0±1.6 $\Delta\%V_{mean}$/mm Hg in T2DM− [$P<0.05$] and

Table 1. Baseline Group Characteristics

	Groups		
Characteristic	HT (n=16)	T2DM− (n=18)	T2DM+ (n=17)
Male:female, n	7:9	10:8	10:7
Age, y	52±13	54±6	57±8
Body mass index, kg/m^2	28.3±4.1	29.1±4.5	31.5±5.7
Known duration of diabetes mellitus, y	—	8.1±4.3	12.5±8.1†
Microvascular complications			
Retinopathy	—	0	7
Nephropathy	—	0	14
Polyneuropathy, sensorimotor	—	0	11
Oral hypoglycemic agents	—	16	11
Insulin	—	6	15
Plasma glucose, mmol/L	5.0±0.4	8.1±2.0*	8.3±2.3*
Glycosylated hemoglobin, % hemoglobin	5.7±0.5	7.4±1.2*	8.2±1.9*
Albumin/creatinine ratio, mg/mmol	1.3±0.6	1.3±0.8	10.2±12.2*‡
Cholesterol			
Total, mmol/L	4.66±0.86	4.30±0.95	4.31±0.80
High-density lipoprotein, mmol/L	1.33±0.26	1.24±0.30	1.22±0.47
Low-density lipoprotein, mmol/L	2.73±0.26	2.18±0.86	2.21±0.65
Triglycerides, mmol/L	1.20±0.74	1.93±1.39	2.09±1.80
Cerebral CO_2 responsiveness, $\Delta\%V_{mean}$/mm Hg	6.6±1.7	6.0±1.6	4.6±1.1*†

Data are mean±SD.
*$P<0.01$ vs HT.
†$P<0.05$ vs T2DM−.
‡$P<0.01$ vs T2DM−.

6.6±1.7 $\Delta\%V_{mean}$/mm Hg in HT [$P<0.01$]). Three patients in the T2DM− group and 7 in the T2DM+ group had abnormal heart rate responses to a Valsalva maneuver and standing procedures, indicating parasympathetic dysfunction. Sympathetic cardiovascular function was intact in all of the patients. MAP, heart rate, stroke volume, cardiac output, systemic vascular resistance, MCA V_{mean}, CVRi, cerebrovascular conductance index, and P_{ETCO_2} were comparable among groups (Table 2).

BP, Hemodynamic Variables, and Cognitive Function

The use of antihypertensive agents was similar among groups of patients at 6 months of treatment (see online Data Supplement Table S1 at http://hyper.ahajournals.org). Twenty-four–hours systolic and diastolic BP profiles were also comparable among the groups, and after 3 months of treatment, the targeted BP was reached in HT (after 2.1±1.5 months) and T2DM− (after 3.0±1.7 months) but not for the T2DM+. In 3.9±2.0 months, the targeted 24-hour BP was reached also for the T2DM+ group ($P<0.01$ versus HT). The reduction in systolic and diastolic BPs was related to a balanced reduction in cardiac output and systemic vascular resistance. Before treatment, the number of errors with the Stroop color test and the duration of the digit linking test were higher in T2DM+ patients (see Table S2) and remained so after 6 months.

Static CA

After 6 months of tight BP control, P_{ETCO_2} had not changed, and MCA V_{mean} had remained unchanged in the HT group, whereas there was a reduction in T2DM− at 3 months (54±12 versus 58±9 $cm \cdot s^{-1}$; $P<0.05$), which regained baseline after 6 months (see Figure S1). In contrast, in the T2DM+ group the reduction in MCA V_{mean} at 3 months (52±11 versus 57±13 $cm \cdot s^{-1}$; $P<0.05$) had progressed after 6 months ($P<0.05$). Thus, MCA V_{mean} became lower in T2DM+ versus HT and T2DM− (48±8 versus 56±10 and 56±14 $cm \cdot s^{-1}$, $P<0.05$; Figure 1), supported by a lower cerebrovascular conductance index in T2DM+ (0.53±0.12 versus 0.60±0.09 [HT] versus 0.63±0.17 [T2DM−] $cm \cdot s^{-1} \cdot mm\,Hg^{-1}$; $P<0.05$). Accordingly, the CVRi decreased in HT and T2DM− but did not change in T2DM+ (2.0±0.4 versus 1.7±0.3 [HT] and 1.7±0.4 [T2DM−] $mm\,Hg \cdot cm^{-1} \cdot s^{-1}$; $P<0.05$).

Dynamic CA

In 3 HT patients, 6 T2DM− patients, and 5 T2DM+ patients transfer function coherence was <0.5, and these data were excluded from further analysis. At baseline, MAP power tended to be lower in T2DM versus HT, whereas MCA V_{mean} power was comparable between groups (Figure 2). The phase difference of the MAP-MCA V_{mean} transfer function at baseline was normal (50±9°) in HT but lower in T2DM− (41±7°; $P<0.01$ versus HT) and impaired in T2DM+ (31±6°; $P<0.01$ versus T2DM−), indicating less effective dynamic CA.

Table 2. Cerebrovascular and Cardiovascular Responses to Hypertension Treatment

Variables	Groups	Baseline	t=3 mo	t=6 mo
MAP, mm Hg	HT	104±12	93±9§	93±10§
	T2DM−	102±8	96±6‡	90±5§
	T2DM+	103±9	98±8‡	92±9§
Heart rate, beats · min^{-1}	HT	71±11	70±10	72±15
	T2DM−	79±12	80±11†	78±10
	T2DM+	79±14	79±13*	77±15
Stroke volume, mL	HT	93±29	91±26	81±16
	T2DM−	79±21	76±21	79±22
	T2DM+	83±34	84±32	82±35
Cardiac output, L · min^{-1}	HT	6.4±1.5	6.4±1.7	6.0±1.3§
	T2DM−	6.4±1.5	6.1±1.4‡	6.0±1.6§
	T2DM+	6.3±2.1	6.4±2.0	6.0±2.3§
SVR, dyn · s · cm^{-5}	HT	1368±395	1284±533§	1279±293§
	T2DM−	1357±355	1305±286‡	1274±322§
	T2DM+	1437±462	1331±411‡	1413±545
MCA V_{mean}, cm · s^{-1}	HT	57±7	57±9	56±10
	T2DM−	58±9	54±12‡	56±14
	T2DM+	57±13	52±11‡	48±8§*¶‖
CVRi, mm Hg · cm^{-1} · s^{-1}	HT	1.9±0.3	1.7±0.3‡	1.7±0.3‡
	T2DM−	1.8±0.4	1.9±0.4	1.7±0.4
	T2DM+	1.9±0.4	1.9±0.4*	2.0±0.4*¶
CVCi, cm · s^{-1} · mm Hg^{-1}	HT	0.55±0.10	0.62±0.13†	0.60±0.09
	T2DM−	0.58±0.11	0.57±0.13	0.63±0.17
	T2DM+	0.56±0.16	0.54±0.13	0.53±0.12*§
$P_{ET}CO_2$, mm Hg	HT	40±3	40±3	40±3
	T2DM−	41±3	40±3	39±4
	T2DM+	40±4	40±4	40±3

SVR indicates systemic vascular resistance; CVCi, cerebrovascular conductance index.
*$P<0.05$ vs HT.
†$P<0.01$ vs HT.
‡$P<0.05$ vs baseline.
§$P<0.01$ vs baseline.
‖$P<0.05$ vs 3 months.
¶$P<0.05$ vs T2DM−.

Discussion

The results of this study provide insight into the effects of tight BP control on cerebrovascular autoregulatory capacity and its consequences for cerebral perfusion in patients with T2DM. Static CA reports the overall efficiency of the cerebral vasoregulatory system, whereas dynamic CA reflects the latency and time constant of CA.[7,8] Linking static and dynamic components, the degree of overall CA impairment appeared related to the presence of clinically manifested microvascular complications. An impaired cerebrovascular CO_2 responsiveness signifies impaired vasodilatory capacity of the brain. Together these results indicate impairment of both mechanoregulation and chemoregulation as the 2 major operative mechanisms responsible for maintaining CBF, rendering T2DM+ patients susceptible to ischemic episodes.

Target BP was reached within 3 months in HT versus 3 to 6 months in T2DM+. The finding in HT that, for a comparable reduction in BP, cerebral blood velocity in HT was maintained conforms to observations in patients with mild or moderate hypertension during long-term BP treatment.[11] Improved cerebral perfusion has been observed in elderly uncontrolled hypertensive subjects after 6 months of aggressive BP control,[18] but in patients with malignant hypertension static CA is impaired.[12,19] Bentsen et al[20] showed pressure dependency of CBF in a subgroup of patients with long-standing type 1 diabetes mellitus. This study extends these observations to T2DM patients with moderate microvascular complications for whom a decline in MCA V_{mean} was in proportion to the reduction in BP by antihypertensive treatment. In T2DM− patients a transient reduction in MCA V_{mean} was observed after 3 months of strict BP treatment, subsequently regaining baseline level after 6 months. In contrast, in T2DM+ patients the MCA V_{mean} continued to decline during the course of 6 months of treatment rendering a recovery of static CA at a later stage unlikely. These different findings in the T2DM+ and T2DM− groups dem-

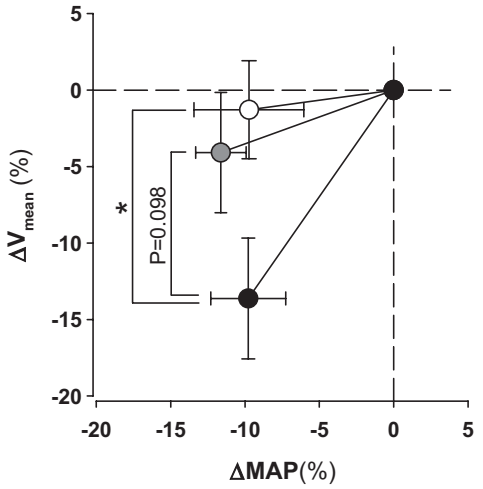

Figure 1. Effects of intensive BP treatment on group averaged MAP versus MCA V_{mean} in HT (white circle), in T2DM− (dark gray circle), and in T2DM+ (black circle) patients. *$P<0.05$ vs HT. Values are mean±SEM.

onstrate that progressive impairment in cerebral autoregulation first affects the latency and then the efficiency of the cerebral autoregulation response. The recovery of static but not of dynamic CA with continuation of tight BP control suggests nervous system plasticity in T2DM− patients.

Hypertension is the leading modifiable risk factor for both first-ever and recurrent stroke. The association between BP and stroke risk is continuous, and tight control of BP substantially reduces not only the expression of both microvascular and macrovascular complications but also increases survival and the complication-free interval.[2] Current guidelines emphasize tight hypertension treatment in T2DM subjects to reduce the risk of stroke.[2] Tight BP management has even been suggested to provide for greater benefit than strict plasma glucose control in T2DM patients.[2,21] However, the findings in the T2DM+ group indicate that, once vascular damage is present, cerebral control mechanisms no longer safeguard brain perfusion, even for a reduction in BP within what is referred to as the normal autoregulatory range.

Physiological aging is associated with a decline in resting cerebral metabolism and CBF.[22] The observed decline in cerebral perfusion by antihypertensive treatment adds to the physiological ≈15% reduction in gray matter flow between the third and fifth decades.[23] This relates to the concern that lowering BP carries a risk of provoking cerebral hypoperfusion, in particular in elderly patients with cerebrovascular disease. Cerebral hemispheric white matter lesions have been attributed to cerebral hypoperfusion.[24,25] Vascular risk factors are thought to have importance for dementia,[26] and although Alzheimer disease is considered being a nonvascular disease,

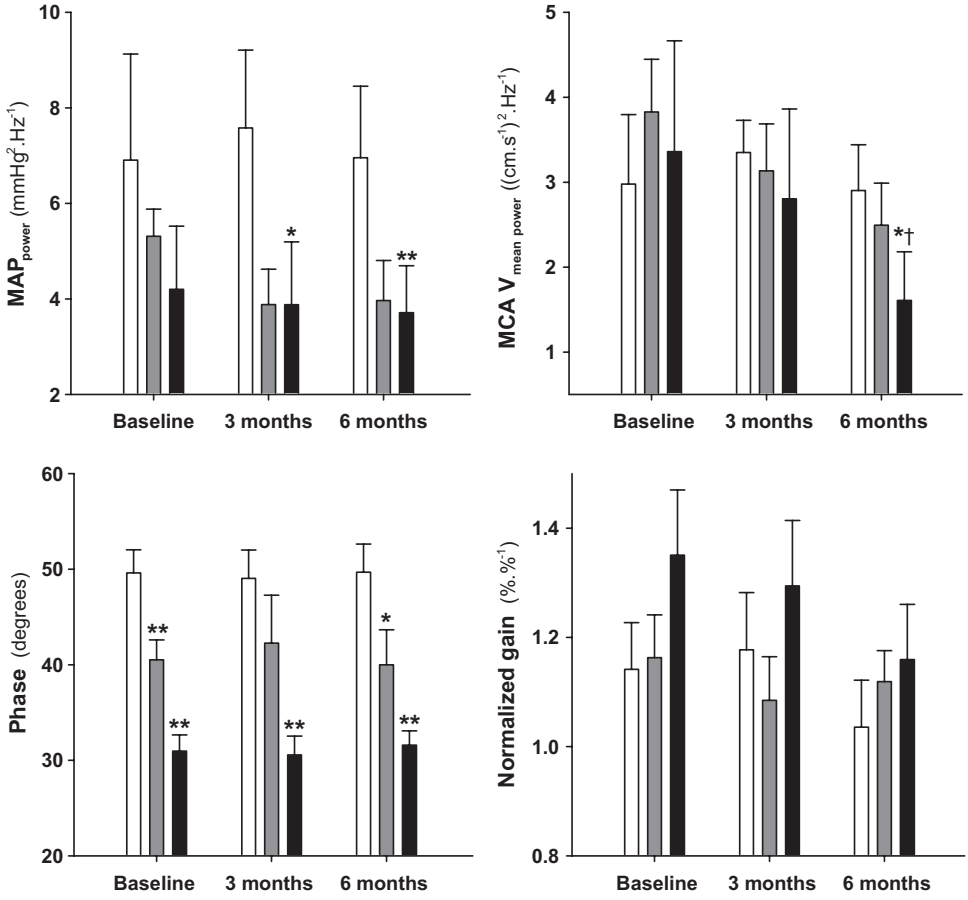

Figure 2. Group-averaged low-frequency (0.07 to 0.15 Hz) MAP power (MAP_{power}), MCA mean blood velocity power (MCA $V_{mean\ power}$), transfer function phase, and normalized gain between MAP and MCA V_{mean} in HT (white bars), T2DM− (dark gray bars), and T2DM+ (black bars) patients at baseline and after 3 and 6 months of BP treatment. *$P<0.05$ vs HT, **$P<0.01$ vs HT, †$P<0.05$ vs baseline. Values are mean±SEM.

vascular factors may contribute.[27,28] Both high[29] and low BP[30] have been forwarded as critical factors for the development of Alzheimer disease and cognitive decline.[26–29] In cross-sectional studies cognitive decline and dementia are associated with a lower BP,[31] and there is a curvilinear relationship between systolic BP and cognitive function.[32,33] The suggestion that cerebral hypoperfusion is associated with later cognitive decline[26] was not substantiated within the time span of the present study, where the difference in cognition score for T2DM+ versus T2DM− subjects, present before the start of antihypertensive treatment, remained, notwithstanding a reduction in MCA V_{mean} in T2DM+ patients.

A strategy of intensive BP control for patients with T2DM has been challenged in that targeting a systolic BP of ≤120 versus 140 mm Hg did not reduce the rate of a composite outcome of nonfatal cardiovascular events.[34] However, the reported stroke incidence was not classified further into brain infarction versus hemorrhage, leaving the Scylla-and-Charybdis issue of hypertension- versus hypoperfusion-related brain damage in T2DM subjects as yet unanswered. The lower limit of CA has not been established in T2DM patients, but impaired CA in T2DM patients with microvascular damage and a permanent reduction in MCA V_{mean} raise concern. An optimal BP may be indicated for a population, but the data indicate that this is not the case for the individual patient with T2DM.

Several mechanisms involved in a reduction in CBFV related to tight hypertension treatment are to be considered. CBF is influenced by neural activity, CA, and the arterial CO_2 tension.

Cerebral perfusion becomes jeopardized when cerebral vasodilatory capacity becomes exhausted, and in T2DM+ patients, a lower cerebrovascular reserve and absence of a reduction in CVRi after 6 months of antihypertensive treatment may contribute. CBF is influenced by the arterial CO_2 tension, but P_{ETCO_2} levels were comparable among groups. Cerebral perfusion depends on the arterial perfusion pressure, but the influence of cardiac output is also of importance.[35] Cardiac output supports the cerebral perfusion both at rest and during exercise,[36,37] independent from cerebral autoregulation.[38] The magnitude of the reduction in cardiac output during treatment was comparable between groups, but the reduction in CVRi observed in HT and T2DM− patients was absent in T2DM+ subjects. In healthy subjects, cardiac output does not affect the dynamic cerebral autoregulatory response to hypotension.[39] Nevertheless, we cannot exclude that this adverse cerebrovascular response is related to an effect of cardiac output and/or central blood volume establishing the CBF to be regulated. The MCA V_{mean} was chosen for evaluation of changes in CBF assuming that changes in MCA V_{mean} are representative of those in CBF. TCD monitors blood velocity rather than CBF, and changes in the diameter of the insonated vessel by enhanced sympathetic activity could modulate velocity independent of flow. However, large cerebral arteries, including the MCA, are conductance rather than resistance vessels, and moderate sympathetic activation does not modify the luminar diameter of a systemic conduit artery. Also, by comparison of TCD with CBF measurements according to the Fick principle, TCD has been shown valid for static, or steady-state, measurements of CA. Thus, the constancy of the MCA diameter links changes in cerebral blood velocity to those in flow. Carotid artery diameter was not assessed, and we cannot exclude that some of the patients may have had significant carotid artery stenosis.

We considered that different antihypertensive agents have had a variable effect on CBF. If so, an effect of additional antihypertensive agents throughout the 6 months of the study, if any, would be expected to influence CBF to the same extent for all of the groups. Cerebral vascular angiotensin receptors may account for the improved CBF and favorable autoregulatory responses in hypertensive patients treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[40] Calcium channel blockers have variable specificity for cerebral vessels potentially beneficial by increasing CBF,[41,42] whereas β-blockade studies revealed either no effect on CBF at rest or a slight decrease.[43,44] Under the resting condition of this study, an effect of β-adrenergic receptor blockade on cardiac output and MCA V_{mean} has probably been low, if there has been any effect at all. However, during exercise, β-adrenergic receptor blockade attenuates the increase in cardiac output and also the increase in MCA V_{mean}, typically to half of the normal response.[45,46] The implication is that the observed reduction in resting MCA V_{mean} in T2DM+ underestimates the effect on CBF when exercising under β-adrenergic receptor blockade. In addition, single drug treatment with a diuretic did not affect ^{133}Xe-determined gray matter flow or modified cerebrovascular resistance in elderly hypertensive subjects.[47] The distribution of antihypertensive agents across groups was comparable so that, together with a similarly balanced reduction in cardiac output and vascular resistance, it renders an influence of antihypertensive medication on the reduction in CBF in T2DM+ subjects unlikely. Acute hyperglycemia reduces CVRi, and such cerebral vasodilation does not depend on the dynamic CA efficacy.[48] Thus, an effect of hyperglycemia on the CBF response, if any, would be expected to elevate CBF rather than to reduce it. In the present study, plasma glucose levels at baseline and after 6 months were similar, rendering an influence of glucose on the CBF response during the present antihypertensive treatment unlikely. Rather, we consider the impairment of CA related to general endothelial dysfunction comparable to the situation in sickle cell disease representing nondiabetic small vessel disease.[49] T2DM is associated with early impairment of dynamic CA presenting before the manifestation of diabetic nephropathy, retinopathy, or cardiovascular autonomic neuropathy.[14] The present study confirms impairment of dynamic CA in a larger group of patients and demonstrates that 6 months of effective antihypertensive treatment does not reverse abnormal cerebrovascular control.

Perspectives

Tight hypertension treatment in uncomplicated T2DM challenges CA, but with continued treatment CBFV is preserved. In contrast, a persistent reduction in CBFV in T2DM with microvascular complications indicates that, once microvascu-

lar damage is clinically expressed, static cerebrovascular control is no longer capable of counteractacting a pressure-dependent reduction in cerebral perfusion. Dynamic CA appears to be the more vulnerable component of cerebrovascular control, that is, progressive impairment in CA first affects the latency and then the efficacy of the cerebral autoregulatory response. Accordingly, for optimal cardiovascular benefit, tight BP control should be instituted early in the course of developing hypertension in T2DM when CA is capable of counteractacting the reduction in perfusion pressure. For patients with vascular complications, BP treatment should be individualized, aiming at a balance between the reduction in BP and maintenance of CBFV, targeting an "optimal" rather than a maximal reduction of elevated BP.

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Disclosures

None.

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