Impaired cerebral CO2 vasoreactivity: association with endothelial dysfunction

Shahar Lavi,1,2 Diana Gaitini,3 Victor Milloul,1 and Giris Jacob1,4

1J. Recanati Autonomic Dysfunction Center, 2Cardiology Department, 3Radiology Department, and 4Internal Medicine A, Rambam Medical Center and Technion-Israel Institute of Technology, Haifa, Israel

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Lavi, Shahar, Diana Gaitini, Victor Milloul, and Giris Jacob. Impaired cerebral CO2 vasoreactivity: association with endothelial dysfunction. Am J Physiol Heart Circ Physiol 291: H1856–H1861, 2006. First published June 9, 2006; doi:10.1152/ajpheart.00014.2006.—Conflicting data exist on the role of nitric oxide (NO) in cerebral blood flow (CBF) autoregulation. Previous studies involving human and animal subjects seem to indicate that NO involvement is limited to the CO2-dependent mechanism (chemoregulation) and not to the pressure-dependent autoregulation (mechanoregulation). We tested this hypothesis in patients with impaired endothelial function compared with healthy controls. Blood pressure, heart rate, end-tidal PCO2, CBF velocities (CBFV), forearm blood flow, and reactive hyperemia were assessed in 16 patients with diabetes mellitus and/or hypertension and compared with 12 age- and sex-matched healthy controls. Pressure-dependent autoregulation was determined by escalating doses of phenylephrine. CO2 vasoreactivity index was extrapolated from individual slopes of mean CBFV during repeated after sodium nitroprusside infusion. Indexes of endothelial function, maximal and area under the curve (AUC) of forearm blood flow (FFB) changes, were significantly impaired in patients (maximal flow; 488 ± 75 vs. 297 ± 31%; P = 0.01, AUC ΔFFB: 173 ± 17 vs. 127 ± 11; P = 0.03). Patients and controls showed similar changes in cerebrovascular resistance during blood pressure challenges (identical slopes). CO2 vasoreactivity was impaired in patients compared with controls; 1.19 ± 0.1 vs. 1.54 ± 0.1 cm·s−1·mmHg−1; P = 0.04. NO donor (sodium nitroprusside) offsets this disparity. These results suggest that patients with endothelial dysfunction have impaired CO2 vasoreactivity and preserved pressure-dependent autoregulation. This supports our hypothesis that NO is involved in CO2-dependent CBF regulation alone. CBFV chemoregulation could therefore be a surrogate of local cerebral endothelial function.


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Address for reprint requests and other correspondence: G. Jacob, J. Recanati Autonomic Dysfunction Center, Medicine A, Rambam Medical Center, PO Box 9602, Haifa 31096, Israel (e-mail: g_jacob@rambam.health.gov.il).
infusion of SNP. Finally, phenylephrine was given in escalating doses, if not contraindicated, to determine the CBFV mechanoregulation.

**Measurements.** Continuous three-lead ECG and beat-to-beat radial arterial tonometric BP (CBM 7000, Colin, TX) were monitored and displayed on a computer screen and on a thermal array recorder (TA-6000, Gould, Valley View, OH). Concomitantly, data were digitized at 500 Hz by an analog-to-digital converter, using the WinDaq pro+ software (WinDaq, version 2.27, DATAQ Instruments). Data were stored onto a personal computer for offline analysis using locally developed software (12). Calibration of the tonometric BP was performed by using cuff BP before each investigational procedure. The middle cerebral artery (MCA) was insolated through the temporal window with a 2-MHz probe mounted to a fixation helmet for continuous measurement (EZ-Dop, DWL Elektronische Systeme, Sipplingen, Germany). TCD signals were obtained by adjusting the position for maximal reflected signal at a depth of 50–60 mm (35 ± 0.4 mm). Peak (PV), diastolic, and mean velocities (MV) were monitored. Velocities were averaged over at least four cardiac cycles. Finger O2 saturation and end-tidal PCO2 (PETCO2) were monitored. Velocities were averaged over at least four cardiac cycles. Finger O2 saturation and end-tidal PCO2 (PETCO2) were detected by a nasal capnostat CO2 sensor and analyzed by using an infrared gas analyzer (CO2SMO 7100, Novametrix, Wallingford, CT). Forearm blood flow was assessed by using a venous occlusion plethysmograph (ECSR plethysmograph, Hokanson, Bellevue, WA). A Silastic, mercury-based strain gauge was fixed on the largest part of the forearm. A cuff positioned above the elbow was connected to a rapid-cuff inflator (model E20, Hokanson). Flow measurements were recorded for 7 s every 15 s, after exclusion of hand circulation by inflating a wrist cuff to suprasystolic pressure. Baseline measurements were averaged over at least four cycles. The endothelium-dependent vasodilatation was assessed by comparing baseline flow to hyperemic flow after 5 min of blood flow occlusion to the arm (33). Cerebral vascular chemoregulation was determined by measuring CBFV at baseline (normocapnia), after 3 min of controlled hyperventilation (PeTCO2 of ~25 mmHg) and during hypcapnia induced by an inhaled mixture of 5% CO2-95% O2 for 6 min. The CBFV measurements were repeated during steady-state infusion of SNP after reaching a drop in mean BP of 5–10 mmHg without causing significant hemodynamic changes. Mechanical autoregulation of CBFV was assessed by administering graded doses of phenylephrine, 25–250 μg. Before each procedure, we allowed a rest of 15 min and repeated the baseline measurements.

**Measurement of carotid IMT.** Segments of the common carotid arteries were scanned on both sides by two angles for common carotid IMT measurements. Scans were analyzed offline after digital storage. Four to six measurements of IMT were measured at end-diastolic frame, and average values were used (HDI 5000, ATL, Bothell, WA).

**Data analysis and statistics.** Mean arterial pressure (MAP) was calculated as 1/3 systolic BP + 1/6 diastolic BP. Estimated regional cerebrovascular resistance was calculated as CVR = MAP/CMV (35). The CO2 vasoreactivity index of CBFV was determined as the slope of the linear correlation between MV and PeTCO2 measured during hypcapnia, normocapnia, and hypercapnia. The mechanoregulation of CBFV was plotted as the individual changes in systolic BP, induced by phenylephrine, against the corresponding changes in CVR. Endothelium-dependent vasodilatation response was represented by the maximal changes in forearm blood flow and AUC0–60 (area under curve of percent change from baseline during 60 s) after cessation of forearm ischemia. Power spectral analyses of R-R intervals and beat-to-beat systolic BP were calculated as previously described (12). Two subsets of the frequency domain were used for R-R interval (RRi) and systolic BP variability: low frequency (LFRRi: 0.04 to 0.14-Hz band) and high frequency (HFRRi: 0.15 to 0.4-Hz band). Time domain data of RRi were used for the calculation of cardiac vagal tone indexes: root mean square successive differences (rMSSD) and proportions of cycles where the differences are >50 ms (pNN50), which mainly reflect the cardiac vagal activity. Baroreflex sensitivity was calculated from the time domain data of RRi and beat-to-beat systolic BP (30). The baroreflex sensitivity (BRS) slopes +BRS and −BRS (in ms/mmHg) represent the vagal and sympathetic arm of the baroreflex, respectively.

**RESULTS**

Sixteen patients (12 men, 4 women) and twelve controls (9 men, 3 women) were included in the study. Nine patients had diabetes mellitus (mean duration 13 ± 3 yr, median 10 yr), and 12 patients had hypertension (mean duration 9 ± 1 yr, median 10 yr). Six patients were treated with beta blockers, seven with angiotensin-converting enzyme inhibitors, and four with calcium antagonists. Four diabetic patients were treated with oral hypoglycemic drugs, three with insulin, and two with special diet only. As depicted in Table 1, patient weight, body mass index, and systolic and mean BP were all higher compared with those of the controls. Correlates of atherosclerosis, such as IMT measurements, cholesterol, triglycerides, and C-reactive protein were similar in both groups. Glycosylated hemoglobin levels were higher in patients with diabetes mellitus (8 ± 0.6%) and similar among nondiabetic hypertensive patients and controls (5.5 ± 0.1% vs. 5.2 ± 0.1%).

**Autonomic nervous system indirect indexes of cardiovascular control are depicted in Table 2. Patients had impaired vagal and sympathetic cardiac control. However, sympathetic vascular control was similar in both groups (LFRRi). Both vagal (+BRS) and sympathetic (−BRS) baroreflex arms tended to be impaired in patients. Baseline forearm blood flow and forearm vascular resistance were nonsignificantly different in patients**

### Table 1. General characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>52±2</td>
<td>48±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83±3</td>
<td>72±2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28±0.7</td>
<td>25±0.7</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>147±5</td>
<td>112±3</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>101±4</td>
<td>80±2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68±3</td>
<td>63±2</td>
</tr>
<tr>
<td>Forearm flow, ml/min·1·dl⁻¹</td>
<td>4.4±0.4</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>Forearm resistance, mmHg·ml−¹·mmHg⁻¹</td>
<td>25±2.2</td>
<td>26±3.3</td>
</tr>
<tr>
<td>Peak velocity, cm/s</td>
<td>91±5</td>
<td>87±6</td>
</tr>
<tr>
<td>Mean velocity, cm/s</td>
<td>58±3.3</td>
<td>58±3.3</td>
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<tr>
<td>IMT, mm</td>
<td>0.94±0.07</td>
<td>0.88±0.07</td>
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<tr>
<td>Glucose, mmol/l</td>
<td>8.7±1</td>
<td>6.0±5</td>
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<tr>
<td>HbA1c, %</td>
<td>6.9±0.5</td>
<td>5.2±0.14</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>5.4±0.3</td>
<td>5.2±0.2</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.74±0.3</td>
<td>1.36±0.15</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>0.85±0.05</td>
<td>0.96±0.08</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>3.7±0.2</td>
<td>3.7±0.2</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>2.6±0.3</td>
<td>3.2±1.1</td>
</tr>
</tbody>
</table>

All values are expressed as means ± SE. BMI, body mass index; BP, blood pressure; HR, heart rate; IMT, intima-media thickness; HbA1c, glycosylated hemoglobin; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.
unchanged during hyperventilation: 149 mmHg in patients and controls, respectively. Systolic BP remained 113 beats/min (P < 0.001) in patients and controls, respectively. Hypercapnia induced by an inhaled mixture of 5% CO2-95% O2 for 6 min resulted in ~10% increase in PETCO2 (PETCO2 = 48.6 ± 2.6 mmHg in patients and 48.5 ± 2.6 mmHg in controls). During hypercapnia, systolic and mean BP increased in patients from 146 ± 6 to 153 ± 6 mmHg (P = 0.12) and 98 ± 3 to 104 ± 4 mmHg (P = 0.03), respectively; and 115 ± 4 to 122 ± 4 mmHg (P < 0.001) and 82 ± 3 to 86 ± 4 mmHg (P = 0.1) in controls. Heart rate decreased nonsignificantly from 67 ± 3 to 62 ± 3 beats/min and 68 ± 3 to 61 ± 3 beats/min in patients and controls, respectively.

The vasoreactivity index, extrapolated from the individual linear correlation between PETCO2 values against the corresponding MVs, was significantly lower in patients vs. controls, as shown in Fig. 3. During SNP infusion, the vasoreactivity index dropped significantly in controls but remained unchanged in patients.

Incremental boluses of phenylephrine caused similar increases in systolic BP in both groups. This part of the protocol was not done in five patients because of high BP. The individ-

compared with controls. However, patients showed impaired endothelial function indexes as illustrated in Fig. 1.

CBFV regulation. Our results demonstrate that patients with endothelial dysfunction have compromised CBFV chemoregulation with preserved mechanoregulation. Baseline CBFV, PV, and MV were similar in both groups (Table 1). CVR was significantly higher in patients compared with controls (2.3 ± 0.1 vs. 1.62 ± 0.1 cm⁻¹.s⁻¹.mmHg; P = 0.02). Mean infused dose of SNP was similar in both groups (0.4 ± 0.05 μg·kg⁻¹·min⁻¹), MAP decreased by 12 ± 2 and 11 ± 1%, and heart rate increased by 13 ± 4 and 12 ± 2% during SNP infusion in patients and controls, respectively. The absolute decrease in patients’ systolic and mean BP was higher than that of controls with the same dose of SNP. Baseline CVR decreased similarly by 8%. The individual changes in PV from baseline during steady-state SNP infusion are shown in Fig. 2A.

Hyperventilation caused a similar decrease in PETCO2, from 44 ± 1 to 25 ± 0.4 mmHg and from 45 ± 1 to 26 ± 1 mmHg in patients and controls, respectively. Systolic BP remained unchanged during hyperventilation: 149 ± 6 vs. 146 ± 6 mmHg in patients and 113 ± 4 vs. 115 ± 4 mmHg in controls. Heart rate increased significantly from 67 ± 3 to 80 ± 5 beats/min (P < 0.001) and from 62 ± 3 to 72 ± 3 beats/min (P < 0.001) in patients and controls, respectively. Hypercapnia induced by an inhaled mixture of 5% CO2-95% O2 for 6 min resulted in ~10% increase in PETCO2 (PETCO2 = 48.6 ± 2.6 mmHg in patients and 48.5 ± 2.6 mmHg in controls). During hypercapnia, systolic and mean BP increased in patients from 146 ± 6 to 153 ± 6 mmHg (P = 0.12) and 98 ± 3 to 104 ± 4 mmHg (P = 0.03), respectively; and 115 ± 4 to 122 ± 4 mmHg (P < 0.001) and 82 ± 3 to 86 ± 4 mmHg (P = 0.1) in controls. Heart rate decreased nonsignificantly from 67 ± 3 to 62 ± 3 beats/min and 68 ± 3 to 61 ± 3 beats/min in patients and controls, respectively.

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Table 2. Cardiovascular autonomic nervous system control

<table>
<thead>
<tr>
<th>Time domain analysis</th>
<th>Patients</th>
<th>Control</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>RRI ms</td>
<td>863±32</td>
<td>950±32</td>
<td>0.10</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>21.6±2.6</td>
<td>31±3.7</td>
<td>0.03</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>4.4±1.5</td>
<td>10.3±4.2</td>
<td>0.13</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Frequency domain analysis</th>
<th>Patients</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFHR, ms²</td>
<td>558.5±102.4</td>
<td>1.173±237</td>
<td>0.02</td>
</tr>
<tr>
<td>LFHR, ms²</td>
<td>109.6±18.5</td>
<td>232.2±52</td>
<td>0.015</td>
</tr>
<tr>
<td>HFHR, ms²</td>
<td>105.2±23.7</td>
<td>206.8±47</td>
<td>0.04</td>
</tr>
<tr>
<td>+BRS, ms/mmHg</td>
<td>10.7±1.3</td>
<td>16.6±3.3</td>
<td>0.065</td>
</tr>
<tr>
<td>−BRS ms/mmHg</td>
<td>10.8±1.1</td>
<td>17.4±4.1</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Plasma catecholamines
| Norepinephrine, nmol/l | 1.41±0.3 | 1.47±0.3 | 0.88    |
| Epinephrine, pmol/l    | 136±21   | 169±49   | 0.58    |

Values are means ± SE. RRI, R-R interval; rMSSD, root mean square successive differences; pNN50, proportions of cycles where the differences are >50 ms; TFHR, total power of heart rate variability; LF, low frequency; HF, high frequency; BRS, baroreflex slope.

Fig. 1. Maximal percent changes in forearm blood flow (FFB) and area under curve (AUC) of the increments in FFB, after cessation of forearm ischemia.

Fig. 2. Individual systolic blood pressure (BP) changes with the corresponding peak velocity changes during steady-state sodium nitroprusside (SNP) infusion (A) and phenylephrine administration (multiple points for different phenylephrine doses) (B).
ual systolic BP changes with the corresponding PV changes are depicted in Fig. 2B. The CBFV mechanoregulation, represented by plotting the individual changes in systolic BP during phenylephrine and SNP infusion against the corresponding changes in CVR, are illustrated in Fig. 4. Both groups have shown similar mechanoregulation curves. It is noteworthy to mention that CO₂ remained unchanged during these pharmacological maneuvers.

**DISCUSSION**

The results of the present study support our hypothesis that CO₂ vasoreactivity (chemoregulation) of cerebral vasculature is impaired in patients with endothelial dysfunction. We also demonstrated that exogenous NO donor is able to offset the differences between the two groups. Mechanoregulation of CBFV, on the other hand, remains intact in patients compared with controls.

Anatomical and biochemical indexes of systemic atherosclerosis were similar in both patients and healthy controls in this study. Despite the long-standing diabetes and hypertension in patients, both groups showed similar IMT and C-reactive protein readings. Previous studies have shown that increased carotid IMT is associated with evident endothelial dysfunction (17). Endothelial function as determined by reactive hyperemia primarily reflects the ability of the vascular endothelium to release NO (24). Both diabetes and hypertension are known to adversely affect the vascular endothelial production of NO (8). Therefore, impairment of endothelial function in our patients depended, for the most part, on the incidence of the qualifying illnesses. It is worth mentioning that very high plasma glucose concentration could also affect endothelial mechanism (7), but none of our subjects had glucose values exceeding 14 mmol/l on the day of the study.

CBF is protected from changes in pressure because of autoregulation (5). Adequate information regarding the molecular physiology of this autoregulation is limited. Various mechanisms have been implicated in this process, such as neurogenic, endothelial, myogenic, and mixed, but no one explanation has proven to be satisfactory.

Conflicting data exist concerning whether the autonomic nervous system is involved in the mechanoregulation of CBF. Dynamic cerebral autoregulation studies using ganglionic blockade reveal that the autonomic nervous system may indeed have an important role in this setting (45). Patients with long-term diabetes mellitus associated with cardiovascular autonomic neuropathy and orthostatic hypotension showed impaired cerebral autoregulation (22). However, patients with postganglionic autonomic neuropathy (pure autonomic failure) have preserved pressure-dependent CBF autoregulation (14, 28). Patients in our study had intact pressure-dependent cerebral autoregulation despite impaired autonomic cardiovascular control. Isolated sections of human pial arteries have been shown to have poor innervation and attenuated responsiveness to adrenergic vasoconstrictors (4). This may serve as further support for the notion that the autonomic nervous system is not involved in mechanoregulation of CBF. It should be noted that diabetes profoundly alters vascular function, including both endothelial and smooth muscle function (23, 34).

Endothelial dysfunction results in a decreased release of endothelial NO and consequently affects the ability of the smooth muscle cells lining the arterioles to relax efficiently. Experimental findings in animal (32) as well as in human subjects indicate that the mechanoregulation of CBF remains intact despite the aging process or the presence of diseases likely to compromise endothelial function (36). Subjects with long-standing hypertension show a preserved dynamic cerebral...
autoregulation (10, 42). Our study is the first to show that patients with proven endothelial dysfunction maintain their pressure-dependent autoregulation. This study also supports our previous findings that NO is not involved in the mechanoregulation of CBFV (21). Furthermore, blockade of NOS by continued infusion of L-NMMA does not affect pressure-dependent autoregulation in healthy humans (44).

Accordingly, because both neurogenic and endothelial mechanisms seem to barely affect mechanoregulation of CBFV, we can indirectly deduce that this CBFV autoregulation is mainly orchestrated by certain intrinsic myogenic vascular mechanisms. These mechanisms seem to be maintained in our patients. Unfortunately, no accepted method to selectively study the function of cerebrovascular smooth muscle in the human brain is available. Our assumption remains to be confirmed in future studies.

Aging affects cerebrovascular basal tone (11, 18). Administration of L-arginine increases CBF to a lesser degree in the elderly compared with the young (29). The control subjects in the present study were ∼20 yr older than the subjects in the previously studied group (21) but still maintained a similar basal CVR and identical response to SNP (CVR decreased by 8%). Consequently, we can assume that the myogenic response to NO is preserved in our healthy subjects. Intact functioning of the vascular endothelium is not required for release of NO from SNP, whereas the opposite is true for L-arginine (25). Patients had higher baseline CVR than controls. However, exogenous NO donor decreased the CVR in patients to an extent similar to the controls. We suppose that the basal cerebrovascular tone in patients is higher either because of some autoregulatory mechanism or an abnormal endothelial function.

The source of increased NO levels during hypercapnia was explored in animal studies (26, 38, 43). In pigs, hypercapnia caused an increase in CBF and in endothelial NOS (eNOS) mRNA expression, and both were blunted by nonselective NOS inhibitor but not by a selective neuronal NOS (nNOS) inhibitor (26). In rodents, neuronal NO was the more important source (43). The relative importance of eNOS and nNOS is still debated (2). Previously, we demonstrated the importance of NO in the chemoregulation of the CBFV in healthy young humans (21). This study adds further support to our previous findings and shows that cerebral vasoreactivity is associated with impaired vascular endothelial function. Even though basal cerebrovascular tone decreased in both groups, vasoreactivity in patients was unaffected by SNP infusion. We propose that this phenomenon may be due to endothelial dysfunction and a deficient release of NO during CO2 challenges.

Recently, several clinical studies linked the impairment in cerebrovascular vasoreactivity to cerebral ischemic events. Patients with cerebrovascular diseases demonstrated region-related impaired CO2 vasoreactivity. None of these studies assessed the endothelial function. Present and previous results of our studies and other clinical reports support the fact that the chemoregulation of CBF depends on the integrity of the vascular endothelium (20, 21, 37).

Several reports found an association between carotid IMT and systemic endothelial function (15, 17). However, because our small sample of patients had IMTs similar to those of the control group, we were not able to confirm this relationship. Direct and indirect data from animal and human studies support the proposal that the CO2-NO axis is a key pathway in CBF regulation (13, 16, 24, 41). The exact molecular links between components of this axis are unknown, but possible associations have been discussed in our previous report (21). Briefly, CO2-dependent pH changes that modulate NOS activity (27), opiate receptors (19), prostaglandin production (31), and ATP-dependent K+ channel activation (3) have all been suggested as possible contributors to the CO2-NO axis. This issue remains to be researched in the future.

Limitations and clinical perspectives. Our CBFV data were obtained by Doppler studies. Regional CBF is proportional to the Doppler velocity time integral in the corresponding cerebral arteries (1). This method was validated by MRI and angiography that showed a stable MCA diameter under a wide range of PaCO2 levels (9, 35). Similar data on the effect of SNP and phenylephrine are not available. However, our previous data from normal volunteers showed that they do not affect CBFV in these low doses (21). During hypercapnia, activation of chemoreceptors causes an increase in peripheral sympathetic activity (39). We observed a similar increase in BP during hypercapnia in both patients and controls. This effect is buffered in both groups by a similar CBFV mechanoregulation. For ethical reasons, we restricted the dose response of phenylephrine to a limited component of the wide autonomoregulatory range. Therefore, our conclusion that the mechanoregulation is intact in patients applies only to the studied range. We used reactive hyperemia to assess peripheral endothelial function. Flow-mediated dilatation is more commonly used for this purpose, but available data suggest that reactive hyperemia can also be a measure of endothelial dysfunction, and abnormal hyperemia implies abnormal NO release, at least in part (24).

The source of NO during hypercapnia can be the endothelium or neuronal. According to our findings, CO2 vasoreactivity could be a valuable method to assess the function of the cerebral vessels in a way comparable to flow-mediated dilatation in the peripheral vasculature. In conclusion, compromised endothelial function is associated with impaired CO2 cerebrovascular reactivity in the setting of preserved pressure-dependent CBF autoregulation. We propose, according to our present and previous data, that CO2 vasoreactivity could be a surrogate of cerebrovascular endothelial function.

GRANTS

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