Changes in cerebral blood flow during PaCO$_2$ variations in patients with severe closed head injury: comparison between the Fick and transcranial Doppler methods

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Object. The aim of this study was to reassess whether middle cerebral artery blood flow velocity (MCAv) variations measured by transcranial Doppler ultrasonography during acute PaCO$_2$ manipulation adequately reflect cerebral blood flow (CBF) changes in patients with severe closed head injury.

Methods. The study was performed by comparing MCAv variations to changes in CBF as assessed by measurements of the difference in the arteriovenous content in oxygen (AVDO$_2$). The authors initiated 35 CO$_2$ challenges in 12 patients with severe closed head injury during the acute stage. By simultaneous recording of systemic and cerebral hemodynamic parameters, 105 AVDO$_2$ measurements were obtained. Patients were stratified into two groups, “high” and “low,” with respect to whether their resting values of MCAv were greater than 100 cm/second during moderate hyperventilation. Four patients displayed an elevated MCAv, which was related to vasospasm in three cases and to hyperemia in one case. The PaCO$_2$ and intracranial pressure levels were not different between the two groups. The slope of the regression line between 1 divided by the change in (Δ)AVDO$_2$ and ΔMCAv was not different from identity in the low group (1/(ΔAVDO$_2$) = 1.08 × ΔMCAv − 0.07, r = 0.93, p < 0.001) and significantly differed (p < 0.05) from the slope of the high group (1/(ΔAVDO$_2$) = 1.46 × ΔMCAv − 0.4, r = 0.83, p < 0.001).

Conclusions. In patients with severe closed head injury, MCAv variations adequately reflect CBF changes as assessed by AVDO$_2$ measurements in the absence of a baseline increase in MCAv. These observations indicate that both moderate variations in PaCO$_2$ and variations in cerebral perfusion pressure do not act noticeably on the diameter of the MCA. The divergence from the expected relationship in the high group seems to be due to the heterogeneity of CO$_2$-induced changes in cerebrovascular resistance between differing arterial territories.

Key Words • Doppler ultrasonography • head injury • cerebral hemodynamics • cerebral vasoreactivity

Changes in cerebral perfusion following modifications in PaCO$_2$ have been shown to be of prognostic value in treating patients suffering from head trauma. The acute manipulation of PaCO$_2$ is also a therapeutic strategy that is routinely used either to control intracranial pressure (ICP) or to adjust cerebral blood flow (CBF) to metabolic needs. The tight correlation between the percentage of change in middle cerebral artery blood flow velocity (MCAv) measured by transcranial Doppler (TCD) ultrasonography and the percentage of change in CBF during PaCO$_2$ variations has encouraged the use of TCD ultrasonography to test CO$_2$ cerebrovascular reactivity. However, in few studies has the validity of using TCD ultrasonography to assess CBF reactivity to CO$_2$ in patients with severe closed head injury been assessed. In these patients, the heterogeneity of lesions could lead to heterogeneity in CO$_2$ reactivity between vascular territories, leading to discrepancies between MCAv changes and global CBF changes. Moreover, in patients suffering from head trauma, CO$_2$ changes can be accompanied by changes in cerebral perfusion pressure (CPP). Both of these parameters can alter the diameter of the MCA, which, in turn, can modify MCAv independently from MCA flow. The aim of this study was to verify the ability of TCD ultrasonography to reflect global CBF changes during PaCO$_2$ variations, as assessed by corresponding changes in the arteriovenous content difference in oxygen (AVDO$_2$) in patients with severe closed head injury.

Clinical Material and Methods

Patient Population

This study was approved by the local ethics committee and informed consent of each patient’s next of kin was obtained.

In each case the study was conducted in the intensive care unit within 10 days after the patient had suffered head trauma and after the evacuation of a large epidural or subdural hematoma if present. We studied 12 head-injured
patients with severe closed multifocal contusions or diffuse axonal injuries (Glasgow Coma Scale score < 8). Patients lay supine with their heads elevated 30° above the horizontal plane. They were sedated by administration of midazolam and fentanyl and paralyzed at the time of the measurement by administration of vecuronium. The mean arterial blood pressure (MABP, by a radial catheter), ICP (by a ventricular catheter), and end-tidal CO₂ were continuously monitored. A catheter was inserted in a retrograde manner, up to the jugular bulb of the dominant jugular vein, and the position of the catheter was verified radiographically. Moderate hyperventilation was induced to obtain a PaCO₂ between 30 and 35 mm Hg. According to the routine management protocol at our institution, if CPP was lower than 80 mm Hg and ICP higher than 20 mm Hg and/or if jugular venous oxygen saturation (SvO₂) was equal to or lower than 55%, norepinephrine was continuously infused after optimization of blood volume. In such cases, CPP was stabilized between 80 and 100 mm Hg to optimize ICP and SvO₂. When CPP was compromised between 65 and 80 mm Hg but ICP was lower than 20 mm Hg and SvO₂ was higher than 55%, no therapeutic action was initiated. Before the CO₂ challenge began, when a steady-state hemodynamic condition was achieved, all patients underwent Doppler measurement (Angiodyn Doppler Measurement System, Montpellier, France) of the MCAv and the cervical internal carotid artery velocities (CICAv) on both sides. The TCD transducer was affixed to a head holder and the MCAv was continuously monitored through the temporal window of the most severely injured hemisphere. The spectral outline of the MCA Doppler time recording, MABP, ICP, and end-tidal CO₂ signals were sampled (digital/analogue converter, National Instruments, Houston TX, used with a personal computer) and stored for off-line analysis. In some patients a continuous SvO₂ signal was also recorded by means of a fiberoptic catheter (Oximetrix, Abbott Lab, North Chicago, IL) that had been positioned, as previously mentioned, by means of the regular SvO₂ catheter insertion procedure.

The studies were conducted in the following manner. Under steady-state conditions, arterial and jugular venous samples were drawn (T₀). Following this step, the patients were gradually hyperventilated until their MCAv stopped decreasing. When this level was achieved, a second set of arterial and jugular venous samples were obtained (T₁). Finally, gradual hypoventilation was allowed up to an end-tidal CO₂ of approximately 40 mm Hg or less if the ICP increased above 35 mm Hg. When the desired level of hyperventilation was achieved, a third set of arterial and jugular venous samples were drawn (T₂). Blood samples were transported to the laboratory on ice for the determination of AVDO₂ (acid–base laboratory cooximeter). We performed two or three of these CO₂ challenges in each patient and allowed a delay of at least 1 day between the challenges.

In selected patients the standardized CO₂ challenges were immediately repeated by insonating the contralateral MCA so that we could compare CO₂ reactivity in both hemispheres.

### Statistical Analyses

Patients were stratified into two groups according to the values of MCAv measured before T₀ (the basal state of moderate hyperventilation). Accordingly, those patients with an MCAv greater than 100 cm/second (either uni- or bilaterally) were placed in the “high” group. Other patients were assigned to the “low” group. This stratification was performed to identify possible heterogeneous responses in CO₂ reactivity between vascular territories as a result of either hyperemia or posttraumatic vasospasm, which could grossly alter the relationship between global CBF CO₂ reactivity and the CO₂ reactivity of the insinuated artery. In the high group the MCAv/ipsilateral CICAv ratio (MCAv/CICAv) was calculated to differentiate vasospasm from hyperemia. According to Lindegaard, et al.,¹³ acceleration of MCAv with an MCAv/CICAv ratio greater than 3 was considered to reflect vasospasm.

In between the times required for each blood sampling (at T₀, T₁, and T₂), the MCAv was averaged in each patient. Then, for each patient we calculated the percentage of variation in MCAv and AVDO₂ between the times T₀ to T₁ and T₀ to T₂, respectively.

In each group, the average values of the variables studied at T₀, T₁, and T₂ were compared using a two-way analysis of variance. The differences between groups were examined for the variables studied, at T₀, T₁, and T₂ by

### TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Group</th>
<th>Low Group</th>
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<tbody>
<tr>
<td></td>
<td>T₀</td>
<td>T₁</td>
</tr>
<tr>
<td>EtCO₂ (mm Hg)</td>
<td>35 ± 8</td>
<td>26 ± 6†</td>
</tr>
<tr>
<td>MCAv (cm/sec)</td>
<td>114 ± 10</td>
<td>88 ± 18‡</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>99 ± 17</td>
<td>101 ± 17</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>18 ± 5</td>
<td>9 ± 4†</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>81 ± 15</td>
<td>92 ± 16‡</td>
</tr>
<tr>
<td>AVDO₂ (ml/100 ml)</td>
<td>4.5 ± 2.2</td>
<td>6.6 ± 2.0†</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± standard deviation. Differences between means with a probability of less than 0.05 are considered statistically significant. The high group was composed of patients with resting values of MCAv that were greater than 100 cm/second; the low group was composed of patients with resting values of MCAv that were 100 cm/second or lower. Times of blood sampling (T₀–T₂) are explained in Clinical Material and Methods. Abbreviation: EtCO₂ = end-tidal CO₂.

† Significant difference compared with T₀ in the same group.
‡ Significant difference compared with the same condition in the high group.
§ Significant difference compared with T₀ and T₂ in the same group.
using a t-test or the Mann–Whitney rank sum test, as required. Regression analysis was also performed on the change in (Δ)AVDO₂ and ΔMCAv after the expected hyperbolic relationships between these two variables were linearized by replacing ΔAVDO₂ with its reciprocal (see Appendix). Slopes of the regression lines obtained in the high and low groups were compared to assess any significant statistical difference.

Results

In 12 patients (nine men and three women aged 18 to 56 years; mean age 26 ± 11 years), 35 CO₂ challenges were performed and 105 measurements of AVDO₂ were made.

In four patients, we detected an MCAv greater than 100 cm/second and in three of these patients, the MCAv/CICAv ratio was greater than 3. The elevated velocity was unilateral on the side of the hemisphere that received greater injury to two patients and bilateral in one patient. In this patient, the MCAv/CICAv ratio was greater than 3 on the side with greater injury and less than 3 on the opposite site. In the remaining patient, the elevated velocity was bilateral and the MCAv/CICAv ratio was less than 3.

The average values for all variables studied are shown in Table 1. When comparisons were made in each group between T₁, T₂, and T₃ (that is, when we compared the effects of different levels of CO₂) in one patient, we observed similar patterns of change in ICP and MCAv for both the high and low groups: they were lower at T₁, and higher at T₃, compared with T₂ (p < 0.05). Conversely, in the low group, the MABP was significantly less at T₁, compared with T₂ and T₃ (p < 0.05), whereas this variable did not change in the high group. Cerebral perfusion pressure was lower at T₁, and higher at T₃, compared with T₂ (p < 0.05), whereas this variable did not change in the high group.

In this patient, the MCAv/CICAv ratio was greater than 3 (that is, when we compared the MCAv in the low group at T₁, and T₃, respectively) from one group to another, we did not observe differences in CO₂ and ICP. In contrast, the MABP and CPP were significantly lower in the low group at T₁ (p < 0.05), whereas we only observed a trend toward a higher AVDO₂ at T₁ in the low group, as compared with the high group. The MCAv was consistently less in the low group under all three conditions (T₁, T₂, and T₃) (p < 0.01). The average hematocrit level was significantly greater in the low group than in the high group (38 ± 4% compared with 33 ± 4%, p < 0.01).

We observed a high correlation between 1/ΔAVDO₂ and ΔMCAv in the low group (r = 0.93, p < 0.001; slope = 1.08) and also in the high group (r = 0.83, p < 0.001, slope 1.46). It is noteworthy that the slopes of the regressions between 1/ΔAVDO₂ and ΔMCAv differed between the two groups (p < 0.05) and the slope in the low group was not different from identity (Fig. 1).

Time recordings of the CO₂ tests made during bilateral recording of the MCAv and the corresponding ICP/MCAv relationships are shown in Figs. 2 and 3.

Discussion

The principal result of this study is that MCAv variations adequately reflect AVDO₂ changes during a CO₂ challenge in patients with severe closed head injury with a basal MCAv below 100 cm/second.

Before discussing our results further, some methodological aspects deserve comment. We sampled jugular blood in a single jugular vein. Hence, one could argue that the sample failed to represent true mixed cerebral venous blood. Stocchetti, et al., found significant differences in oxygen saturation between both jugular veins. This observation has led some authors to recommend monitoring the right side, which is presumed to be the side of the dominant jugular vein, in accordance with the findings of Lam and colleagues, who found a statistically significant correlation between SO₂ in the right jugular vein and venous saturation in the sagittal sinus. However, other investigators recommend that one should monitor the jugular vein on the side that has experienced greater injury because of a possible difference in SO₂ between both jugular veins.

With respect to jugular drainage, the dominant side is not always the right side. Thus, alternate jugular compression or comparison of the two jugular foramina on computerized tomography scanning could determine the dominant jugular vein whose saturation must be the closest estimation of true mixed cerebral venous blood. Accordingly, we relied on a compression test to define the side for jugular catheterization. The side of the dominant jugular vein was defined as the side in which compression generated the greater increase in ICP.

Another classic question is whether TCD ultrasonography can reliably assess changes in CBF. Indeed, flow velocity is expected to remain proportional to flow, provided that the diameter of the insonated artery remains constant. This is considered to be true because PaCO₂-induced variations in the pH of cerebrospinal fluid act on pial arterioles downstream of the circle of Willis. Bishop and associates validated this assumption in humans with no cerebral pathological condition by finding a significant correlation between the percentage of variations in MCAv and CBF during changes in PaCO₂. Simi-
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Fig. 2. Time recording graphs obtained during sequential bilateral recording following a standardized CO$_2$ challenge in a patient belonging to the high group with unilateral MCAv acceleration (end-tidal CO$_2$ = 25, 21, and 35 mm Hg at T$_0$, T$_1$, and T$_2$, respectively). The upper graph corresponds to the right MCA and the lower one to the left MCA. Open circles represent MCAv; ticked lines, MABP; solid line, SvO$_2$; dotted line, end-tidal CO$_2$; open triangles, ICP. The dashed lines show the MCAv value at T$_0$. In the upper graph (normal MCAv), one sees a continuous increase in MCAv, ICP, and SvO$_2$ between T$_0$ and T$_2$, and a 25% increase in MCAv between T$_1$ and T$_2$. In the lower graph, one sees the elevated MCAv with a MCAv/CICAv ratio of 4, which characterizes vasospasm. Between T$_1$ and T$_2$, a state of maximum MCAv is reached for an end-tidal CO$_2$ level of 28 mm Hg. Additional increases in end-tidal CO$_2$ lead to a steady MCAv, whereas both ICP and SvO$_2$ continuously rise. Note a transient rise in MCAv at the onset of hyperventilation, which may result from the abrupt decrease in ICP and the slightly higher MABP, which both improve CPP.

Fig. 3. Time recording graphs showing the transition between T$_1$ and T$_2$ during a CO$_2$ challenge in a patient with bilaterally elevated MCAv (end-tidal CO$_2$: 18 and 37 mm Hg at T$_1$ and T$_2$, respectively). Open circles represent MCAv; ticked lines, MABP; solid line, SvO$_2$; dotted line, end-tidal CO$_2$; open triangles, ICP. The dashed lines show the MCAv value at T$_1$. Upper: Increased MCAv with a MCAv/CICAv ratio at 2.8, indicative of increased blood flow (hyperemia). Note the continuous increase in MCAv, ICP, and SvO$_2$ between T$_1$ and T$_2$. Lower: Increased MCAv with a MCAv/CICAv ratio of 4, indicative of vasospasm. Between T$_1$ and T$_2$, maximum MCAv is achieved for an end-tidal CO$_2$ of 28 mm Hg. Additional increases in end-tidal CO$_2$ levels led to an abrupt decrease in MCAv and to a continuous increase in ICP and SvO$_2$. Note a transient increase in MCAv at the onset of induced hyperventilation.

Similarly, during craniotomy for aneurysm surgery, Giller, et al.,$^9$ found a minimum MCA diameter change of 1.7% during moderate variations in PaCO$_2$. Moreover, these authors found no correlation between the direction of change in the PaCO$_2$ and the direction of change in the diameters of the arteries of the circle of Willis. However, one could question the assumption that MCA diameter remains constant in closed head injuries when PaCO$_2$ variations induce variations in ICP. Indeed, during hyperventilation, the rise in ICP decreases the CPP and may effect a passive decrease in MCA diameter. This situation may lead to an overestimation of flow changes by measuring changes in velocity. In such a case, the TCD assessment of CBF would overestimate AVDO$_2$ variations during hypercapnia, whereas the opposite effect would be expected in hypocapnia.

We shall also assess the specific role of cerebrospinal fluid, which in our patients was contrary to that found in patients during craniotomy by Giller, et al.$^9$ The presence of cerebrospinal fluid could have induced a change in pH around the arteries of the circle of Willis. If the arteries of the circle of Willis are responsive to PaCO$_2$ variations, vasodilation of the MCA at a high PaCO$_2$ should lead to TCD underestimation of CBF, as assessed by AVDO$_2$ measurement, and overestimation during acute hypocapnia. The slope of the regression line between 1/AVDO$_2$ and DMCav indicates that variations in MCAv underestimate variations in AVDO$_2$ by nearly 8%. Thus we cannot
exclude that there may be a slight direct effect of CO₂ on MCA diameter. It is noteworthy that, as ICP increased and CPP decreased in our patients during hypercapnia, such a direct vasodilatory effect of CO₂ was possibly counteracted by a passive collapse of the MCA lumen. Alternatively, interhemispheric ICP gradients could also have affected the MCAv reactivity to CO₂ of the insonated hemisphere, leading to discrepancies between changes in MCAv and those in AVDO₂. Nevertheless, the statistically significant correlation we found in the low group between 1/ΔAVDO₂ and ΔMCAv, with a regression slope not different from identity, suggests that such effects are negligible, at least in the ranges of ICP, CPP, and PaCO₂ variations observed in our study.

Another important point is to assess the specificity of the patients in the high group who had both a basal increase in MCAv and a relationship between 1/ΔAVDO₂ and ΔMCAv defined by a slope different from identity. Acceleration of MCAv is a common finding after head trauma, which was not caused by a higher PaCO₂ or greater CPP compared with the low group. Moreover, there was no difference in AVDO₂ between each group at T₀. Thus, another cause must be sought that would increase MCAv independently from the factors we discussed earlier. The mean hematocrit level was significantly lower in patients in the high group. According to Brass and associates, who modeled the expected flow velocity for different hematocrit values, the difference in the mean hematocrit level that we observed in our study between groups (33 ± 4% compared with 38 ± 4% in the high and low groups, respectively) should have led to a value of MCAv not greater than 18% in the high group compared with the low group and, thus, far from the magnitude we observed in our study. One should suspect vasospasm or some other cause for elevated CBF. Using the criteria proposed by Lindegaard, et al., three patients in our study had unilateral vasospasm and another one showed a state of increased flow. The diagnosis of vasospasm in three of four patients in the high group justified therapeutic efforts to support general hemodynamics by optimizing systemic blood volume. This may explain the lower hematocrit level in the high group and why, despite the increase in mean thoracic pressure secondary to hyperventilation, the MABP did not change at T₀ compared with T₀ in the high group in contrast to what was observed in the low group.

If patients in both groups had the same relationship between 1/ΔAVDO₂ and ΔMCAv, one should have found the same regression lines, despite a difference in baseline velocity. This was not the case in our study. In the low group the MCAv variation during the CO₂ challenge adequately reflects global cerebral AVDO₂ changes because the slope of 1/ΔAVDO₂ compared with ΔMCAv was not different from identity. Consequently, the reactivity of CBF to CO₂ must be homogeneous in the different vascular territories. In the high group, the regression line between 1/ΔAVDO₂ and ΔMCAv was significantly higher than identity. This indicates that during the CO₂ challenge the MCAv variation provides a systematic underestimation of the CBF variations as assessed by AVDO₂ measurement. Theoretically, this could be due to MCA vasodilation during hypercapnia and vasconstriction during hypocapnia, leading, respectively, to an under- and overestimation of flow by velocity measurements. Because we did not observe such an effect in the low group, a possible contribution of vasospasm or hyperemia to the difference we found between groups merits further discussion.

Vasospasm is a common occurrence after head trauma and represents a possible cause of hypoperfusion and inhomogeneity in oxygen extraction between different cerebral arterial territories. Hyperemia has also been shown to occur frequently after head trauma and could result from an excessive increase in MABP and/or a disturbed autoregulation. It could also be a local phenomenon because contused hypoperfused areas are surrounded by hyperemic ones. Both vasospasm and hyperemia reduce CO₂ reactivity and are accompanied by autoregulatory dysfunction in the affected vascular territories. Moreover, by definition vasospasm is a regional phenomenon. On the other hand, AVDO₂ remains a global measurement and cannot reflect possible heterogeneity in blood flow and oxygen extraction in various vascular territories. Accordingly, in the high group, discrepancies between the limited reactivity to CO₂ in the insonated artery and the preserved reactivity in other territories could explain the systematic underestimation of AVDO₂ variation by Doppler assessment.

Performing the CO₂ challenge on both MCAs indicated that increasing the PaCO₂ from an initial state of hyperventilation induces first a rise in MCAv in both hemispheres and then a global rise in ICP. As previously mentioned, the increase in MCAv is the consequence of the diminution of cerebrovascular resistance downstream of the circle of Willis. This decrease in cerebrovascular resistance, which results from the rise in CO₂, is accompanied by a slight increase in cerebral blood volume, which has been estimated to be 0.05 ml/100 g of brain tissue for each millimeter of mercury of PaCO₂ variation. In a state of reduced cerebral compliance, even a slight increase in cerebral blood volume may induce a rise in ICP. Consequently, as MCAv increases in response to the rise in CO₂, CPP decreases secondary to the rise in ICP under conditions of stable MABP. In other words, the observed increase in MCAv is simply the net result of the opposite influences of the decrease in cerebrovascular resistance and the resulting decrease in CPP.

In patients in the high group, additional increases in PaCO₂ led to a steady or decreasing MCAv on one side as the MCAv further increased on the other side. (Figs. 2 and 3). Thus, as the ICP continuously increased, a stable or decreasing MCAv indicated that above a given level of PaCO₂, the decrease in cerebrovascular resistance in this territory was equal to or less than the general decrease in CPP induced by vasodilation in the other vascular territories.

Conclusions

We conclude that the CO₂ reactivity test in patients with severe closed head injury shows that variations in MCAv adequately reflect CBF changes assessed by variations in AVDO₂ in patients without an elevated MCAv caused by vasospasm or hyperemia. These results indicate that PaCO₂ variations and moderate ICP changes do not noticeably act on MCA diameter. When an increase is pres-
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ent, variations in velocity failed to reflect AVDO variations adequately, although that probably reflects only flow changes in the insonated artery. This discrepancy seems to be due to a heterogeneity in the CO2-induced changes in cerebrovascular resistance between territories. Indeed, in some patients with posttraumatic vasospasm and intracranial hypertension, PaCO2 manipulations can induce opposite changes in MCAv in each hemisphere. Such an effect must be taken into account when the therapeutic adjustment of ventilation is used, and this situation is best detected at the bedside by bilateral TCD monitoring.

Appendix

The Fick principle applies to cerebral metabolism and flow. Accordingly,

\[ \text{CMRO}_3 = \text{AVDO}_3 \times \text{CBF} \]  
\( \text{Eq. 1} \)

where CMRO3 is cerebral metabolic rate of oxygen (ml/100 g/minute) and CBF is total cerebral blood flow (ml/100 g/minute). Doppler MCA velocity (MCAv) is related to CBF by an equation that can be simplified:

\[ \text{MCAv} \times (\pi \times r^2) \times k = \text{CBF} \]  
\( \text{Eq. 2} \)

where \( r \) is the radius of the MCA and \( k \) is a general constant. Thus, by combining Equations 1 and 2,

\[ \text{CMRO}_3 = \text{AVDO}_3 \times \text{MCAv} \times (\pi \times r^2) \times k \]  
\( \text{Eq. 3} \)

and

\[ \text{CMRO}_3 / (\pi \times r^2) \times k \times \text{MCAv} = \text{AVDO}_3. \]  
\( \text{Eq. 4} \)

If one considers normalized values, changes (\( \Delta \)) in AVDO3 and MCAv are expressed in the forms

\[ \Delta \text{AVDO}_3 = 1 + \left[ \left( (\text{AVDO}_3) - \left( \text{AVDO}_3 \right) \right) / (\text{AVDO}_3) \right] \]  
\( \Delta \text{MCAv} = 1 + \left[ \left( (\text{MCAv}) - (\text{MCAv}) \right) / (\text{MCAv}) \right] \)

where subscripts denote Observations 1 and 2, respectively.

Accordingly, if CMRO3 and \( r \) remain constant, any relative change in AVDO3 (\( \Delta \text{AVDO}_3 \)) will induce an inverse change in MCAv.

Thus:

\[ 1/\Delta \text{AVDO}_3 = \Delta \text{MCAv}. \]  
\( \text{Eq. 5} \)

If the two variables, \( \Delta \text{AVDO}_3 \) and \( \Delta \text{MCAv} \), are related in each patient between \( T_1 \) and \( T_1 \), and between \( T_1 \) and \( T_1 \), and fit Equation 5, one may conclude that CMRO3/(\( \pi \times r^2 \)) \times k in Equation 4 is constant.

If CMRO3 remains stable between \( T_1 \) and \( T_1 \), then \( r \) does not vary.

References


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