Patterns of Cerebrovascular Reactivity in Patients With Unilateral Asymptomatic Carotid Artery Stenosis

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Background and Purpose Intracranial hemodynamic status varies in patients with unilateral significant carotid artery stenosis. It ranges from normal, because of sufficient collaterals, to poor, because of a severely reduced blood supply that puts the patient at an increased risk of stroke or cerebral ischemia. The present study examined patterns of abnormal cerebrovascular hemodynamics in patients with asymptomatic carotid artery stenosis.

Methods The CO2 reactivity of the cerebral resistance index (CR) and of mean blood flow velocity (vmean) was determined via transcranial Doppler sonography in 91 patients with unilateral high-grade to threadlike carotid artery stenosis and in 37 control subjects. The interhemispheric asymmetry of CR, reactivity of the control group was used to differentiate between normal and abnormal findings.

Results We found that 64.8% of the patients demonstrated normal CR, asymmetry with comparable CR, reactivity (ipsilateral, 4.42±0.44 %CR/vol%CO2; contralateral, 4.51±0.39 %CR/vol%CO2) and vmean reactivity (ipsilateral, 0.080±0.004 m/s per vol%CO2; contralateral, 0.107±0.005 m/s per vol%CO2) at both hemispheres. In 16.5% of the patients, CR, reactivity was supranormal at the affected hemisphere. This phenomenon was due to an exaggerated dilatory response of the ipsilateral hemisphere and was combined with an absent CR, reactivity of the contralateral hemisphere (ipsilateral, 6.63±1.03 %CR/vol%CO2; contralateral, −1.16±1.78 %CR/vol%CO2). In contrast, hemispheric vmean reactivities were comparable (ipsilateral, 0.078±0.008 m/s per vol%CO2; contralateral, 0.077±0.008 m/s per vol%CO2). The remaining 18.7% showed severely diminished ipsilateral CR, reactivity (ipsilateral, 1.91±0.83 %CR/vol%CO2; contralateral, 8.48±1.00 %CR/vol%CO2) and vmean reactivity (ipsilateral, 0.073±0.007 m/s per vol%CO2; contralateral, 0.108±0.012 m/s per vol%CO2; P<.01), compatible with a significantly reduced perfusion pressure at the poststenotic hemisphere.

Conclusions Most asymptomatic patients do not suffer from severely abnormal hemodynamics at the poststenotic hemisphere. One small subgroup of patients presented with severely disturbed ipsilateral hemodynamics; another small subgroup demonstrated a steal phenomenon with secondary dilation of large cerebral vessels at the contralateral hemisphere. These subgroups require specific evaluation of proper treatment. (Stroke. 1994;25:1193-1200.)

Key Words • carotid artery diseases • hemodynamics • ultrasonics

The value of carotid endarterectomy for managing asymptomatic carotid artery disease remains in question. Proposed recommendations for carotid endarterectomy focus on those patients with hemodynamically significant carotid artery stenosis who are at risk of either thromboembolic stroke or cerebral ischemia of a hemodynamic cause (reduced poststenotic perfusion pressure). The latter occurs only if the carotid artery lesion decreases in diameter by more than 50% and in cross-sectional area by more than 75%. Furthermore, the cerebral autoregulatory response also must be depleted. However, decreased intracranial perfusion pressure may be prevented by flow from the external carotid artery or, more importantly, by cross-flow from the opposite hemisphere (collateral circulation through the circle of Willis), but such hemodynamic compensation is not always possible because of anatomic variations in the circle of Willis and in the external carotid/internal carotid artery (ICA) collaterals. Transcranial Doppler sonography (TCD), single-photon emission-computed tomography (SPECT), or positron emission tomography (PET) demonstrated an extremely variable hemodynamic pattern, ranging from nearly normal readings to pathological increases in oxygen extraction caused by insufficient blood supply. However, the frequency of these hemodynamic variations in patients with asymptomatic carotid artery disease is not known.

Previous small longitudinal PET studies, which defined abnormal cerebral hemodynamics by an increase in the ratio of cerebral blood volume to cerebral blood flow, could not identify a significant relation of abnormal hemodynamics to stroke risk. However, it has been suggested that a more restrictive criterion (increased oxygen extraction fraction) may be associated with a higher risk for stroke. Correspondingly, other reports suggest that abnormal intracerebral hemodynamics (as indicated by pathological reserve capacity testing or oculare pneumoplethysmography) are associated with a significantly higher incidence of ischemic hemispheric events. Because the compensatory hemodynamic response to carotid artery stenosis varies, it is possible that specific subgroups exist among carotid artery patients who have, despite an identical degree of stenosis, a greater risk of stroke or cerebral ischemia and thus require different treatment.
To determine the existence of these subgroups in a population with asymptomatic carotid artery stenosis, we examined cerebrovascular resistance, a hitherto un-studied variable of intracerebral hemodynamics, using TCD of the middle cerebral artery (MCA). Previous investigators mainly used TCD to measure cerebral blood flow velocity or indexes of cerebral blood flow at rest or during pharmacological manipulation (CO₂, acetazolamide) of cerebral vessel diameter.15,16 It was reported recently that, based on the physiology of pulsatile flow (vascular impedance), a cerebral resistance index (CR) as a measure of peripheral wave reflection can be derived from the shape of the blood flow velocity curve at the middle cerebral artery.14

There is evidence that the relative peak-to-peak velocity of the flow velocity curve may be used as an indicator of peripheral resistance. Relative peak-to-peak velocity (also known as Pourcelot's index) is, furthermore, superior to the pulsatility index with regard to resistance measurement. Several phenomena of pulsatile flow, such as wave reflection and linearity of impedance, will only become evident if peak-to-peak velocity is referred to maximum blood flow velocity and not to mean blood flow velocity (as with the pulsatility index). A further advantage of relative peak-to-peak velocity is its insensitivity to rises in heart rate, as they can be observed during CO₂ reactivity testing (at hypocapnia).14

By comparing CR, reactivity of one hemisphere with the reactivity of the contralateral hemisphere (side-to-side asymmetry), an age-independent definition of normal values was obtained, which allowed clear differentiation between normal and pathological hemodynamic situations. We hypothesized that the asymmetry of CR, reactivity between the affected and the unaffected hemispheres might allow identification of patients with unilateral ICA disease who simultaneously demonstrate insufficient intracerebral collaterals.

Subjects and Methods

Subjects

Studies were performed in completely asymptomatic subjects seeking treatment in our hospital for a variety of reasons from 1989 to 1991. Carotid artery disease was diagnosed accidentally during preoperative evaluation or during routine examination in vascular high-risk patients. All patients had unilateral high-grade to threadlike ICA stenosis (n=91 [68 men, 23 women]; mean age, 66.3±1.0 years). High-grade stenosis corresponds to a maximum percent reduction in the angiographic diameter of the relevant carotid artery of 80% or more. A threadlike stenosis corresponds to a 99% diameter reduction. All patients underwent careful neurological examination. Extracranial and intracranial supra-aortic vessels were screened by transcranial Doppler sonography, duplex sonography, color-flow Doppler imaging, and continuous-wave Doppler sonography. Color-flow Doppler imaging and continuous-wave Doppler sonography have recently been shown to be more than 90% accurate in identifying carotid artery stenosis with a luminal diameter reduction from 80% to 99%.15,16 Arterial digital subtraction angiography was performed in nine selected preoperative patients to exclude carotid artery occlusion. However, the procedure used (aortic arch angiography) did not allow reliable and constant identification of intracerebral collaterals.14

Exclusion criteria included luminal diameter reduction of less than 80% at the extracranial ipsilateral ICA, luminal diameter reduction of more than 50% at the contralateral ICA, previous ischemic hemispheric symptoms (ipsilateral or contralateral stroke or transient ischemic attack), current nonspecific neurological symptoms (headache, migraine), tandem lesions of the ICA/MCA, subclavian steal syndrome, vertebral artery occlusion or stenosis, lumen diameter reduction of more than 50% at the common carotid artery, previous ipsilateral or contralateral carotid endarterectomy or extracranial/intracranial bypass, and uncontrolled atrial fibrillation (absolute arrhythmia).

Twenty-five patients with threadlike ICA stenosis who subsequently underwent surgery had a preoperative cranial computed tomography (CT). In three of these patients, small lacunar infarctions were found (two at the poststenotic hemisphere and one at the contralateral hemisphere). No CT scans were performed in the remaining asymptomatic patients after the cost-benefit ratio was considered. Unidentified cerebral lesions in the latter group should not affect the results of our study because reduced cerebrovascular reactivity was observed only in patients with low-flow infarctions but not in patients with territorial infarctions and because surgery may normalize poor cerebrovascular reactivity at the hemisphere with documented preoperative minor stroke.

Measurements

Systolic and diastolic blood flow velocity of the MCA in both hemispheres was measured by TCD as described previously.14 In brief, a 2-MHz TCD sonography transducer (Vingmed SD 50, Sonotron) was placed on the "skull window" above the zygomatic arch, and the MCA was studied at a depth of 50 to 60 mm. Average blood flow velocity at peak systole and diastole was transferred to a personal computer (Macintosh II CI, Apple) for further off-line data processing. To evaluate the complete reactivity of blood flow velocity to changes in CO₂ concentrations, the arterial CO₂ content was measured by nomocapnia (CO₂ concentration at rest) to hypercapnia and hypocapnia. To produce hypercapnia the subjects were connected through a mouthpiece with a nonreturn valve to a tank containing 5% CO₂. Hypocapnia was achieved by having the patient hyperventilate. During the CO₂ manipulation, the end-expiratory CO₂ content (vol%) was recorded continuously by an infrared CO2 analyzer (Engstrom Eliza, CO2 Analyzer). Mean end-tidal values were used to estimate the arterial CO₂ content. Flow velocity in the MCA was recorded when a steady state was reached in end-tidal CO₂ and in flow velocity.

Calculations

Each examination yielded values of minimal diastolic and maximal systolic flow velocity (vmin and vmax, respectively) in the MCA in both hemispheres during normocapnia, hypocapnia, and hypercapnia. Flow velocities were used to calculate the relative peak-to-peak velocity (referred to vmin) of the flow velocity wave: (vmax-vmin)/vmin. The relative peak-to-peak velocity represents a measure of cerebral resistance during pulsatile flow and is named the cerebral resistance index (CR). We calculated the relative reactivity of CR to changes in the arterial CO₂ content. The relative change of CR, is referred to hypocapnic CR, to obtain positive values of cerebrovascular reactivity (CR is larger in hypocapnia than in hypercapnia). The exact rationale behind the formula below is discussed in detail in Reference 14.

Total CR, reactivity (%CR/vol%CO₂) was quantified as:

\[
\text{CR} \text{ at Hypocapnia} - \text{CR} \text{ at Hypercapnia} \\
\underline{\text{CR} \text{ at Hypocapnia}} \\
1
\]

\[
\text{CO}_2 \text{ Concentration at Hypercapnia} - \text{CO}_2 \text{ Concentration at Hypocapnia}
\]

Fig 1 illustrates the derivation of the formula. The corresponding formula was used to analyze dilatory and constrictory components of total CR reactivity. Dilatory CR, reactiv-
ity was quantified by referring the relative change of CR, between normocapnia and hypercapnia to the corresponding CO₂ concentration difference. To calculate constrictory CR, reactivity, the relative change of CR, between hypercapnia and normocapnia was divided by the corresponding CO₂ concentration difference. To calculate the reactivity of $v_{\text{mean}}$, $v_{\text{max}}$, and $v_{\text{nea}}$, the absolute change of the respective velocity between hypercapnia and hypcapnia or between normocapnia and hypercapnia was referred to the corresponding CO₂ concentration difference.

To define normal values, a control group of elderly subjects (n=37 [18 men, 19 women]; mean age, 65±3.5 years) was studied. Subjects of this control group were suffering from different degrees and manifestations of peripheral atherosclerosis at the lower extremities (La Fontaine stage IIa to IIb). Significant atherosclerotic changes of the extracranial and intracranial arteries were excluded by Doppler and duplex sonography. None of these patients presented with or ever had symptoms of cerebrovascular disease as evaluated by careful neurological examination.

To classify the patients according to normal values obtained from control subjects, the following procedure was used: at first, the normal absolute side-to-side asymmetry was determined. This was done by arbitrarily subtracting right CR, reactivity from left CR, reactivity in control subjects. Subtracting left from right would have yielded the same result because in control subjects we made no difference between positive or negative side-to-side asymmetry (absolute side-to-side asymmetry had to be determined). The normal range of absolute side-to-side asymmetry was defined as mean±2 SD. The next step was to calculate absolute side-to-side asymmetry in the patients. This was done by subtracting (again arbitrarily) CR, reactivity of the opposite hemisphere from CR, reactivity of the poststenotic hemisphere. This allowed us to refer side-to-side asymmetry in the patients to the hemisphere of ICA stenosis and not to left or right hemisphere. Then the sign of side-to-side asymmetry was ignored, and patients could be classified into those with normal absolute side-to-side asymmetry and those with abnormal absolute side-to-side asymmetry. Subsequently, patients with abnormal absolute side-to-side asymmetry were further analyzed by looking at the sign of the original side-to-side asymmetry and dividing them into those with abnormal negative and those with abnormal positive side-to-side asymmetry (referred to the poststenotic hemisphere).

Thus, in control subjects mean absolute side-to-side asymmetry (irrespective of whether side-to-side asymmetry was positive or negative) amounted to 1.6±0.2 [1.2] %CRᵢ/\text{vol}%CO₂ (mean±SEM [SD]). Normal values were derived from these numbers as described above. We obtained a normal span for absolute side-to-side asymmetry ranging from 0 to 4 %CRᵢ/\text{vol}%CO₂. Then we determined in all patients the side-to-side asymmetry of total CR, reactivity and differentiated between normal, abnormal positive, and abnormal negative asymmetry of CR, reactivity. Patients with an absolute side-to-side asymmetry of more than 4.0 %CRᵢ/\text{vol}%CO₂ and with a greater CR, reactivity of the affected hemisphere than of the contralateral hemisphere were classified as having an abnormal positive side-to-side asymmetry. Correspondingly, patients with an absolute side-to-side asymmetry of more than 4.0 %CRᵢ/\text{vol}%CO₂ and with less CR, reactivity of the affected hemisphere than of the contralateral hemisphere were placed into an abnormal negative side-to-side asymmetry category.

Analysis of side-to-side asymmetry of CR, reactivity in ICA occlusive disease may allow classification by the quality of patients' intracerebral collaterals. This conclusion is based on results of a recent study in which cross-filling in the circle of Willis via the anterior communicating artery was examined in a separate group of 18 preoperative patients with unilateral high-grade to threadlike ICA stenosis and with either normal, abnormal negative, or abnormal positive side-to-side asymmetry. All patients underwent selective arterial digital subtraction angiography at the hemisphere contralateral to the ICA stenosis. The degree of cross-filling was graded negative if no major vessel of the affected hemisphere was filled through the circle of Willis; it was graded positive if at least one major vessel faintly opacified in the hemisphere ipsilateral to ICA stenosis. All nine patients with abnormal absolute side-to-side asymmetry in whom CR, reactivity at the hemisphere of ICA stenosis was lower than CR, reactivity at the opposite hemisphere (abnormal negative side-to-side asymmetry) did not demonstrate intracerebral cross-flow from the contralateral to the affected hemisphere through the circle of Willis. In contrast, we identified this cross-flow in the other nine patients who had either normal or abnormal positive side-to-side asymmetry (CR, reactivity at the affected hemisphere higher than that at the contralateral hemisphere).

**Statistical Analysis**

The differences between means of the two hemispheres and of different groups were compared with the paired and the unpaired $t$ tests, respectively. Because means of several variables were compared, the Bonferroni method was applied, taking into account the multiplicity of comparisons. For con-
venience, a significance level of \( P = 0.01 \) was used throughout the study.

**Results**

Normal side-to-side asymmetry of CR, reactivity, which had been derived from the control group,\(^1\) allowed differentiation of our patients into three subgroups that did not differ with respect to age, severity, or localization of carotid artery stenosis. Most patients (group 1; \( n = 59 \) (64.8\%)) demonstrated an absolute side-to-side asymmetry in the normal range (2.16 ± 0.16 \%CR, \%/vol%CO\(_2\), mean ± SEM). The corresponding hemispheric CR, and \( \nu_{max} \) reactivities were as follows: CR, reactivity ipsilateral, 4.42 ± 0.44 \%CR, \%/vol%CO\(_2\); CR, reactivity contralateral, 4.51 ± 0.39 \%CR, \%/vol%CO\(_2\); \( \nu_{max} \) reactivity ipsilateral, 0.080 ± 0.004 m/s per vol%CO\(_2\); and \( \nu_{max} \) reactivity contralateral, 0.079 ± 0.005 m/s per vol%CO\(_2\).

The remaining patients had an abnormal side-to-side asymmetry (>4.0 \%CR, \%/vol%CO\(_2\)) and could be separated into two subgroups: (1) patients in whom CR, reactivity of the affected hemisphere was smaller than that of the opposite hemisphere (group 2, \( n = 17 \) (18.7\%); absolute side-to-side asymmetry = 6.57 ± 0.51 \%CR, \%/vol%CO\(_2\)) and (2) patients in whom CR, of the affected hemisphere was larger than that of the opposite hemisphere (group 3, \( n = 15 \) (16.5\%); absolute side-to-side asymmetry = 7.98 ± 1.16 \%CR, \%/vol%CO\(_2\); \( P = NS \) versus absolute side-to-side asymmetry in patients of group 2). The latter finding was a surprise because it indicates that some patients with unilateral ICA stenosis may have extremely good CR, reactivity at the site of ICA stenosis, whereas at the opposite unaffected hemisphere, total CR, reactivity was comparably poor (CR, reactivity ipsilateral, 6.63 ± 1.03 \%CR, \%/vol%CO\(_2\); contralateral, −1.16 ± 1.78 \%CR, \%/vol%CO\(_2\)). In contrast, \( \nu_{max} \) Reactivities were comparable at both hemispheres (\( \nu_{max} \) reactivity ipsilateral, 0.078 ± 0.008 m/s per vol%CO\(_2\); contralateral, 0.077 ± 0.008 m/s per vol%CO\(_2\)). Patients in group 2 (abnormal negative side-to-side asymmetry, ipsilateral CR, reactivity less than contralateral CR, reactivity) demonstrated the opposite situation. CR, and \( \nu_{max} \) reactivity were markedly lower at the affected hemisphere (CR, reactivity ipsilateral, 1.91 ± 0.83 \%CR, \%/vol%CO\(_2\); CR, reactivity contralateral, 8.48 ± 1.00 \%CR, \%/vol%CO\(_2\); \( \nu_{max} \) reactivity ipsilateral, 0.073 ± 0.007 m/s per vol%CO\(_2\); \( \nu_{max} \) reactivity contralateral, 0.108 ± 0.012 m/s per vol%CO\(_2\); \( P < 0.01 \) versus ipsilateral \( \nu_{max} \) reactivity). Ipsilateral CR, reactivity in group 3 (abnormal positive side-to-side asymmetry) and contralateral CR, reactivity in group 2 (abnormal negative side-to-side asymmetry) significantly surmounted that in group 1 (normal side-to-side asymmetry) (\( P < 0.01 \)).

Further analysis of CR, reactivity in group 3 (abnormal positive side-to-side asymmetry) showed that the dilatary component of CR, reactivity (=relative change of CR, between normocapnia and hypercapnia per vol%CO\(_2\)) was significantly larger at the affected side than at the unaffected side (ipsilateral, 6.83 ± 1.88 \%CR, \%/vol%CO\(_2\) and contralateral, −2.35 ± 1.7 \%CR, \%/vol%CO\(_2\); \( P < 0.01 \)). The constrictory component of CR, reactivity (=relative change of CR, between normocapnia and hypercapnia per vol%CO\(_2\)) was not significantly different between the two hemispheres (\( P = 0.02 \)). These findings indicate the excellent total CR, reactivity of the affected hemisphere in these patients primarily because of an increased response of CR, to hypercapnia. Although dilatary \( \nu_{max} \) reactivities were comparable (dilatary \( \nu_{max} \) ipsilateral, 0.073 ± 0.012 m/s per vol%CO\(_2\); contralateral, 0.077 ± 0.014 m/s per vol%CO\(_2\)), contralateral dilatary \( \nu_{max} \) reactivity significantly surmounted that at the ipsilateral hemisphere (dilatary \( \nu_{max} \) ipsilateral, 0.079 ± 0.015 m/s per vol%CO\(_2\); contralateral, 0.118 ± 0.014 m/s per vol%CO\(_2\); \( P < 0.01 \)), whereas contralateral dilatary \( \nu_{max} \) reactivity was smaller than that at the ipsilateral hemisphere (dilatary \( \nu_{max} \) ipsilateral, 0.067 ± 0.012 m/s per vol%CO\(_2\); contralateral, 0.036 ± 0.008 m/s per vol%CO\(_2\); \( P < 0.01 \)).

Analysis of baseline normocapnic hemodynamics in the different groups (Table) revealed that in group 1 (normal side-to-side asymmetry), normocapnic CR, and \( \nu_{max} \) of the ipsilateral hemisphere were significantly lower than the contralateral CR, and \( \nu_{max} \). In group 2 (abnormal negative side-to-side asymmetry), patients did not demonstrate a significant difference in normocapnic CR, between both hemispheres. However, in these patients normocapnic \( \nu_{max} \) of the affected hemisphere was significantly reduced compared with the contralateral \( \nu_{max} \) in group 3 (abnormal positive side-to-side asymmetry), CR, and \( \nu_{max} \) were comparable between both hemispheres.

Scatterplots of hemispheric CR, reactivity and of side-to-side asymmetry in the three groups are presented in Figs 2 and 3.

**Discussion**

Using the side-to-side asymmetry of CR, reactivity in healthy control subjects, we developed three patient groups, consisting of those with (1) normal side-to-side asymmetry (group 1, 64.8\%), (2) abnormal side-to-side asymmetry with ipsilateral CR, reactivity lower than contralateral CR, reactivity (group 2, 18.7\%), and (3) abnormal side-to-side asymmetry with ipsilateral CR, reactivity higher than contralateral CR, reactivity (group 3, 16.5\%).

Most patients (approximately 65\%, group 1) exhibited an apparently normal hemispheric CR, response to CO\(_2\). However, analysis of the baseline hemodynamics in the three different subgroups revealed that only few patients (approximately 17\%, group 3, which had ab-
normal side-to-side asymmetry with an ipsilateral CRi reactivity higher than that of the contralateral hemisphere) were fully compensated at the poststenotic hemisphere. Normocapnic CRi and v_{max} were identical only in the latter group in both hemispheres, indicating that poststenotic perfusion pressure (of which v_{max} is an indicator if vessel diameter and stroke volume are comparable), cerebrovascular resistance, and blood flow could be kept in the normal range (Fig 4A). Surprisingly, this condition was combined with an extremely good CRi reactivity at the side of ICA stenosis and absent CRi reactivity at the unaffected hemisphere (abnormal positive side-to-side asymmetry, n=15); ○, poststenotic hemisphere; and ●, contralateral hemisphere.

The exact underlying pathophysiology of this hitherto undescribed subgroup is not directly evident from our data. It can be assumed that sufficient intracerebral collaterals existed in this group. When patients of this subgroup undergo selective angiography, significant intracerebral collateral flow through the circle of Willis can be identified.12 Furthermore, PET or SPECT studies did not demonstrate evidence of a reduced contralateral blood supply in patients with strictly unilateral ICA disease, nor are there reports of a contralateral drop in perfusion pressure or increased cerebral blood volume (indicating vasodilation) compared with the affected hemisphere.3,8

As indicated by our data, patients with abnormal positive side-to-side asymmetry demonstrated strong dilatory CRi reactivity at the hemisphere of ICA stenosis. Dilatory CRi reactivity at this hemisphere significantly exceeded the dilatory reactivity at the opposite hemisphere, at which a dilatory CRi response was virtually absent. The reason for this difference (despite adequate collaterals) is not obvious, and it indicates that patients with unilateral carotid artery disease and adequate collaterals are especially sensitive to dilatory stimuli at the affected hemisphere. The exaggerated dilatory response of the affected hemisphere, such as the foregoing, resulted in supranormal total CRi reactivity. The latter significantly exceeded not only the contralateral CRi reactivity but also the ipsilateral CRi reactivity in patients with normal side-to-side asymmetry.

Surprisingly, however, despite the marked difference in hemispheric CRi reactivity, hemispheric v_{mean} reactivities were comparable. This finding indicates that a significant change of cerebral blood flow should have occurred at both hemispheres during CO₂ reactivity testing, since v_{mean} reactivity was found to correlate with cerebral blood flow reactivity.13 To explain this apparent discrepancy between v_{mean} and CRi reactivity one must consider the physiology of pulsatile flow. The shape of the flow velocity curve, which is obtained by TCD measurement at the MCA, is determined by input and by characteristic impedance.16 Input impedance mainly reflects changes in peripheral flow velocity wave reflection, whereas characteristic impedance predominantly reflects changes in vessel diameter and elastic modulus at the site of measurement and/or at some distance downstream. When a flow velocity curve is subjected to Fourier analysis, wave reflection determines the amplitudes of low frequencies, and characteristic impedance determines the amplitudes of middle and high frequencies. Furthermore, the peak-to-peak velocity of a biological flow wave approximately corresponds to the square root of the sum of all quadratic amplitudes as obtained by Fourier analysis.19 In prac-
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Figure 4. Schematic illustrates the hypothesis that a diameter change of contralateral large cerebral arteries compensates the steal phenomenon during strong ipsilateral vasodilation. The panels represent different hemodynamic states of the cerebral circulation in patients of group 3. The circle of Willis is fed by two hemispheric arteries that represent the sum of the total hemispheric blood supply, one of which is significantly obstructed. From the circle of Willis, two hemispheric middle cerebral arteries (MCA) originate, which feed peripheral vessels, represented by the two smaller vascular branches. A, Hypothetical baseline conditions with unilateral high-grade to threadlike internal carotid artery (ICA) stenosis. Hemodynamics are presented according to laws of steady flow. Regional pressure values are derived from Reference 17. Note the pressure equilibration between left and right hemispheres due to an efficient circle of Willis and the pressure drop along the MCA, indicating large-artery resistance. Total resistance reflects the sum of large-artery resistance and of peripheral resistance and is calculated from the ratio of arteriovenous pressure difference to flow. For convenience, venous pressure was assumed to be 0, and baseline hemispheric flow was arbitrarily set at 1. B, Vascular steal at hypercapnia from the opposite to the poststenotic hemisphere. Note the microvascular pressure drop in both hemispheres. Steal is produced by an abnormal reduction of poststenotic peripheral resistance due to the exaggerated dilation of peripheral vessels (ipsilateral shaded area). Contralateral peripheral resistance also falls with a subsequent rise of blood flow. This fall is expected to be in the normal range but less than that at the ipsilateral hemisphere. However, the corresponding rise in contralateral blood flow will be smaller than expected because of the steal-induced reduction of microvascular pressure. Apparently, a mismatch exists at the contralateral hemisphere during hypercapnia between the decrease in both total and peripheral resistance and in microvascular perfusion pressure and the resulting rise in blood flow. It seems that in this situation the brain aims at the equilibration of hemispheric blood flow and volume. C, Equilibration of hemispheric, hemodynamic variables is brought about by dilation of contralateral large arteries (contralateral shaded area) with secondary rise of microvascular perfusion pressure and equilibration of total resistance. It can be assumed that with a defined neurohumoral response, the compensatory MCA dilation will be more pronounced in the distal segments. The alternative compensatory reaction—further reduction of contralateral peripheral resistance—does not occur, perhaps because of the already stimulated contralateral CO₂ response.

Aortic pressure

Total resistance

Microvascular pressure

MCA pressure

Blood flow

A.) Baseline

B.) Hemispheric steal

C.) Compensatory contralateral MCA dilatation

Note the pressure equilibration between left and right hemispheres due to an efficient circle of Willis and the pressure drop along the MCA, indicating large-artery resistance. Total resistance reflects the sum of large-artery resistance and of peripheral resistance and is calculated from the ratio of arteriovenous pressure difference to flow. For convenience, venous pressure was assumed to be 0, and baseline hemispheric flow was arbitrarily set at 1. B, Vascular steal at hypercapnia from the opposite to the poststenotic hemisphere. Note the microvascular pressure drop in both hemispheres. Steal is produced by an abnormal reduction of poststenotic peripheral resistance due to the exaggerated dilation of peripheral vessels (ipsilateral shaded area). Contralateral peripheral resistance also falls with a subsequent rise of blood flow. This fall is expected to be in the normal range but less than that at the ipsilateral hemisphere. However, the corresponding rise in contralateral blood flow will be smaller than expected because of the steal-induced reduction of microvascular pressure. Apparently, a mismatch exists at the contralateral hemisphere during hypercapnia between the decrease in both total and peripheral resistance and in microvascular perfusion pressure and the resulting rise in blood flow. It seems that in this situation the brain aims at the equilibration of hemispheric blood flow and volume. C, Equilibration of hemispheric, hemodynamic variables is brought about by dilation of contralateral large arteries (contralateral shaded area) with secondary rise of microvascular perfusion pressure and equilibration of total resistance. It can be assumed that with a defined neurohumoral response, the compensatory MCA dilation will be more pronounced in the distal segments. The alternative compensatory reaction—further reduction of contralateral peripheral resistance—does not occur, perhaps because of the already stimulated contralateral CO₂ response.
pressure and the resulting rise of blood flow (Fig 4B). Significant interhemispheric differences in blood volume and brain pressure can also be expected. However, compensation for this mismatch and these imbalances via further vasodilation of contralateral peripheral vessels may no longer be possible. Faraci and Heistad have provided evidence that resistance of large cerebral arteries is an important determinant of microvascular pressure during regional control of blood flow. They described neurohumoral mechanisms by which large cerebral arteries can dilate in situations with local cerebral steal to effectively reduce large-artery resistance and to maintain microvascular perfusion pressure and blood flow.

Therefore, hypercapnic steal most likely leads to dilation of the contralateral MCA, and characteristic impedance at the site of TCD measurement will thereby fall, resulting in increased flow velocity amplitudes at middle and high frequencies. The reduced low-frequency flow velocity amplitudes from decreased wave reflection and the increased middle- to high-frequency amplitudes from decreased characteristic impedance may balance each other, leaving their algebraic net sum (peak-to-peak velocity) and the corresponding maximum-minimum ratio (and therefore also CR) essentially unchanged during hypercapnia. Steal-induced vasodilation of the MCA may mask the effect of reduced wave reflection (by peripheral vasodilation) on the flow velocity curve. In contrast, the response of vmean to hypercapnia will be maintained, since the decrease in characteristic impedance alters blood flow velocities so that vmin rises and vmax diminishes. This phenomenon is due to the reduced "windkessel" effect with vasodilation. Furthermore, dilation of large arteries will lower large-vessel resistance and thereby total cerebral resistance and will increase microvascular perfusion pressure again, resulting in a further rise of vmax and vmin (CR), will remain unchanged with isolated pressure changes due to the so-called linearity of impedance. Thus, vmin will not only be the same as without the diminished windkessel effect but will even be higher with peripheral vasodilation alone, and no interhemispheric vmean difference may be apparent. Because vmax reactivity was comparable at both hemispheres, apparently as the net result of all changes, a comparable CBF increase also existed at both hemispheres during hypercapnia (Fig 4C).

Windkessel-like effects indicate that in elastic vessels a portion of the kinetic energy at systole is converted into pressure energy at the vascular wall (wall distension). This mechanism reduces local systolic blood flow velocity, which is mainly determined by the kinetic energy of the blood. At diastole, pressure energy is converted back into kinetic energy by contraction of the vascular wall. This mechanism increases diastolic blood flow velocity. Thus, if the cross-sectional area of an elastic vessel rises, the windkessel effect will diminish. This mechanism will result in increased systolic and decreased diastolic flow velocity, with simultaneous enlargement of the peak-to-peak amplitude. Reduction of the windkessel effect at the contralateral hemisphere should enlarge hypercapnic vmin and reduce hypercapnic vmax in comparison with the ipsilateral hemisphere. Consequently, in group 3 there should be higher hypercapnic vmax recoveries and lower vmin recoveries at the contralateral hemisphere than at the ipsilateral hemisphere. This exact phenomenon was observed in patients with abnormal positive side-to-side asymmetry.

Analysis of group 1 (normal side-to-side asymmetry; Table) showed that this group had comparable CR, and vmax reactivity at both hemispheres, despite the significantly smaller baseline CR, and vmax of the affected hemisphere compared with that of the contralateral hemisphere. The latter finding indicates relative vasodilation and reduction of perfusion pressure at the poststenotic hemisphere in this group. Nevertheless, in contrast to what one would expect theoretically (reduced CR, reactivity by preexisting vasodilation), CR, and vmin reactivity of the affected hemisphere corresponded to the contralateral CR, and vmax reactivity. Apparently, enough collaterals still existed in this group to maintain sufficient perfusion pressure to allow functioning of a compensatory mechanism (ipsilateral dilatory hyperreactivity similar to group 3), thereby equalizing the CR, reactivities at both hemispheres.

A different situation was seen in group 2 patients with abnormal low CR, and vmax reactivity at the affected side compared with the opposite unaffected hemisphere (Table). Surprisingly, baseline CR, was comparable between both hemispheres, whereas ipsilateral vmax was significantly lower than that at the contralateral unaffected hemisphere. Taking vmax as an indicator of perfusion pressure, a significant drop of ipsilateral perfusion pressure compared with the opposite hemisphere should have taken place. In addition, the magnitude of ipsilateral perfusion pressure reduction is clearly above that seen in group 1 (normal side-to-side asymmetry; Table) and indicates, together with the decrease of ipsilateral CR, reactivity and vmax reactivity, inadequate intracerebral collaterals and secondary vasodilation. Thus, the explanation for the absent interhemispheric difference in normocapnic CR, cannot be that peripheral resistance was comparable at both hemispheres. Most likely, the cause of the missing normocapnic CR, difference in group 2 resembles the cause of the missing contralateral CR, change during hypercapnia in group 3 (see above). In group 2, ipsilateral circulation may also have responded to the reduction of perfusion pressure by dilation of large arteries. Subsequent reduction of the windkessel effect will counteract the effect of peripheral vasodilation on CR,. As a net result, normocapnic CR, will rise again to pseudonormal values, which cannot be distinguished from contralateral true-normal values.

Because our data suggest a low prevalence of severely reduced poststenotic perfusion pressure, it will be necessary to carefully screen cerebral hemodynamics in asymptomatic patients to identify this small but significant risk group. Whether a contralateral steal phenomenon represents an independent risk factor for asymptomatic patients with critical stenosis will require examination in future prospective studies.

References


Patterns of cerebrovascular reactivity in patients with unilateral asymptomatic carotid artery stenosis.

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