Analysis of CO₂ Vasomotor Reactivity and Vessel Diameter Changes by Simultaneous Venous and Arterial Doppler Recordings

José Manuel Valdueza, MD; Bogdan Draganski; Olaf Hoffmann; Ulrich Dirnagl, MD; Karl Max Einhäupl, MD

Background and Purpose—The use of flow velocity changes in the middle cerebral artery (MCA) measured by Doppler techniques as an index of corresponding cerebral blood flow (CBF) changes is based on the assumption that the insonated arterial diameter remains stable. The postulate of unchanging vessel calibers during CBF changes, however, is still under debate. We performed simultaneous measurements of arterial and venous blood flow velocities by transcranial Doppler ultrasound during various stages of hypercapnia to analyze diameter changes in the insonated vessels by comparing differences in the vasomotor reactivity.

Methods—Simultaneous Doppler recordings of 1 MCA and of a contralateral venous vessel thought to represent the sphenoparietal sinus (SPS) were carried out with a pair of 2-MHz range-gated transducers in 16 young healthy subjects during variations of end-tidal PaCO₂.

Results—During hypercapnia the mean blood flow velocity of the MCA rose from 62.5±10.2 to a maximum of 99±12.2 cm/s (vasomotor reactivity of 60.1±17.3%). The corresponding values in the SPS were significantly higher (P<0.001), revealing a rise from 17.8±5.7 to 34.9±14.3 cm/s (vasomotor reactivity of 91.4±25.9%). Exponential and linear regression analyses revealed an identical high correlation (r²=0.97 and 0.98 for the MCA and SPS, respectively). Slopes were 0.034±0.01 on the arterial and 0.048±0.01 on the venous side. The CO₂ reactivity (percentage per mm Hg, EtCO₂) was found to be 4.5±1%/mm Hg in the MCA and 6.8±1.5%/mm Hg in the SPS. This difference indicates a vasodilation of the MCA in comparison to the venous vessel.

Conclusions—We have demonstrated a different reaction pattern between intracranial venous and arterial vessels related to end-tidal CO₂. Relating the flow velocities to the square of the vessel diameter and assuming a global rise of CBF and not extensible sinus walls, our results indicate that the MCA undergoes a vasodilation of 9.5±7% in maximal hypercapnia. (Stroke. 1999;30:81-86.)

Key Words: cerebral blood flow ■ cerebral veins ■ hypercapnia ■ ultrasonography, Doppler

One of the most controversial issues in the field of cerebral hemodynamics is the question of whether changes in the diameter of large cerebral arteries occur during alterations in cerebral blood flow (CBF). This aspect has gained more attention with the introduction of transcranial Doppler ultrasound (TCD) in 1982. Since then, TCD has been widely used as a noninvasive tool for recording changes in CBF. The assumption that blood flow velocity changes measured by TCD directly reflect corresponding changes in CBF, however, is correct only if the diameter of the insonated vessel remains unchanged.

As a new approach to the measurement of possible changes in middle cerebral artery (MCA) diameter, we report on the simultaneous assessment of arterial and venous blood flow velocities during various stages of hypercapnia by TCD. Assuming a global rise of CBF during hypercapnia, with an equal rise in the cerebral arterial inflow and venous outflow, the insonation of a venous vessel may serve as reference marker for analyzing diameter changes in the MCA. The sphenoparietal sinus (SPS) collecting the superficial sylvian vein system² represents a major part of the venous outflow of the MCA territory. It also presents not extensible venous sinus caliber that will allow measurement of absolute differences in diameter changes. To our knowledge, this approach for the evaluation of the vasomotor properties of cerebral venous vessels has not yet been performed with TCD or other techniques.

Subjects and Methods

The study group comprised 16 healthy subjects (8 women and 8 men) ranging in age from 24 to 38 years (mean, 27.2±3.8 years). All subjects gave informed consent prior to examination. Transcranial
and extracranial Doppler ultrasound findings were normal. With patients in the supine position, TCD examinations were performed with two 2-MHz pulsed Doppler transducers (Multidop X 4, DWL) with fixed probes in a special metal frame provided by the manufacturer. The M1 segment of the MCA was obtained, as described elsewhere, at a depth of approximately 50 mm. For detection of the SPS, the contralateral internal carotid siphon was insonated at a depth of approximately 50 to 60 mm by the anterior transtemporal approach. A venous signal, slightly more lateral and anterior with a low-pulsatile flow away from the probe at a depth of 40 to 50 mm, was considered to represent the SPS. Only subjects who demonstrated a stable venous signal, allowing reliable recordings, were included into the study. Mean blood flow velocities (VMCA and VSPS) were recorded in centimeters per second.

The subjects inhaled normal air at rest and a gas mixture of air and 100% CO₂ through a mouthpiece connected to a reservoir of 25 l content. Breathing through the nose was avoided by use of a clip. Increasing CO₂ concentrations of the gas mixture were produced by raising the CO₂ flow. The end-tidal CO₂ partial pressure (EtCO₂) was recorded by an infrared analyzer (Datex SC-103, Hoyer). Mean arterial blood pressure (MAP) was measured noninvasively (Finapres, Model 2300, Ohmeda). Oxygen saturation was monitored on-line by a finger clip (Datex SC-103, Hoyer).

Baseline values during breathing of normal air were obtained after a steady state was reached for arterial and venous velocities and EtCO₂. Subsequently, an air mix with stepwise increasing CO₂ concentrations was given. Measurements of VMCA, VSPS, and EtCO₂ were performed under steady state conditions for all values, which were reached in general after 20 to 30 seconds. All data were stored for computer-assisted off-line analysis. Figure 1 shows a typical recording in 1 subject as plotted by the Doppler instrument. Blood flow velocities at rest were regarded as 100%. The percentage changes of flow velocities under maximal hypercapnia were expressed as vasomotor reactivity. The CO₂ reactivity was expressed as the relative change of velocity per mm Hg of EtCO₂. VMCA and VSPS of every volunteer were plotted as a function of EtCO₂.

For statistical evaluation, ANOVA and paired t tests were performed. Pearson’s correlation coefficient was used for the analysis of correlation between 2 subsets of variables. A value of $P<0.05$ was assumed to be significant.

### Results

The MCA was insonated on the left side in 10 subjects and on the right side in 6. Tables 1 and 2 summarize the basic data of our study. VMCA and VSPS at rest ranged from 51.1 to 82.1 cm/s (mean ± SD, 62.5 ± 10.2 cm/s) and from 10.6 to 28.9 cm/s (mean ± SD, 17.8 ± 5.7 cm/s), respectively.
led to a increase of venous and arterial velocities, with a significant higher rise \((P<0.001)\) in \(V_{\text{SPS}}\) (mean, 91.4\(\pm\)25.9\%) compared with the change in \(V_{\text{MCA}}\) (mean, 60.1\(\pm\)17.3\%). Baseline mean \(\text{Et CO}_2\) was 41.4\(\pm\)5.5 mm Hg. During maximal hypercapnia, \(\text{Et CO}_2\) increased significantly by 33.2\(\pm\)9.8\% \((P<0.001)\), to a mean of 54.8\(\pm\)5.1 mm Hg. No hypoxia was detected during the experiments. MAP revealed a moderate yet significant increase of 10.8\(\pm\)8.6\% from 85\(\pm\)12 mm Hg at rest to 94\(\pm\)11 mm Hg during hypercapnia \((P<0.04)\).

Typical arterial and venous Doppler recordings during stepwise increase of \(\text{Et CO}_2\) in 1 subject is shown in Figure 2.

In the examined range of \(\text{Et CO}_2\), an identical high correlation was found for the \(\text{CO}_2\) reactivity by a linear and exponential function (mean \(r^2=0.97\) and 0.98 for the MCA and the SPS, respectively). The exponential function is described by \(y=a \cdot e^{bx}\), where \(y\) is velocity \(v\) (cm/s), \(x\) is \(\text{Et CO}_2\) (mm Hg), \(a\) corresponds to the theoretically measured velocity at a \(\text{Et CO}_2\) of 0 mm Hg, and \(b\) corresponds to the slope defining the grade of reactivity. The mean slope of the velocity/\(\text{Et CO}_2\) relationship was 0.034\(\pm\)0.01 for the MCA and 0.048\(\pm\)0.01 for the SPS \((P<0.001)\). Considering a linear regression, the mean \(\text{CO}_2\) reactivity of the MCA was found to be 4.5\(\pm\)1\% and that of the SPS 6.8\(\pm\)1.5\% \((P<0.001)\). No significant differences between men and women in regard to arterial and venous velocities, vasomotor reactivity, \(\text{CO}_2\) reactivity, and slopes were found. Analyzing the individual \(\text{CO}_2\) reactivity, 2 different patterns were observed. Two subjects revealed an almost parallel rise of arterial and venous blood flow velocities with a difference in vasomotor reactivity of \(<4\%\). In the remaining subjects, differences of \(\text{CO}_2\) reactivity of up to 70\% were found. In most cases, the difference between arterial and venous increments was more obvious at higher \(\text{Et CO}_2\) values (Figure 3).

**Discussion**

TCD allows noninvasive and on-line measurements of changes of blood flow velocities. It is widely believed that velocity changes represent equivalent changes of CBF.\(^4\) As blood flow is proportional to the square of the arterial diameter, TCD will be able to measure CBF changes only if the insonated artery diameter remains stable during the examination. Consequently, one of the most discussed issues in cerebral hemodynamics is whether the large cerebral arteries—especially the MCA—should be considered as rigid tubes or if they possess dilatory properties that come to play during variations of CBF.\(^5\)

Increasing \(\text{Pa CO}_2\) is known to lead to a marked rise of CBF. Various attempts have been made to validate TCD as a tool for measuring relative changes in CBF in response to variations of \(\text{Pa CO}_2\). When CBF measurements by intravenous xenon\(^\text{133}\) and TCD recordings of blood flow velocities during hypercapnia were compared, a tight relationship was observed, arguing against relevant diameter changes of the MCA, whereas no correlation was seen at rest.\(^6\)\(^,\)\(^7\) A good correlation between flow and velocity during hypercapnia was also seen intraoperatively in patients who underwent carotid endarterectomy. With use of electromagnetic flowmeters in the exposed extracranial internal carotid artery (ICA), changes of flow in the ICA were similar to changes of blood flow velocities in the ipsilateral MCA as measured by TCD, again indicating no relevant change of MCA caliber.\(^8\)\(^,\)\(^9\) Using the Doppler signal power as an index of MCA diameter during flow variations induced by hypercapnia, contradictory findings were reported that ranged from a 20\% increase of

**TABLE 2. Vasomotor and \(\text{CO}_2\) Reactivity, Slopes, and Calculated Vasodilation of the MCA**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Vasomotor Reactivity, %</th>
<th>(\text{CO}_2) Reactivity, %/mm Hg</th>
<th>Slope</th>
<th>MCA Vasodilation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>4.3</td>
<td>0.032</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>5.4</td>
<td>0.038</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>5.1</td>
<td>0.036</td>
<td>4.2</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>5.4</td>
<td>0.038</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>3.9</td>
<td>0.032</td>
<td>17.8</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>6.1</td>
<td>0.042</td>
<td>9.3</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>2.5</td>
<td>0.02</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>4</td>
<td>0.029</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>5.3</td>
<td>0.042</td>
<td>-0.9</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>3.5</td>
<td>0.03</td>
<td>4.9</td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>4.7</td>
<td>0.034</td>
<td>7.7</td>
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<td>12</td>
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<td>5.3</td>
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<td>2.8</td>
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<tr>
<td>13</td>
<td>47</td>
<td>4.9</td>
<td>0.04</td>
<td>11.6</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>3.6</td>
<td>0.03</td>
<td>20.3</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>4</td>
<td>0.031</td>
<td>11.5</td>
</tr>
<tr>
<td>16</td>
<td>41</td>
<td>3.2</td>
<td>0.026</td>
<td>10.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>60.1 ± 17.3</td>
<td>91.4 ± 25.9</td>
<td>4.5 ± 1</td>
<td>6.8 ± 1.5</td>
</tr>
</tbody>
</table>
Doppler power to nonsignificant changes. In the study of Poulin and Robbins, only moderate hypercapnic states were achieved with a mean of 8.5 to 9.5 mm Hg over the baseline. Consequently, the increase of VMCA was also limited to 28.4%. A similar weak increase of 28.5% was reported by Kleiser et al during inhalation of 5% CO2. In one part of this study, concomitant insonation of the MCA and ipsilateral extracranial ICA were performed that revealed a close correlation between velocity changes in the MCA and ICA. Because no measurable diameter changes of the extracranial ICA were observed, an unchanged caliber of the MCA was assumed. In a more refined study comparing CBF and blood flow velocity measurements at different and higher stages of PaCO2, the percentage increase of CBF (102.5%) measured by xenon clearance was higher than the increase of velocity (62.1%) after a rise of PaCO2 from 38.5 to 49.9 mm Hg. Hypercapnia in this series was performed under hyperoxic conditions which did not alter the relationship between PaCO2 and VMCA. Using their own data and the results of Du Boulay and Symon reporting an association between MCA diameter and PaCO2, they calculated an 11% increase in MCA diameter.

Visualization and direct measurement of the MCA diameter were performed during variations of PaCO2 by several groups. In the most frequently cited work using an angiographic technique, the vessel reactivity to inhalation of 9% CO2 was investigated under general anesthesia in 10 patients. At rest, the diameter of the main stem of the MCA was found to range from 1.5 to 2.5 mm; the diameter of the ICA was found to be 2.5 mm. Under hypercapnia the mean PaCO2 increased from 39.7 mm Hg to 57.4 mm Hg. No significant changes of the ICA diameter were observed. In vessels in the range of 2 to 2.5 mm and of 1.5 to 2 mm, a significant vasodilation of 3.8% and of 5%, respectively, were found. Similar findings without quantification of diameter changes have also been reported by other groups. In the experimental setting, consistent results were found angiographically in baboons, with an average change of diameter of 3.4%±1.44 in the main basal arteries during CO2 varia-
tions from 28 to 59 mm Hg. In several arteries, a diameter enlargement of >10% was observed. Direct visualization of the M1 segment of the MCA was reported in 2 patients during neurosurgical procedures. In this study, a mean change in diameter of 1.7% during a maximal rise in Paco2 of 10 mm Hg was seen.

Owing to the rigid structure of the skull, cerebral blood volume is tightly controlled to prevent elevation of intracranial pressure. In contrast to the cutaneous and splanchnic circulation, the cerebral venous vessels therefore have to be considered mainly as conduits with low capacitance properties. In case of increasing CBF, eg, during hypercapnia, venous volume changes follow with little delay after a rise of arterial flow, as shown experimentally in baboons. Besides slight differences in the regional distribution of CBF, the response to changes on PaCO2 are quite similar, even in the comparison of white and gray matter. Therefore it seems reliable to compare the vasomotor response to CO2 in arterial and venous vessels.

In our study involving 16 healthy subjects, the mean increase in arterial blood flow velocity was 60.1%. The values published by Ringelstein et al were somewhat lower (52.5%), which may be caused by the lower examined range of EtCO2. Considering an exponential function for the CO2 reactivity, the mean slope in the MCA was 0.034, which correlates excellently with the values of Maeda et al and Markwalder et al, who found a mean scope including the hypocapnic range of 0.033 and 0.035, respectively. Assuming a linear relationship between Vmca and EtCO2, we calculated a mean arterial CO2 reactivity of 4.5%/mm Hg. This is comparable to the published TCD data of 3.4% by Widder et al, 5% by Ringelstein et al, and 5.3%/mm Hg by Diehl et al. During hypercapnia, we observed a moderate rise in MAP of 10.8%. In this physiological range, MAP is known not to influence the CO2 reactivity.

The increase of blood flow velocity and CO2 reactivity in the venous vessel exceeded significantly the corresponding changes in the MCA in almost all subjects. Assuming a global elevation of CBF under hypercapnic conditions, the difference between arterial and venous response can be explained by a more prominent vasodilation in the vessel with the lower increase of velocity. Relative changes of vessel diameters can be calculated accurately from the inverse relationship of blood flow velocities to the square of the lumen diameter. Assuming a not extensible venous caliber of the SPS, MCA lumen changes obtained by this approach showed a wide variability of vasodilation, ranging from −0.9% to 22% (mean±SD, 9.5±7%). There was, however, a high interindividual variability regarding both the extent of vasodilation and the level of hypercapnia at which the difference became obvious.

A striking congruence of our findings was found with the results of Clark et al. Using simultaneous measurements of CBF and blood flow velocity at different Paco2 levels, their increase in arterial velocity of 62.1% at a 29.6% rise in Paco2 is in good agreement with our result of 60.1% at an increase in EtCO2 of 32.4%. The rise in CBF of 102.5% reported in their study is comparable to the increase in venous velocity of 91.4% in our series. The authors calculated an 11% increase in MCA diameter, which is quite similar to our results of a mean enlargement of the MCA of 9.5%. The simultaneous study of venous velocities in our study permits more accurate analysis of intraindividual properties and fine-tuned relationship to particular EtCO2 values. Using the inverse relationship between velocities and the square of the diameter and assuming fixed venous diameters, the mean caliper change of 9.5% may lead to an underestimation of the true flow by 16.6%, which may be acceptable in clinical practice. Considering those cases with a more pronounced MCA vasodilation of 22%, the estimated error increases to 32.8%. The contradictory findings of Poulin and Robbins and Kleiser et al, revealing no significant diameter change of the MCA may be largely explained by the weak rise of Vmca (<30%) compared with the results of our study and that of Clark et al, in which an increase of Vmca of >60% was achieved. As we have shown that the vasodilation usually rises in a more exponential manner within the measured range of EtCO2, a negligible vasodilation of 2.5% to 3.5% may be extrapolated for both studies.

Some possible sources of error and limitations need to be addressed. We assumed an unchanged diameter of the insonated venous vessel when calculating the caliber changes of the MCA in hypercapnia. In some instances the insonated venous vessel may have been a vasoreagible sylvian vein instead of the SPS. This possibility cannot be excluded, especially in subjects with similar arterial and venous responses to changes of EtCO2. This may have led to an underestimation in calculation of the real vasodilation of the MCA. Furthermore, theoretically, the difference in arterial and venous velocities may be partially induced by venoconstriction, which counteracts the requirement of vasodilation during hypercapnia. A paradox arterial vasodilation is known to occur in severe hypocapnia; however, the reverse event seems very unlikely. A venous constriction due to raised ICP under hypercapnia seems unlikely. Studies in healthy dogs have shown that even in marked elevation of Paco2 up to 73.6 mm Hg, only a mild increase of ICP is observed.

In conclusion, our results argue that CO2 does affect the diameter of the large cerebral arteries and that no direct coupling between flow velocities and CBF can be assumed. At least during hypercapnia and in young individuals, changes of blood flow velocities cannot be considered proportional to changes in CBF. This should be considered when calculating CBF changes from velocity-based examinations.

References


Analysis of CO\textsubscript{2} Vasomotor Reactivity and Vessel Diameter Changes by Simultaneous Venous and Arterial Doppler Recordings

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*Stroke*. 1999;30:81-86
doi: 10.1161/01.STR.30.1.81

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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