Acta Neurochir (Wien) (2003) 145: 1053–1060
DOI 10.1007/s00701-003-0137-8

Acta Neurochirurgica
Printed in Austria

Clinical Article

Bilateral severe carotid artery stenosis or occlusion – cerebral autoregulation dynamics and collateral flow patterns

M. Reinhard[1], **T. Müller**[2], **M. Roth**[2], **B. Guschlbauer**[1], **J. Timmer**[2], and **A. Hetzel**[1]

[1] Department of Neurology and Clinical Neurophysiology, University of Freiburg, Freiburg, Germany
[2] Freiburg Center for Data Analysis and Modelling, University of Freiburg, Freiburg, Germany

Published online November 3, 2003

Summary

Background. Bilateral severe obstruction of the internal carotid artery is a hemodynamically critical state. We aimed to (1) analyze dynamic cerebral autoregulation (DCA) in affected patients, and (2) to correlate DCA data with different collateral flow patterns.

Methods. DCA was assessed noninvasively by transfer function analysis (phase shift) of respiratory-induced oscillations at 0.1 Hz of arterial blood pressure (Finapres method) and cerebral blood flow velocity (transcranial Doppler) in 30 patients with severe bilateral carotid stenosis ($\geq$75%) or occlusion. CO_2-reactivity was measured via inhalation of 7% CO_2. 30 patients with unilateral stenosis were recruited as controls.

Results. Patients with bilateral 75–89% stenosis had a virtually preserved phase shift. A pronounced reduction was found in bilateral critical stenosis or obstruction (90–100%). Patients with ipsilateral 90–100% and contralateral 75–89% stenosis had a significantly less severe reduction of phase shift on the ipsilateral side. CO_2-reactivity showed a less marked reduction in patients with bilateral critical stenosis or occlusion. Phase shift was best if "Willisian" collaterals were present. Significantly reduced values were found if only secondary collaterals (ophthalmic artery, leptomeningeal flow) were detected. Poorest values occured with recruitment of functionally stenosed "Willisian" collaterals. CO_2-reactivity showed poor values with sole recruitment of secondary collaterals, whereas functionally stenosed primary collaterals did not show values as poor as for phase shift. Clinically symptomatic patients had significantly lower phase shift and CO_2-reactivity values.

Conclusions. DCA is severely impaired in bilateral critical carotid stenosis or occlusion. Sole recruitment of secondary collaterals and signs of a functional stenosis in primary ("Willisian") collaterals reflect insufficient collateral supply with a poor hemodynamic status. CO_2-reactivity assessing the vasodilatory reserve and DCA represent different information for characterizing cerebral hemodynamic impairment. Determining transfer function phase might be a physiologically well supported approach for analysis of cerebral hemodynamic compromise.

Keywords: Bilateral carotid artery stenosis; cerebral autoregulation; vasomotor reactivity; transcranial Doppler sonography.

Introduction

Occlusive carotid artery disease due to arteriosclerosis is usually asymmetric with hemodynamically effective stenosis ($>$80%) limited to one side of the internal carotid artery (ICA). This is important because hemodynamic collateral flow compensation of the territory supplied by the affected ICA is regularly guaranteed by the contralateral ICA via a cross-over flow through the anterior communicating artery (ACoA) [10, 13]. *Bilateral* severe stenosis or occlusion of the ICA is thus a hemodynamically critical state. Often collaterals via the posterior circulation (posterior communicating arteries (PCoA) leptomeningeal collaterals, LM), which are more prone to anatomical variability and thus nonfunctioning, become pivotal in this situation to maintain hemodynamic stability [18].

A number of studies has shown recently for patients with *unilateral* carotid obstruction that the presence or absence of hemodynamic compensation predicts whether patients will become clinically symptomatic [12, 19]. It is thus crucial to assess cerebral hemodynamics in the high-risk group of patients with *bilateral* carotid obstruction, both with regard to prognosis and therapeutic decisions. However, neither assessment of cerebral autoregulation nor its relation to different collateral flow patterns has been studied in these patients on a larger scale.

The concept of dynamic cerebral autoregulation, which analyzes small fluctuations of arterial blood pressure (ABP) and cerebral blood flow velocity (CBVF) assessed by transcranial Doppler sonography, offers completely

non-invasive insight into cerebral autoregulation dynamics. It overcomes the substantial, potentially hazarduous ABP changes required for determination of the upper and lower limits of the classical cerebral autoregulatory plateau [1, 14].

In the present study, we aimed (1) to analyze cerebral hemodynamics in patients with bilateral severe carotid stenosis or occlusion by assessing dynamic cerebral autoregulation, and (2) to compare the autoregulation data with the patients' different collateral flow patterns.

Subjects and methods

Over a period of 20 months, 30 patients with severe high-grade (i.e., ≥75%) bilateral ICA stenosis or occlusion were studied (mean age 68 ± 7 yrs, 26 men). 18 of them had had a previous ischemic event (TIA or stroke) within the previous 24 months. As a neurovascular control group, 30 randomly selected patients with *unilateral* severe stenosis or occlusion and no contralateral stenosis were studied (mean age 66 ± 8 yrs, 28 men). Exclusion criteria were an absent temporal bone window for Doppler insonation, missing tolerance of CO_2 inhalation or inability of regular breathing at 0.1 Hz. All patients underwent a complete neurosonological workup in our neurovascular lab, including extra-/intracranial Doppler-/duplexsonography (HDI 3500©, ATL, Bothell, WA, USA). Ultrasonographic grading of stenosis was performed using Doppler frequency shifts pre-, intra and poststenotically in combination with B-mode imaging [4]. Internal audit in our department showed a high accuracy of ultrasonography for determining high-grade carotid stenoses and occlusions [7]. Division into different groups was done according to different degrees of stenosis.

Measurement of CO_2-reactivity and dynamic cerebral autoregulation: Measurements were performed with subjects in a supine position with 50° inclination of the upper body. Cerebral blood flow velocity (CBFV) was measured in both middle cerebral arteries (MCA) by insonation through the temporal bone window with 2 MHz transducers attached to a headband (DWL-Multidop-X©, Sipplingen, Germany). Continuous non-invasive ABP recording was achieved via a servo-controlled finger plethysmograph (Finapres© 2300, Ohmeda, Englewood, USA) with the subject's right hand positioned at heart level. End-tidal CO_2 partial pressure (P_{ETCO_2}) was measured in mmHg with an infrared capnometer (Normocap©, Datex, Helsinki, Finland) during nasal expiration. P_{ETCO_2} values have been shown to correlate closely to intra-arterial CO_2 values [23]. After stable baseline values had been recorded for at least 60 seconds, 7% CO_2-enriched air was directed towards the patient via a tube system, a two-way valve and a mask. This led to stable hypercapnia which was maintained for 60–90 seconds as controlled by P_{ETCO_2} values. After withdrawal of CO_2 patients continued to breathe via the mask for another 60 seconds until baseline values were again reached.

For assessment of dynamic cerebral autoregulation, respiratory-induced oscillations were evoked by regular deep breathing at a rate of 6/min (0.1 Hz) over a period of 180 s. This was achieved by visual feedback control using a large clock and by additional acoustic directions of the investigator. In order to avoid hypocapnia, patients were instructed to breathe with small tidal volumes.

Collateral flow patterns: Spontaneously recruited intracranial collaterals (cross-flow via anterior communicating artery (ACoA), flow via posterior communicating arteries (PCoA), leptomeningeal flow (LM) and a retrograde ophthalmic artery (OA)) were assessed by transcranial Doppler and duplexsonography according to our laboratory standard (established in [22]). In short, cross flow via ACoA was indicated by a reversed A1 segment of the ACA ipsilateral to the stenosed ICA. Functional stenosis of the ACoA or juxtaposed ACA segments was presumed when Doppler frequencies >6 kHz or a turbulent spectrum of >5 kHz with musical murmurs were observed. Collateral flow via the PCoA was indicated by a marked increase of CBFV (>70 cm/s time mean) in the P1 segment of the posterior cerebral artery (PCA), and/or by direct identification with transcranial Duplex sonography. Spontaneous leptomeningeal collateral flow (LM) was indicated by a side-to-side asymmetry of >30% in the P2 segment of the PCA ipsilateral ICA [13] and a reduced pulsatility of the Doppler flow spectrum. In case of bilateral leptomeningeal flow, analysis of side-to-side differences was not possible. In this situation, an increased flow velocity of more than 50 cm/s time mean, a pulsatility comparable to that in the MCA and an absent difference of flow velocity and pulsatility between the P1 and P2 segments was interpreted as leptomeningeal collateral flow. Collateral supply via the ophthalmic artery was indicated by retrograde peri-orbital arteries as assessed by compression of external carotid artery branches and a pulsatility comparable with that of the intracranial vessels.

Data analysis: All parameters were recorded with a data-acquisition software package (TurboLab© V4.3; Bresser Electronic, Munich, Germany) at a sampling rate of 100 Hz and further analyzed using custom-written software developed in-house. Conventional CO_2-reactivity was calculated as the maximum percentage increase in mean CBFV during hypercapnia divided by the concomitant P_{ETCO_2} increase (in mmHg).

In order to assess dynamic cerebral autoregulation, data were analyzed in the frequency domaine using transfer function analysis (i.e. cross-spectral methods). From given time-courses of ABP and CBFV, the power spectra S_{ABP} and S_{CBFV} and the cross spectrum CS were estimated by periodogram smoothing [3]. We have described this method in detail elsewhere [17]. In short, the whole data sets of ABP and CBFV were transformed to the frequency domain by discrete Fourier transform and the periodograms for ABP and CBFV as well as the cross periodogram were derived. Estimates for the power spectra of ABP and CBFV as well as for the cross spectrum were obtained from the respective periodograms. With the smoothing we used, the coherency is significant (at the 95% level) if it exceeds 0.49. The phase is the argument of the complex-valued cross spectrum. In the present study we concentrated on the phase, since this parameter is widely accepted [5] and was one of the most reliable out of a larger number of parameters obtained by transfer function analysis [17].

Since values were not normally distributed on visual inspection (histograms), statistical analysis was carried out using nonparametric tests (Kruskal-Wallis, Wilcoxon, Mann-Whitney, Spearman's rank order correlations). A p value of less than 0.05 was considered statistically significant. Data are reported as mean ± SD and illustrated by box-and-whiskers plots (median, boxes indicating the second and third quartile).

Results

An illustrative recording of CO_2-reactivity measurement and deep breathing with subsequent transfer function analysis is given in Fig. 1a–c. Results of different groups are presented in Table 1 and illustrated in Fig. 2.

Patients with bilateral 75–89% stenosis had virtually preserved phase shift values on both sides compared with the unaffected side of patients with unilateral stenosis. A pronounced reduction of phase shift was found in patients with bilateral critical stenosis or obstruction (90–100%). Patients with bilateral 90–100% stenosis had significantly poorer values than patients with 90–100% stenosis in combination with a 75–89% stenosis. Comparison of

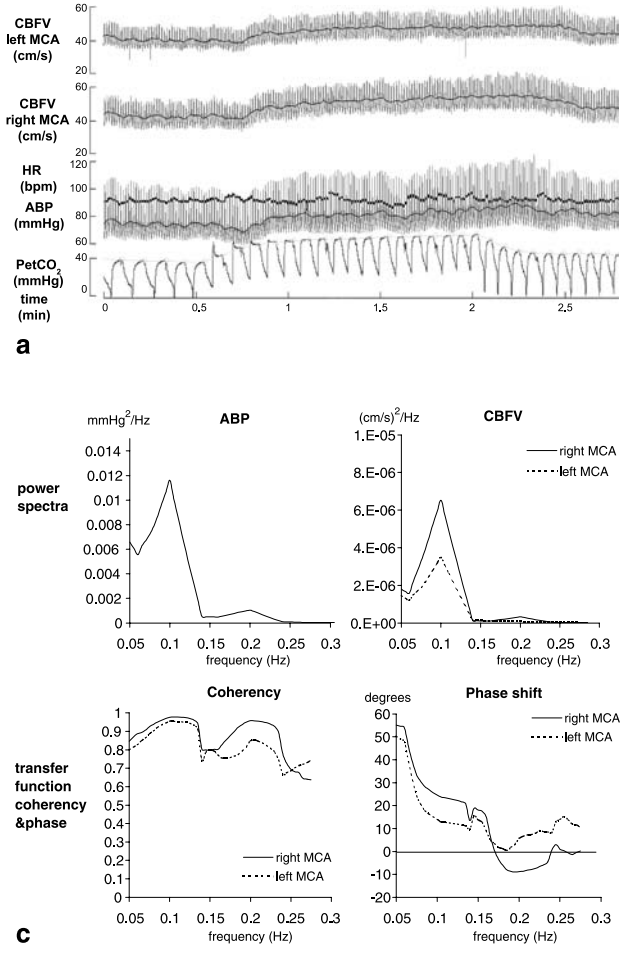

Fig. 1. 63-yr-old patient with bilateral 80–90% stenosis of the ICA and collateral supply via the PCoA (on the left side with functional stenosis). (a) CO_2-reactivity testing. Values were 1.85%/mmHg on the right and 1.41%/mmHg on the left side. (b) Raw data of regular deep breathing, showing induced sinusoidal oscillations of the vascular system. (c) Transfer function analysis of b. Spectral analysis shows a peak at 0.1 Hz, coherency showed significant values at 0.1 Hz (0.05 level at a coherency of 0.49). Transfer function phase reduced on both sides, substantially more on the left side

Table 1. *Results of phase shift and CO_2-reactivity in different groups of ICA stenosis*

	Bilateral stenosis			Unilateral stenosis	
	Bilateral 75–89% n = 6	90–100%/75–89% n = 16	Bilateral 90–100% n = 8	75–89%/none n = 15	90–100%/none n = 15
Phase shift (degrees, at 0.1 Hz)					
Ipsilateral	53.6 ± 33.7	27.1 ± 29.8	8.6 ± 15.6	53.2 ± 26.9	30.1 ± 25.4
Contralateral	60.2 ± 32.9	49.0 ± 26.9	13.5 ± 34.0	58.9 ± 29.4	64.4 ± 28.5
CO_2-reactivity (%/mmHg)					
Ipsilateral	1.57 ± 0.45	1.07 ± 0.65	0.63 ± 0.67	1.57 ± 0.41	1.27 ± 0.89
Contralateral	1.48 ± 0.44	1.81 ± 0.74	0.95 ± 0.56	1.95 ± 0.41	2.08 ± 0.63

In groups with bilateral stenosis of the same range, the more severely affected side was determined as 'ipsilateral'. Significances are given in Fig. 2.

bilateral 90–100% with unilateral 90–100% stenosis showed a trend towards poorer values, but this did not reach statistical significance ($p = 0.08$). CO_2-reactivity in bilateral 75–89% stenosis did not differ significantly from unaffected sides of unilateral stenosis patients. Patients with 90–100% obstruction on one or both sides had significantly lower values compared with bilateral 75–89% stenosis. Comparison with unilateral stenosis of the same degree did not show a clear trend towards lower values. In contrast to phase shift, no poorer values were observed in patients with bilateral 90–100% stenosis in comparison with patients suffering from 90–100% stenosis in combination with a contralateral 75–89% stenosis (cf. Fig. 2).

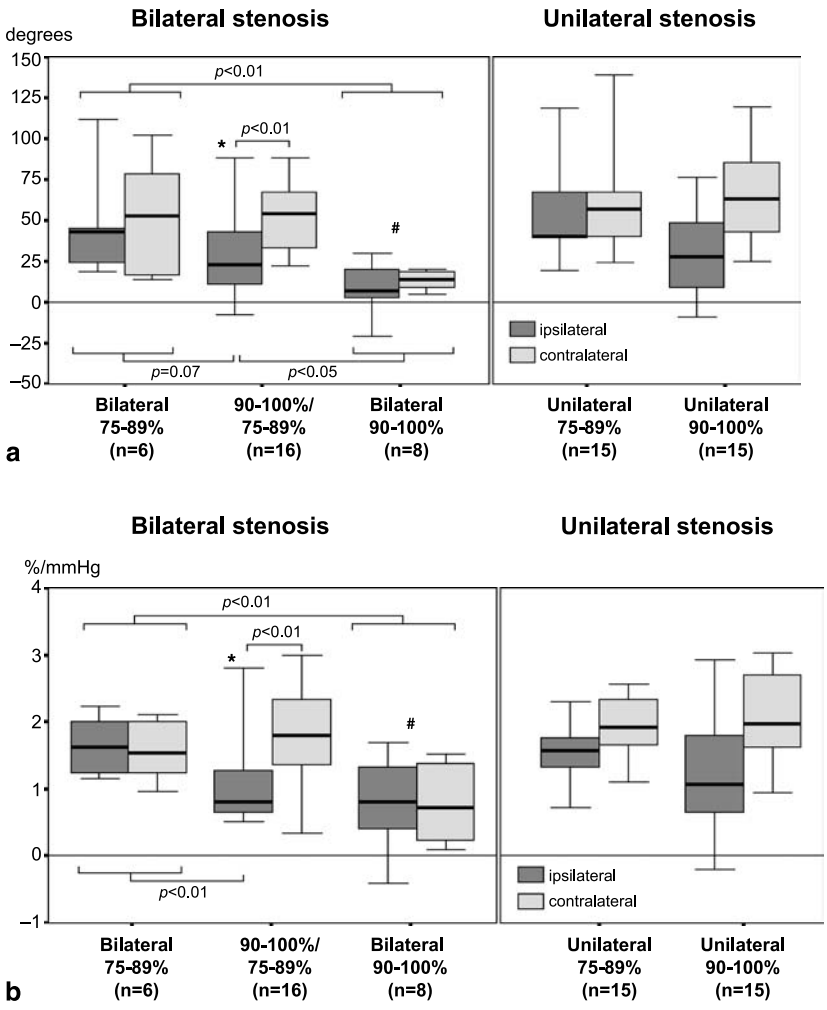

Fig. 2. Box-and-whiskers plots. Patients and controls pooled into different groups of stenosis. (a) Phase shift. $^{*}p<0.01$ vs. the contralateral side of unilateral stenosis. $^{\#}p<0.001$ vs. the contralateral side of unilateral stenosis and $p=0.08$ vs. the affected side of 90–100% unilateral stenosis. (b) CO_2-reactivity. $^{*}p<0.001$ vs. the contralateral side of unilateral stenosis. $^{\#}p<0.001$ vs. the contralateral side of unilateral stenosis

Correlation between phase shift and CO_2-reactivity pooling all sides of patients with uni- and bilateral stenosis (n = 120) was $r=0.55$ ($p<0.001$).

Different groups of collateral flow patterns were defined via recruitment of primary or secondary (extra-Willisian) collaterals and the presence of functional stenosis of primary collaterals (see methods section). Overall, 60 MCA sides of the 30 patients with bilateral stenosis were eligible. Table 2 gives results for different patterns of collateral flow analyzed separately for all

Table 2. *Results for specific collateral flow patterns*

Collateral pathways	Sides n	Phase shift (degrees) ipsilateral	CO_2-reactivity (%/mmHg) ipsilateral
PcoA	6	31.3 ± 27.9	1.90 ± 0.53
PCoA + OA/LM	5	24.8 ± 20.8	0.81 ± 0.57
ACoA + PCoA	2	33.6 ± 17.7	1.41 ± 0.78
ACoA + OA and/or LM	5	43.2 ± 27.4	0.96 ± 0.61
OA and/or LM	10	13.2 ± 15.6	0.66 ± 0.66
ACoA(fs) or PCoA(fs) ± OA/LM	10	9.0 ± 10.3	0.89 ± 0.39
No collateral flow	22	59.5 ± 26.0	1.82 ± 0.57
Number of collaterals: 1	15	23.7 ± 28.6	1.22 ± 0.82
Number of collaterals: 2	19	16.3 ± 20.2	0.68 ± 0.44
Number of collaterals: 3	4	19.9 ± 21.4	0.97 ± 0.37

ACoA Anterior communicating artery, *PCoA* posterior communicating artery, *OA* retrograde ophthalmic artery, *LM* leptomeningeal collateral flow, *fs* functional stenosis. No significances are given due to the small n of single groups. Refer to Figure 3 for significances after pooling of different patterns into 4 different groups.

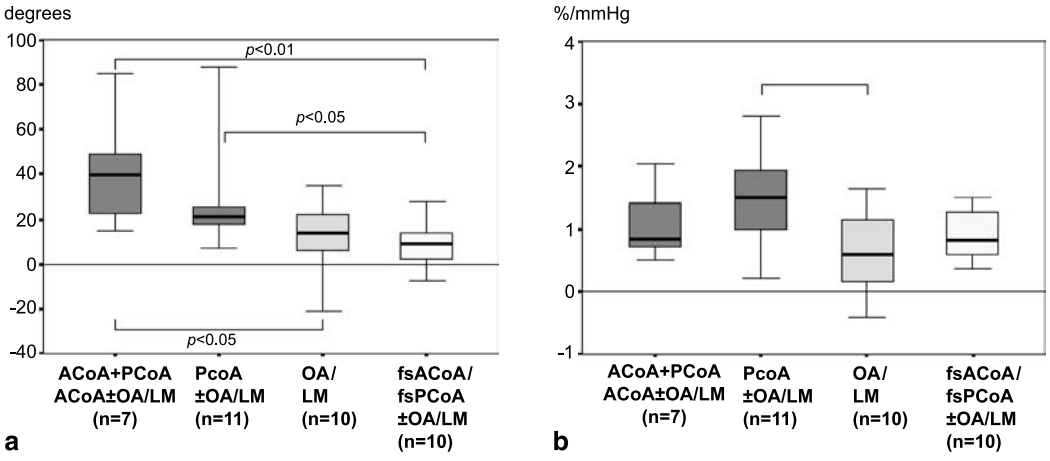

Fig. 3. Box-and-whiskers plots. Indiviudal MCA sides pooled into different groups of collateral flow

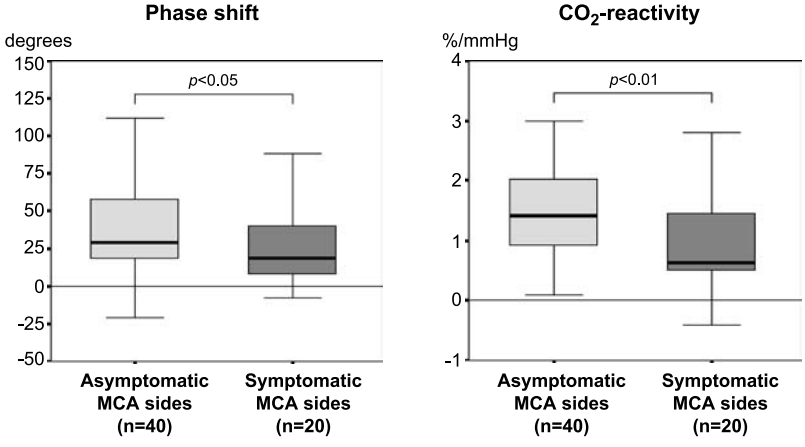

Fig. 4. Box-and-whiskers plots. Differences between clinically symptomatic and asymptomatic sides in patients with bilateral stenosis or occlusion

hemispheres. No collateral flow was present on 22 sides, of which all but one had an upstream ICA stenosis of less than 90%. These patients had widely preserved hemodynamic parameters. In patients with bilateral critical stenosis or occlusion, no cross-over flow via the ACoA was detected. Figure 3 illustrates phase shift and CO_2-reactivity after pooling patients into different groups according to collateral flow. Significantly impaired dynamic cerebral autoregulation was found with sole recruitment of secondary collaterals and recruitment of functionally stenosed primary collaterals.

CO_2-reactivity did not differ significantly but showed a trend towards better values in patients with collateral flow via the PCoA and poor values with sole recruitment of secondary collaterals, whereas activated but functionally stenosed primary collaterals did not show values as poor as for dynamic cerebral autoregulation.

Dividing patients with recruited collaterals into different groups according to the number of collaterals did not lead to significant differences of phase shift. CO_2-reactivity was significantly lower in patients with two collaterals than in patients with one collateral ($p = 0.019$, cf. Table 2).

Both phase shift and CO_2-reactivity differed significantly between clinically symptomatic and asymptomatic MCA sides (cf. Fig. 4).

Discussion

To the best of our knowledge, the present study is the first to analyze dynamic cerebral autoregulation and the collateral flow situation in patients with bilateral severe obstructive carotid artery disease.

We used the transfer function approach to assess cerebral autoregulation dynamics. This method is accepted

for providing a surrogate for the cerebral autoregulatory feedback control system [6, 24]. The phase shift between ABP and CBFV oscillations derived from transfer function analysis has previously been shown to be reduced in patients with unilateral carotid stenosis [9, 15]. However, the considerable range of autoregulatory impairment in uni- and bilateral carotid stenosis might be better understood by also analyzing the recruited collaterals. Transcranial Duplexsonography, which has been used in our study, is a well established method for the non-invasive determination of intracranial collaterals. However, limitations in accurately detecting the involvement of PCoA flow have been described [2].

Previous findings regarding the influence of collateral flow patterns on cerebral hemodynamic impairment in carotid disease are mostly based on examining patients with unilateral carotid stenosis, using cerebrovascular reactivity. In general, cross-flow via the ACoA seems to be the mainstay for sufficient collateral flow [13], whereas involvement of secondary (extra-Willisian) collaterals was observed together with poorer hemodynamic compensation [8].

In the present study, we found dynamic cerebral autoregulation to be most severely impaired in patients with pure activation of secondary collaterals and in patients with functionally stenosed primary collaterals. We speculate that in the latter case secondary collaterals are insufficient, leading to recruitment of a hypoplastic or arteriosclerotically narrowed collateral. While having no pathological impact on physiological flow situations, these collaterals develop a functional stenosis with an increased flow load. We have already observed this phenomenon in our previous study in patients with unilateral carotid stenosis [16]. In the present study, we observed best values in patients with a regular cross-over flow. This was only the case in patients with a contralateral 75–89% stenosis and an ipsilateral 90–100% stenosis. In this situation, the hemodynamic effect of the 75–89% stenosis seems to be small enough to still provide a sufficient interhemispheric pressure gradient resulting in a cross-over flow. On the other hand, none of the patients with bilateral 90–100% stenosis showed such a cross-over flow.

Rutgers *et al.* studied 21 patients with bilateral ICA occlusion using MR angiography [18]. They found flow via the ophthalmic artery in nearly all of them, while the additional presence of a functioning PCoA was more frequent in patients with preserved CO_2-reactivity. Vernieri *et al.* studied 67 patients with ICA occlusion and contralateral moderate or severe ICA stenosis [20]. As for unilateral carotid occlusion [21], they found the number of activated collaterals to be pivotal for hemodynamic compensation. We could not find such a relation. Our findings rather support the view that not the quantity but the quality of collaterals is essential for hemodynamic compensation.

CO_2-reactivity yielded different results than did dynamic cerebral autoregulation in our study. We hypothesize that certain collateral flow patterns (e.g., functional stenosis of primary collaterals) have a stronger effect on the control system of dynamic cerebral autoregulation. Although both approaches effectively study cerebral arterioles as an effector organ, they seem to represent different parameters of hemodynamic compromise: cerebral autoregulation represents an *intrinsic* hemodynamic control mechanism, while assessment of the cerebral vasodilatory reserve concentrates on *extrinsic* induction of arteriolar vasodilation.

Previously clinically symptomatic patients had significantly lower phase shift and CO_2-reactivity values on the affected side. This indicates that cerebral hemodynamic impairment is associated with an increased risk of cerebral ischemia, as already demonstrated by prospective studies for CO_2-reactivity in patients with unilateral ICA stenosis [12, 19]. However, the present study was not undertaken in this context and a considerable selection bias might be present, i.e. symptomatic patients with relatively good hemodynamic compensation might be overrepresented.

In conclusion, we found that cerebral autoregulation as assessed by transfer function analysis is most severely impaired in bilateral critical carotid stenosis or occlusion and that certain patterns of collateral flow are associated with different degrees of impairment of dynamic cerebral autoregulation. Determining transfer function phase might be a physiologically well-grounded and sensitive complement to the sole determination of vasodilatory reserve capacity for detection of cerebral hemodynamic compromise. In an ongoing prospective study we will evaluate whether modelling which integrates different hemodynamic variables [11] including the cerebral autoregulatory capacity can reliably identify patients with bilateral severe carotid obstructive disease at risk for ischemic events.

Acknowledgements

M.Re. and M.Ro. acknowledge support from the German Federal Ministry of Education and Research (bmb + f).

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Comments

In this paper the authors apply a by now established method for evaluation of cerebral autoregulation in a special group of patients. They studied 30 patients with severe bilateral carotid stenosis and tested cerebral autoregulation with transfer function analysis and CO_2 reactivity. In addition they correlated the results with the existence of collateral blood flow through the circle of Willis and ophthalmic/leptomeningeal anastomoses. The authors used patients with a unilateral carotid stenosis as controls. They report the highest compromised autoregulation with no existing collaterals, furthermore the circle of Willis can provide substantial collateral blood flow and thus improves autoregulation, the ophthalmic/leptomeningeal flow seems to be less important. They conclude, that the transfer function phase analysis might be helpful in the evaluation of compromised cerebral haemodynamics.

From a clinical point of view the results are not surprising, however, the methodology is interesting and should be pursued. So it will be interesting to see influences of various therapies in future studies as the authors already mentioned. This will boost the usefulness of this type of analysis.

A. Brawanski

Reinhard *et al.* have approached patients with symptomatic carotid occlusive disease in an attempt to derive useful indices of cerebral autoregulation based on natural fluctuations in blood pressure and cerebral artery velocity. The analysis depends on an observed change in the phase shift between these two variables which accompanies disturbed autoregulation. They have made a comparison of CO_2 reactivity using conventional methods. Finally they have tried to identify pattern of collateral blood flow at the level of the Circle of Willis and from leptomeningeal shunts.

All in all this is an elegant study which confirms the well rehearsed notion that for those patients with bilateral stenosis or occlusions, cerebral autoregulation is significantly depressed, as is the CO_2 reactivity. In keeping with previous publications, in those patients with unilateral stenosis or occlusions the cerebral autoregulation appears to be remarkably in tact. Predictably, patients with poor anterior communicative collaterals and those with reverse flow in the ophthalmic collateral are most likely to show more disturbed autoregulation.

Although mostly confirmatory, the authors have shown the elegance of providing this information non-invasively and without vascular

stimulation. The plots provided in Figure 2a show significant overlap indicating that the sensitivity and specificity of the method may not be very robust. This is often the case for single methods of assessment. The authors may be encouraged to develop a model using different variables, (for example severe reduction in phase shift, degree of lateral and contra lateral stenosis, contra lateral patterns) which will indicate which patients have severe compromise of the cerebral vascular reserve. This approach has been successfully adopted (Lam *et al* (2000) Brit J Neurosurg 14(5): 441–449).

P. J. Kirkpatrick

Correspondence: Andreas Hetzel, M.D., Department of Neurology, University of Freiburg, Breisacherstr. 64, D-79106 Freiburg, Germany. e-mail: HETZEL@nz11.ukl.uni-freiburg.de