Ultrasound in Med. & Biol., Vol. 29, No. 8, pp. 1105–1113, 2003

0301-5629/03/$–see front matter

ELSEVIER

doi:10.1016/S0301-5629(03)00954-2

● *Original Contribution*

DYNAMIC CEREBRAL AUTOREGULATION AND COLLATERAL FLOW PATTERNS IN PATIENTS WITH SEVERE CAROTID STENOSIS OR OCCLUSION

M. REINHARD,* T. MÜLLER,† B. GUSCHLBAUER,* J. TIMMER† and A. HETZEL*
*Department of Neurology and Clinical Neurophysiology, University Clinics of Freiburg, Freiburg, Germany; and
†Centre for Data Analysis and Modelling, University of Freiburg, Freiburg, Germany

(*Received* 23 *December* 2002; *revised* 4 *April* 2003; *in final form* 8 *April* 2003)

Abstract—The quality of collateral blood supply in carotid disease is pivotal for the resulting hemodynamic compromise. However, the interrelation between different patterns of collateral blood flow and actual impairment of cerebral autoregulation (CAR) has not been analyzed so far. Dynamic CAR was assessed noninvasively by the phase shift between respiratory-induced 0.1-Hz oscillations of arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) in 101 patients with severe unilateral carotid stenosis (≥ 75%) or occlusion. CO_2-vasomotor reactivity was assessed *via* inhalation of 7% CO_2. Spontaneously activated collaterals *via* primary (anterior/posterior communicating artery, type I, $n = 65$) and secondary (ophthalmic artery / leptomeningeal with or without primary pathways, group II, $n = 24$) pathways were assessed by transcranial Doppler/duplex sonography. Signs of functional stenosis in the anterior collateral pathways were subsumed under type III ($n = 12$). Best dynamic CAR (phase shift) on affected sides was observed for type I ($n = 65$), in which values did not differ significantly from contralateral sides. Reduced phase shift values were present in type II; poorest values were observed for type III. CO_2-reactivity differed mainly between type I and the other types. A less distinct differentiation of autoregulatory impairment was found when dividing patients into groups of different degrees of stenosis. Symptomatic patients (previous TIA/stroke) were significantly less frequent in the group with type I collateral flow and had significantly lower phase shift and CO_2-reactivity values. In conclusion, we found that dynamic CAR is substantially impaired if secondary collateral pathways are activated or if functional stenosis in the activated anterior collateral pathway is present. These hemodynamic constellations are also associated with a higher proportion of clinically symptomatic patients. Determination of dynamic CAR by transfer function analysis represents a convenient, sensitive method for detection of cerebral hemodynamic compromise in obstructive carotid disease. (E-mail: HETZEL@nz.ukl.uni-freiburg.de) © **2003 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Carotid artery stenosis, Cerebral autoregulation, Collateral circulation, CO_2-reactivity, Transcranial Doppler sonography.**

INTRODUCTION

Hemodynamic compromise plays a crucial role in the development of clinical symptoms in patients with high-grade carotid stenosis or occlusion (Markus and Cullinane 2001; Silvestrini et al. 2000). The extent of hemodynamic compromise as indicated by a reduction of cerebrovascular reserve capacity and regional cerebral blood flow (rCBF) measurements depends on the quality of intracranial collateral flow (Norrving et al. 1982). Viewed pathophysiologically, insufficient collateral blood supply leads to a reduced perfusion pressure in the area downstream of the carotid obstruction, resulting in autoregulatory dilation of cerebral arterioles. The anterior and posterior communicating arteries (ACoA, PCoA) of the circle of Willis are regarded as primary collateral pathways. Secondary pathways involve ophthalmic and leptomeningeal anastomoses. Their activation can be associated with a reduction of cerebrovascular reserve capacity (Smith et al. 1994; Müller and Schimrigk 1996).

Even though collateral flow is clinically important, we are not aware of any studies in patients with obstructive carotid artery disease focusing on the relationship between different patterns of collateral flow and the actual impairment of cerebral autoregulation. This might

Address correspondence to: Dr. Andreas Hetzel, Department of Neurology and Clinical Neurophysiology, University of Freiburg, Neurocenter, Breisacherstr. 64, Freiburg D-79106 Germany. E-mail: HETZEL@nz.ukl.uni-freiburg.de

be due to the fact that a deliberate reduction of arterial blood pressure (ABP) for the determination of the lower limits of cerebral autoregulation can be harmful in these patients. Yet, the assessment of cerebral autoregulatory capacity is of particular interest in these patients to gain insight into their cerebral hemodynamic situation, especially because a reduction of cerebrovascular reserve capacity does not necessarily correspond to autoregulatory impairment (White and Markus 1997; Reinhard et al. 2001). Cerebral autoregulation testing reveals information about the "intrinsic" ability of the cerebral vessel system to guarantee sufficient blood supply and, therefore, might be a (patho)physiologically more appropriate method for evaluation of cerebral hemodynamic impairment.

Over the last years, our view on cerebral autoregulation has changed substantially. Since the advent of transcranial Doppler ultrasonography (TCD), which measures cerebral blood flow velocity (CBFV) with a high temporal resolution, the noninvasive evaluation of dynamic properties of a supposed cerebral autoregulatory feedback system has begun to replace the classical approach of analyzing the upper and lower limits of the cerebral autoregulation plateau (Panerai 1998). Although the seminal contribution by Aaslid et al. (1989) concentrated on analysis of the amplitude and time course of CBFV during a rapid step change in ABP, recent methods are using more complex analysis techniques, both in the time and frequency domain; in the latter case, especially spectral and transfer function analysis (Giller 1990; Hu et al. 1999; Kuo et al. 1998). The frequency (or "transfer function") analysis approach is based on a high-pass filter model of the cerebral autoregulatory feedback system. According to that model, intact cerebral autoregulation is characterized by high-pass filter properties leading predominantly to a phase shift between spontaneous oscillations of CBFV and ABP in a low-frequency (LF) range around 0.1 Hz (Diehl et al. 1998). Such oscillations (so-called Mayer- or M-waves) occur physiologically, but can also be evoked by regular deep breathing at a rate of 6/min (Diehl et al. 1995). The characteristic feature of the frequency analysis method is that it supersedes the need for external ABP manipulation as a stimulus for cerebral autoregulation.

Thus, the aim of the present study was 1. to analyze dynamic cerebral autoregulation by means of transfer function analysis in patients with severe unilateral carotid stenosis or occlusion, and 2. to find out if the activation of different collateral flow patterns is associated with different degrees of impairment of dynamic cerebral autoregulation.

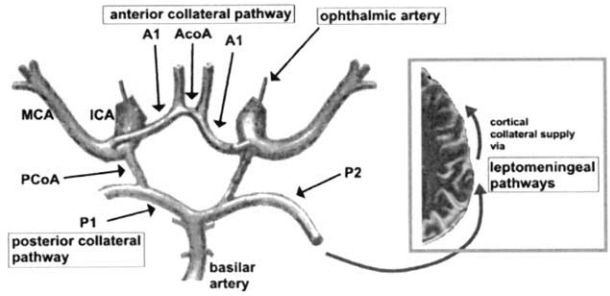

Fig. 1. Scheme of primary and secondary collateral pathways. Primary pathways involve the communicating arteries of the circle of Willis: the anterior collateral pathway *via* the A_1 segment of the anterior cerebral artery and the anterior communicating artery (ACoA) and the posterior collateral pathway *via* the P_1 segment of the posterior cerebral artery and the posterior communicating artery (PCoA). Secondary pathways involve extrawillisian collaterals: a retrograde flow *via* the external carotid and ophthalmic artery and leptomeningeal collateral flow *via* the posterior cerebral artery (P_2 segment), leptomeningeal and cortical vessels.

SUBJECTS AND METHODS

Over a period of 2 years, 111 patients with severe unilateral stenosis ($\geq$ 75%) or occlusion of the internal carotid artery (ICA) were studied. Exclusion criteria included an insufficient temporal bone window, current atrial fibrillation and contralateral ICA stenosis of $\geq$ 75%. A clinical history with special regard to previous symptoms and signs of cerebral or retinal ischemic events and major vascular risk factors was obtained from all patients, and a thorough clinical examination was performed. Both symptomatic and asymptomatic patients were studied. Patients were defined as clinically asymptomatic if no hemispheric or retinal ischemic symptoms ipsilateral to the stenosed side had occurred during the previous 2 years. In every patient, a complete neurosonological workup in our neurovascular lab was performed, including extracranial and intracranial color-coded duplex sonography (HDI 3500© ATL, Bothell, WA). Grading of stenosis was performed using Doppler velocities in combination with B-mode imaging according to standard criteria (de Bray and Glatt 1995; Hetzel et al. 1998).

Spontaneous intracranial collateral flow patterns: cross-flow *via* anterior communicating artery (ACoA), collateralization *via* posterior communicating arteries (PCoA), leptomeningeal collateralization (LPM) and a retrograde ophthalmic artery (OA), were assessed by transcranial Doppler and/or duplex sonography according to our laboratory standard (established by von Reutern and von Büdingen 1993). A schematical illustration of the different collateral pathways analyzed in the present study is given in Fig. 1. In detail, a cross flow *via*

ACoA was indicated by a reversed flow direction in the A_1 segment of the ACA ipsilateral to the stenosed ICA, functional stenosis of the anterior collateral pathway (ACoA or juxtaposed A_1 segments of the ACA) was presumed when Doppler frequencies >6 kHz or a turbulent spectrum of >5 kHz with musical murmurs were observed. A pure circumscribed turbulent spectrum at the ACoA without an increase in flow velocity over 5 kHz was not regarded as a sign of functional stenosis. Collateral flow *via* the PCoA was indicated by a marked increase of CBFV in the P_1 segment of the posterior cerebral artery (PCA) ipsilateral to the stenosed ICA (>50% compared with the contralateral side) and/or by direct visual identification of the PCoA on transcranial duplex sonography. Spontaneous leptomeningeal (LPM) collateral flow was indicated by a mean flow velocity increase of >30% in the P_2 segment of the PCA ipsilateral to the stenosed ICA compared with the P_2 segment of the contralateral PCA (Müller and Schimrigk 1996) and, at the same time, a reduced pulsatility with a side-to-side difference of more than 30%. Collateral supply *via* the OA was indicated by retrograde periorbital arteries as assessed by compression of external carotid artery branches and a pulsatility of the Doppler flow spectrum comparable with that of the intracranial vessels.

Assessment of CO_2-reactivity and cerebral autoregulation

Measurements were performed with subjects in a supine position with 50° inclination of the upper body. CBVF was measured from the envelope curve of Doppler spectra 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 noninvasive ABP recording was achieved *via* a servo-controlled finger plethysmograph (Finapres© 2300, Ohmeda, Englewood, CO) with the subject's right hand positioned at heart level. End-tidal CO_2 partial pressure (P_{ETCO2}) was measured in mmHg with an infrared capnometer (Normocap© Datex, Helsinki, Finland) during nasal expiration by a probe attached to one nostril (during deep breathing) and by a probe in the expiratory way of the tube system (during CO_2-reactivity testing). P_{ETCO2} values have been shown to correlate closely with intra-arterial CO_2 values (Young et al. 1998). After stable baseline values had been established, dynamic cerebral autoregulation was assessed by regular deep breathing at a rate of 6/min (*i.e.,* 0.1 Hz) over 180 s (Diehl et al. 1995). This led to sinusoidal oscillations of ABP and CBFV at 0.1 Hz in all patients. Patients were carefully instructed to breathe with *low* tidal volumes to avoid hyperventilation with resulting hypocapnia. Note that the term "deep breathing" is based on the original application of this method for assessment of heart rate variability. P_{ETCO2} changes were closely monitored and analyzed at the beginning and end of the deep breathing. Thereafter, a CO_2-reactivity test was performed: after stable baseline values had been achieved, 7% CO_2-enriched air was directed toward the patient *via* a tube system, a two-way valve and a mask. This lead to a stable hypercapnia (as controlled by P_{ETCO2} values), which was maintained for 60 to 90 s. CO_2-reactivity was calculated as the percentage increase in mean CBFV per mmHg increase in P_{ETCO2} (%/mmHg) during stable hypercapnia.

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 (T. Müller). For final data analysis, 10 of the 111 patients had to be excluded: 3 due to Doppler or Finapres signal artefacts, and 7 due to inability to perform a regular deep breathing after repeated instruction ("respiratory apraxia").

Analysis of dynamic cerebral autoregulation

The deep breathing data were analyzed in the frequency domain using cross-spectral methods. From the given time-courses of ABP and CBFV, the power spectra S_{ABP} and S_{CBFV} and the cross spectrum *CSp* were estimated by periodogram smoothing (Bloomfeld 1976). This method is not the same as the popular Welch method. The Welch method divides the given time-course into segments and estimates the spectra by segment averaging. Periodogram smoothing gives a better frequency resolution, which is crucial in the low-frequency range. In short, the whole data sets of ABP and CBFV were transformed to the frequency domain by discrete Fourier transform, employing fast Fourier transform code suitable for arbitrary data length. Given a measurement time $T = 3$ min, the resulting frequency resolution was $1/T = 0.0056$ Hz. From the discrete Fourier transforms, 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 by smoothing with a triangular window of half-width 8 bins. The smoothing decreases the variance of the estimate. The estimated cross-spectrum is complex-valued. The following real quantities were derived from the estimated cross-spectrum:

The coherency:

$$Coh(f) = \frac{|CSp(f)|}{\sqrt{S_{ABP}(f)S_{CBFV}(f)}} \qquad (1)$$

the gain:

$$G(f) = \frac{|CSp(f)|}{S_{ABP}(f)}, \quad (2)$$

and the phase Φ (f), which is defined by the representation

$$CSp(f) = |CSp(f)|\exp[i\Phi(f)]. \quad (3)$$

The coherency is a measure of linear association. If the two signals are linearly related, the coherency is equal to its maximum value 1; if there is no linear association, the coherency is equal to its minimum value 0. Note that, even in the case of a complete linear association, the coherency can be less than 1 due to, for example, observational noise (Timmer et al. 1998). With the smoothing we used, the coherency is significant (at the 95% level) if it exceeds 0.49 (see Reinhard et al. 2003, eqn. 2, for details). The gain describes the frequency-dependent amplitude transmission in the system. The phase is the argument of the complex-valued cross spectrum.

Deep breathing at a rate of 6/min led to a dominant frequency peak at 0.1 Hz. At this peak, we extracted the phase shift between ABP and CBFV oscillations as a parameter for dynamic cerebral autoregulation (Fig. 2).

Statistical analysis

Because especially the dynamic cerebral autoregulatory parameters were not normally distributed on visual inspection (histograms), statistical analysis was carried out using nonparametric tests (Wilcoxon, Mann–Whitney, Spearman's rank order correlations) and Fisher's exact test for 2×2 tables, respectively. When multiple statistical tests were performed to test a single hypothesis (*i.e.,* comparison of n groups, $n > 2$), a Bonferroni correction was applied by multiplying the p value of the single test by n. A resulting p value of less than 0.05 was considered statistically significant. Data are reported as mean $\pm$ SD and illustrated by box-and-whiskers plots.

RESULTS

Illustrative plots of dynamic cerebral autoregulation analysis in two patients with different collateral flow patterns are shown in Fig. 2. Activated primary collateral pathways were found in 65 patients (= type I), activated secondary pathways with or without primary pathways in 24 patients (= type II), and functional stenosis of the activated anterior collateral pathway with or without activation of other pathways in 12 patients (= type III). Type I collateralization was more frequent in the 75 to 89% stenosis group, and no patient with type III collateralization belonged to this group (Fig. 3a). Previous

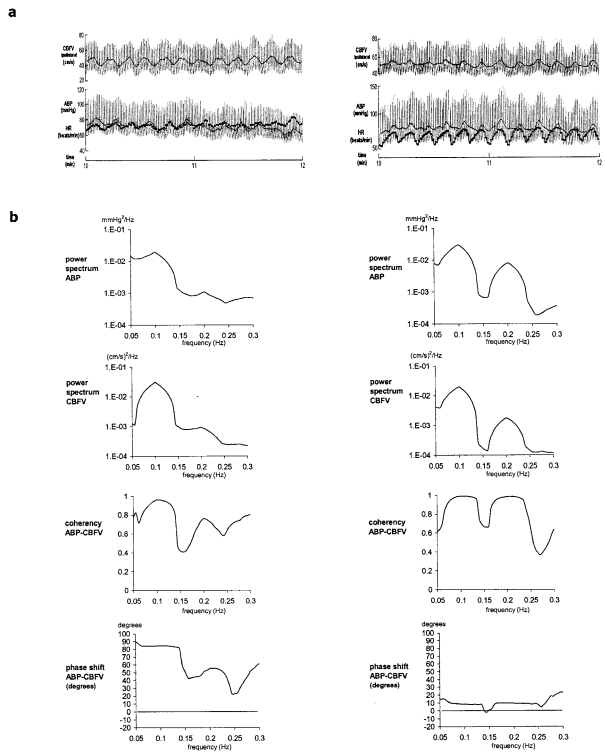

Fig. 2. Illustrative recording of dynamic cerebral autoregulation analysis. The left column is of a 66-year-old patient with occlusion of the left ICA and collateral type I (*i.e.,* flow *via* communicating arteries of the circle of Willis), the right column is of a 57-year-old patient with occlusion of the right ICA and collateral type III (*i.e.,* collateral flow *via* a functionally stenosed anterior pathway). (a) Raw data of deep breathing; note the clear oscillations of ABP, CBFV and heart rate induced by breathing at a rate of 6/min. (b) Results of transfer function analysis; the deep breathing rate of 6/min results in a dominant peak at 0.1 Hz in the power spectra (spectral analysis) of ABP and CBFBV. The coherency at 0.1 Hz is high in both patients (95% level of significance = 0.49). Phase shift between ABP and CBFV oscillations (lower graph) is markedly reduced in the right patient with type III collateral flow.

clinical symptoms on the affected side (TIA/stroke) were significantly less frequent in patients with type I collateral flow (Fig. 3b).

Results of phase shift and CO_2-reactivity in different types of collateral flow are shown in Table 1. Best dynamic CAR (phase shift) on affected sides was observed for type I, in which values did not differ significantly from contralateral sides. Reduced phase shift values were present in type II, poorest values were observed for type III (Fig. 4a). CO_2-reactivity differed mainly between types I and II, and between I and III.

When patients were divided into three groups based solely on the degree of ipsilateral stenosis, a clear differentiation regarding autoregulatory impairment and reduction of CO_2-reactivity was no longer possible (Fig. 4b).

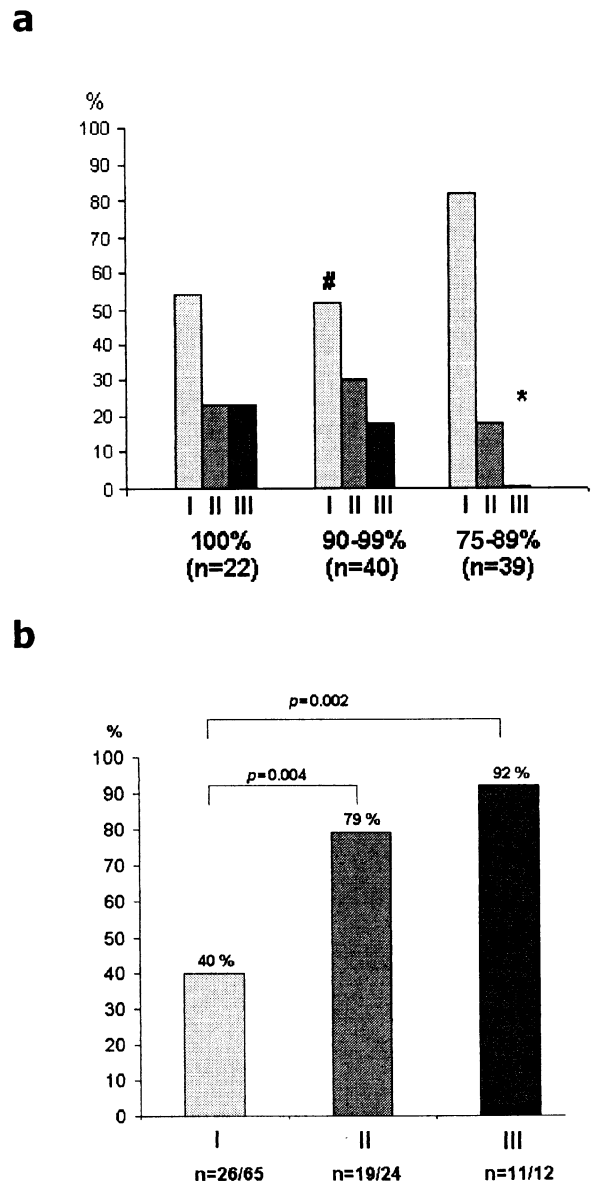

Fig. 3. (a) Proportion of different collateral flow patterns within groups of different stenosis severity. *$p = 0.013$ to 100% stenosis, $p = 0.035$ to 90 to 99% stenosis, # $p = 0.024$ to 75 to 89% stenosis. (b) Proportion of symptomatic patients (TIA/stroke) on the affected side in different collateral flow patterns: I = activated primary pathways, II = activated secondary ± primary pathways, III = functional stenosis of the activated primary anterior collateral pathway (with or without other activated pathways).

Phase shift values and CO_2-reactivity were significantly lower on affected sides in symptomatic patients (Fig. 5). Spearman's correlation coefficient between absolute phase shift values and CO_2-reactivity pooling all patients was moderate ($r = 0.38$; $p < 0.001$). Affected sides of symptomatic patients had a higher correlation coefficient between these two methods (Fig. 6).

DISCUSSION

In this study, we investigated the dynamic cerebral autoregulatory capacity by means of transfer function analysis and illustrated the interrelation between cerebral autoregulation and different patterns of collateral blood supply in patients with carotid disease. Dynamic cerebral autoregulation was significantly impaired if secondary collateral pathways were recruited, and tended to be even poorer when functional stenosis of the anterior collateral pathway was present.

Findings in the literature regarding the influence of collateral flow patterns on impairment of cerebral hemodynamics in carotid disease are somewhat controversial, and various techniques for determining both collateral flow status and hemodynamic impairment have been used (Norrving et al. 1982; Vernieri et al. 2001). However, most studies used cerebrovascular reserve capacity as a surrogate for cerebral autoregulation and little is known about impairment of cerebral autoregulation itself. Overall, cross-flow *via* the ACoA seems to be the mainstay for sufficient collateral flow (Kluytmans et al. 1999; Müller and Schimrigk 1996). The role of the PCoA remains unclear; some results indicate that the presence of PCoA recruitment additionally to ACoA cross-flow is superior to ACoA cross-flow alone (Rutgers et al. 2000), but others reported collateral flow *via* the PCoA alone to be a sign of hemodynamic compromise (Kluytmans et al. 1999). Involvement of secondary (extrawillisian) pathways was observed together with impaired cerebral hemodynamics (Norrving et al. 1982; Muller and Schimrigk 1996; Hofmeijer et al. 2002). In a number of studies examining patients with carotid occlusion by magnetic resonance angiography (MRA) and/or TCD techniques, no significant association has been found between certain collateral flow patterns and the impairment of cerebral hemodynamics (Vernieri et al. 2001; Hedera et al. 1995; van Everdingen et al. 1998). Vernieri et al. (2001) found that the number of collateral pathways was more crucial for the extent of cerebral hemodynamic compromise than the various collateral flow patterns themselves.

We defined three main groups of collateral patterns according to spontaneously activated collateral pathways, because the number of patients in the various single collateral patterns was too small to draw conclusions reliably. For the determination of spontaneously activated primary and secondary collateral pathways we used transcranial Doppler and Duplex sonography. This method is well established for the noninvasive determination of significant collateral pathways (Müller et al. 1995), but limitations have been described in accurately detecting the involvement of PCoA flow (Müller et al. 1995; Droste et al. 2000). However, a relevant contribution of the PCoA should be seen from an increase in

Table 1. Characteristics of stenoses and results of phase shift and CO_2-reactivity in different types of collateral flow

Collateral flow type	I (n = 65)	II (n = 24)	III (n = 12)	Significances
Activated pathways	Primary	Secondary (±primary)	Stenosed anterior	
Degree of ipsilateral ICA stenosis: occlusion	12	5	5	NS
90–99%	21	12	7	NS
75–89%	32	7	0	I–III: $p = 0.003$
Medium ICA stenosis contralaterally (50–74%)	17	1	0	NS
Phase shift at 0.1 Hz (degrees)				
ipsilateral	45.6 ± 31.1	23.1 ± 24.6	7.3 ± 15.8	I–II, I–III: $p < 0.001$, II–III: NS
contralateral	52.5 ± 27.9	67.2 ± 29.6	50.0 ± 36.0	NS; ipsi vs. contra: I: NS, II: $p < 0.001$, III: $p = 0.006$
CO_2-reactivity (%/mmHg)				
ipsilateral	1.47 ± 0.69	0.75 ± 0.55	0.89 ± 0.97	I–II: $p < 0.001$, I–III: $p = 0.009$, II–III: NS
contralateral	1.99 ± 0.67	1.96 ± 0.40	2.10 ± 0.66	NS; ipsi vs. contra: I,II: $p < 0.001$, III: $p = 0.003$

NS = not significant. p values of intergroup comparisons include a Bonferroni correction. Patients with contralateral medium stenosis (50–74%), which was more frequent in group I, had slightly poorer phase shift values on this side compared with patients with non- or minor-stenosed contralateral sides (47.1 ± 31.9° vs. 58.7 ± 27.2°, $p = 0.042$). This did not apply for CO_2-reactivity.

CBFV in the ipsilateral P_1 segment. We did not evaluate potentially recruitable collateral pathways by carotid compression tests but, rather, determined the spontaneously activated ones, because ischemic complications from carotid compression in patients with atherosclerosis have been reported (Mast et al. 1993).

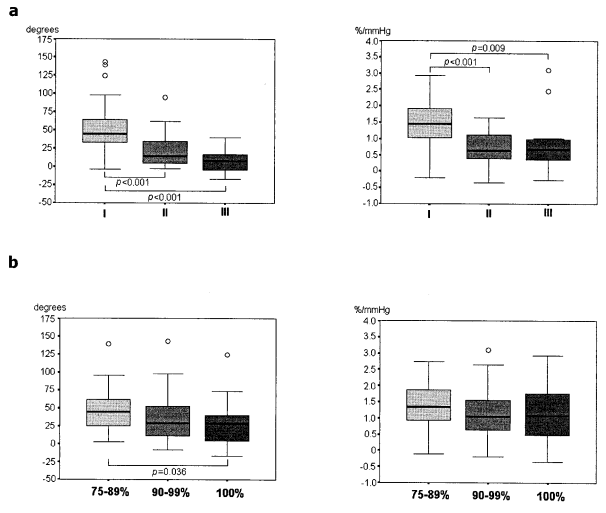

Fig. 4. (a) Influence of the different collateral flow patterns on phase shift of transfer function (left) and CO_2-reactivity (right). There was a nonsignificant trend toward lower phase shift values between patients with type FII and III collaterals. I = activated primary pathways, II = activated secondary ± primary pathways, III = functional stenosis of the activated primary anterior collateral pathway (with or without other activated pathways). o = exceeding values. (b) Influence of different degrees of stenosis on phase shift of transfer function (left) and CO_2-reactivity (right). No significant differences were observed for CO_2-reactivity. For phase shift, only group A and C differed significantly. o = exceeding values.

Dynamic cerebral autoregulation was assessed using phase shift of slow rhythmic oscillations of ABP and CBFV (Birch et al. 1995; Diehl et al. 1995). This parameter, which is derived from transfer function analysis, proved to be a meaningful parameter of cerebral hemodynamic impairment in a number of previous investigations (Diehl et al. 1995; Kuo et al. 1998; Hu et al. 1999; Zhang et al. 1998; Lang et al. 2001; Reinhard et al. 2003). We used the deep breathing approach to evoke standardized oscillations at 0.1 Hz instead of analyzing spontaneously occurring oscillations in this frequency range (Diehl et al. 1995). In contrast to the latter, the deep breathing method has the advantage that it provides univocal phase shift values at the same frequency for all patients and that extraction of phase shift from a more complex spectrum (as occurring when analyzing the variable spontaneous oscillations) is not a critical factor. In a recent study, we also found a higher reproducibility of phase shift derived from the deep breathing approach (Reinhard et al. 2003). In addition to the inability of 5 to 10% of patients to breathe regularly at a comparatively slow rhythm of 6/min, the main disadvantage of this method lies in development of hypocapnia during the deep-breathing maneuver, influencing the autoregulation data. However, by instructing patients to breathe with small tidal volumes, a major decrease in P_{ETCO2} could be avoided.

We have shown, in the present study, that cerebral autoregulation, as indicated by transfer function phase shift, is severely impaired in patients with activation of secondary pathways. Because the number of activated collaterals is high in these patients, our findings conflict with above-mentioned studies that proposed the number of functional collaterals as a critical parameter for preserved hemodynamics (Vernieri et al. 2001). Müller and

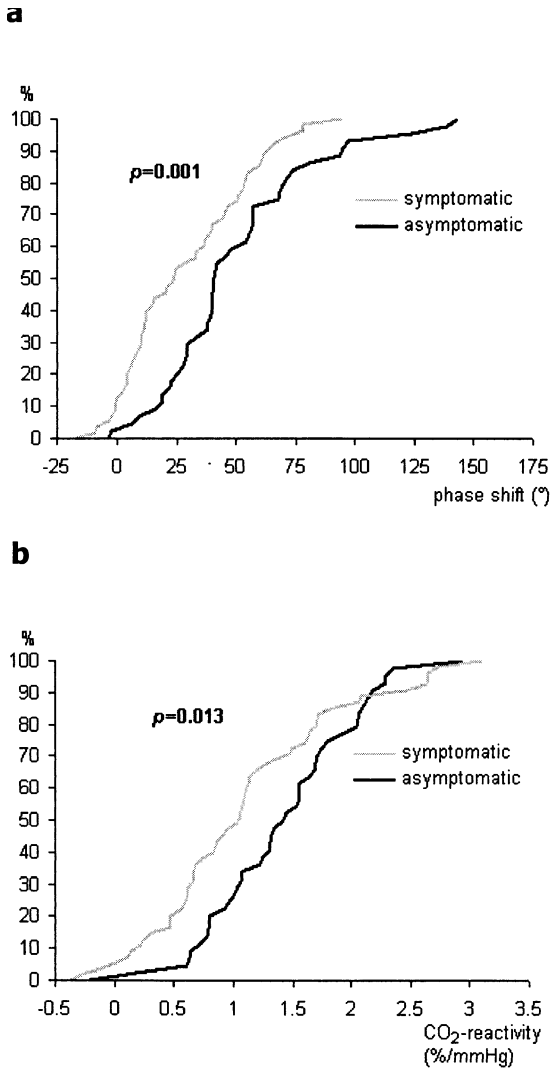

Fig. 5. Relation of hemodynamic parameters to clinical symptomaticity. Cumulative distribution plots of symptomatic vs. asymptomatic patients for (a) phase shift of transfer function and (b) CO_2-reactivity. p values = by the Mann–Whitney test.

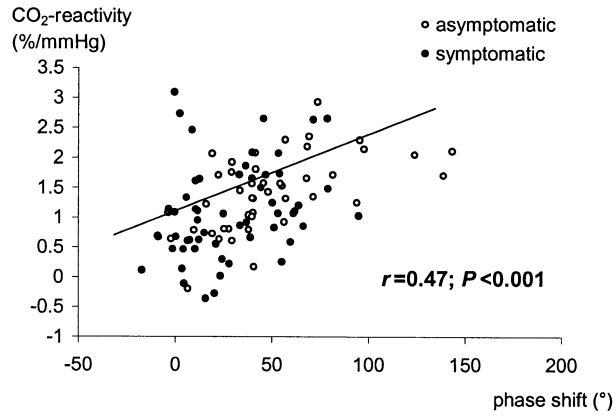

Fig. 6. Scatter plot between phase shift and CO_2-reactivity on affected sides. Analyzing symptomatic sides separately, a considerably higher correlation was found compared with asymptomatic sides ($r = 0.59$; $p < 0.001$ vs. $r = 0.30$; $p = 0.027$).

Schimrigk (1996), in turn, found a significant decrease of vasomotor reactivity in the presence of activated secondary pathways. Our results mostly support the latter study. Additional or sole activation of secondary pathways points to insufficiency of primary pathways (Hofmeijer et al. 2002).

Insufficiency of primary pathways can be due to hypoplasia or stenosis. According to hemodynamic Doppler sonographic criteria, we also found patients with a functionally stenosed anterior collateral pathway. These stenoses are most likely to be functional in the sense that they are due to hypoplasia and become evident only when a high volume flow during recruitment as collateral pathway is needed in the absence of other potent collaterals. A recent study using transcranial Duplex sonography found hypofunction of the anterior pathway in 5% and a hypo- or nonfunctional posterior pathway in almost half the cases, confirming previous anatomic studies (Hoksbergen et al. 2000). In the present study, patients with signs of functional stenosis of the anterior pathway had the poorest cerebral autoregulatory parameters (Fig. 4a). They were all suffering from carotid stenoses of $\geq 90\%$. We hypothesize that, in these patients, alternative primary or secondary pathways are insufficient, leading to recruitment of a virtually insufficient vessel. This situation is characterized by severe hemodynamic compromise as indicated by an almost exhausted dynamic cerebral autoregulation.

Interestingly, most of the previous studies analyzing collateral flow in carotid artery disease focused on carotid occlusion. The present study analyzed patients with severe or critical carotid stenosis as well. We found the degree of stenosis to be a less important discriminator for hemodynamic impairment than the collateral status (Fig. 4b).

A stenosis of $> 70\%$ of the contralateral ICA has been described as an important factor for vasomotor reactivity of the ipsilateral side in carotid occlusion (Visser et al. 1997). In our study, stenosis of $\geq 75\%$ of the contralateral ICA was an exclusion criterion and the proportion of patients with medium ICA stenosis was rather lower in groups with an insufficient collateral flow pattern (types II and III). Therefore, a major confounding factor of medium contralateral stenosis is unlikely in the present investigation.

We also examined the presence of previous clinical symptoms ipsilateral to the affected side ("symptomatic stenosis"). We found that symptomatic patients had significantly poorer phase shift and CO_2-reactivity values. It

is noteworthy that this is a known fact for CO_2-reactivity in both retrospective and prospective studies (Markus and Cullinane 2001), but has not been demonstrated for the phase-shift measure or any other dynamic cerebral autoregulatory parameter so far. We could further show that collateral flow types II and III are significantly more frequently associated with clinical symptoms. Our study, thus, confirms a link between patterns of collateral flow, impairment of cerebral autoregulation and the presence of clinical symptoms in severe carotid stenosis or occlusion.

Both CO_2-reactivity and dynamic cerebral autoregulation tests involve cerebral arterioles as a common effector. However, the complex feedback system of dynamic cerebral autoregulation is not entirely equal to the external stimulus of vasodilation generated by transient hypercapnia. This fact is underlined by the only moderate correlation between these two parameters (Fig. 6). Furthermore, we found that the phase shift parameter tended to differentiate better between different collateral flow types (Fig. 4). Previous studies analyzing dynamic cerebral autoregulation and CO_2-reactivity also reported a possible dissociation with autoregulatory impairment in the presence of a preserved cerebrovascular reserve capacity (White and Markus 1997; Reinhard et al. 2001). Assessment of dynamic cerebral autoregulation might, thus, probably be a more sensitive and physiologically better-supported approach for assessment of cerebral hemodynamic impairment than CO_2-reactivity. Interestingly, both methods showed a better correlation on affected sides in symptomatic patients. This might be explained by the fact that clear impairment of cerebral hemodynamics is both more likely to produce clinical symptoms and to yield similar results in different tests grading the degree of impairment.

In conclusion, we found that 1. certain patterns of collateral flow are associated with impairment of dynamic cerebral autoregulation, and 2. in particular, activation of secondary pathways and—even more—Doppler sonographic signs of a functional stenosis in the anterior collateral pathway are related to major hemodynamic compromise. Also, 3. dynamic cerebral autoregulatory capacity is significantly lower in patients with symptomatic carotid stenosis and 4. assessment of dynamic cerebral autoregulatory capacity by phase shift of transfer function analysis might be more sensitive in detection of cerebral hemodynamic compromise than assessment of cerebrovascular reserve capacity alone. In an ongoing prospective study, we will elucidate the clinical impact of impaired dynamic cerebral autoregulation and different patterns of collateral flow.

Acknowledgements—M. Reinhard and T. Müller acknowledge support from the German Federal Ministry of Education and Research (bmb+f).

REFERENCES

Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45–52.

Birch AA, Dirnhuber MJ, Hartley-Davies R, Iannotti F, Neil-Dwyer G. Assessment of autoregulation by means of periodic changes in blood pressure. Stroke 1995;26:834–837.

Bloomfeld P. Fourier analysis of time series: An introduction. New York: Wiley & Sons, 1976.

de Bray JM, Glatt B. Quantification of atheromatous stenosis in the extracranial internal carotid artery. Cerebrovasc Dis 1995;5:414–426.

Diehl RR, Linden D, Lucke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. Stroke 1995;26:1801–1804.

Diehl RR, Linden D, Lucke D, Berlit P. Spontaneous blood pressure oscillations and cerebral autoregulation. Clin Auton Res 1998;8:7–12.

Droste DW, Jurgens R, Weber S, Tietje R, Ringelstein EB. Benefit of echocontrast-enhanced transcranial color-coded duplex ultrasound in the assessment of intracranial collateral pathways. Stroke 2000; 31:920–923.

Giller CA. The frequency-dependent behavior of cerebral autoregulation. Neurosurgery 1990;27:362–368.

Hedera P, Bujdakova J, Traubner P. Effect of collateral flow patterns on outcome of carotid occlusion. Eur Neurol 1995;35:212–216.

Hetzel A, Eckenweber B, Trummer B, et al. Colour-coded duplex sonography of preocclusive carotid stenoses. Eur J Ultrasound 1998;8:183–191.

Hofmeijer J, Klijn CJ, Kappelle LJ, van Huffelen AC, van Gijn J. Collateral circulation via the ophthalmic artery or leptomeningeal vessels is associated with impaired cerebral vasoreactivity in patients with symptomatic carotid artery occlusion. Cerebrovasc Dis 2002;14:22–26.

Hoksbergen AW, Fulesdi B, Legemate DA, Csiba L. Collateral configuration of the circle of Willis: transcranial color-coded duplex ultrasonography and comparison with postmortem anatomy. Stroke 2000;31:1346–1351.

Hu HH, Kuo TB, Wong WJ, et al. Transfer function analysis of cerebral hemodynamics in patients with carotid stenosis. J Cereb Blood Flow Metab 1999;19:460–465.

Kluytmans M, van der Grond J, van Everdingen KJ, et al. Cerebral hemodynamics in relation to patterns of collateral flow. Stroke 1999;30:1432–1439.

Kuo TB, Chern CM, Sheng WY, Wong WJ, Hu HH. Frequency domain analysis of cerebral blood flow velocity and its correlation with arterial blood pressure. J Cereb Blood Flow Metab 1998;18:311–318.

Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: The phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 2001;29:158–163.

Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001;124:457–467.

Mast H, Ecker S, Marx P. Cerebral ischemia induced by compression tests during transcranial Doppler sonography. Clin Invest 1993;71: 46–48.

Muller M, Schimrigk K. Vasomotor reactivity and pattern of collateral blood flow in severe occlusive carotid artery disease. Stroke 1996; 27:296–299.

Muller M, Hermes M, Bruckmann H, Schimrigk K. Transcranial Doppler ultrasound in the evaluation of collateral blood flow in patients with internal carotid artery occlusion: Correlation with cerebral angiography. AJNR Am J Neuroradiol 1995;16:195–202.

Norrving B, Nilsson B, Risberg J. rCBF in patients with carotid occlusion. Resting and hypercapnic flow related to collateral pattern Stroke 1982;13:155–162.

Panerai RB. Assessment of cerebral pressure autoregulation in humans—A review of measurement methods. Physiol Meas 1998;19: 305–338.

Reinhard M, Hetzel A, Lauk M, Lucking CH. Dynamic cerebral autoregulation testing as a diagnostic tool in patients with carotid artery stenosis. Neurol Res 2001;23:55–63.

Reinhard M, Müller T, Guschlbauer B., Timmer J, Hetzel A. Transfer function analysis for clinical evaluation of dynamic cerebral autoregulation—A comparison between spontaneous and respiratory-induced oscillations. Physiol Meas 2003;24:27–43.

Rutgers DR, Klijn CJ, Kappelle LJ, van Huffelen AC, van der Grond J. A longitudinal study of collateral flow patterns in the circle of Willis and the ophthalmic artery in patients with a symptomatic internal carotid artery occlusion. Stroke 2000;31:1913–1920.

Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000;283:2122–2127.

Smith HA, Thompson-Dobkin J, Yonas H, Flint E. Correlation of xenon-enhanced computed tomography-defined cerebral blood flow reactivity and collateral flow patterns. Stroke 1994;25:1784–1787.

Timmer J, Lauk M, Pfleger W, Deuschl G. Cross-spectral analysis of physiological tremor and muscle activity. I Theory and application to unsynchronized electromyogram. Biol Cybern 1998;78: 349–357.

van Everdingen KJ, Visser GH, Klijn CJ, Kappelle LJ, van der Grond J. Role of collateral flow on cerebral hemodynamics in patients with unilateral internal carotid artery occlusion. Ann Neurol 1998;44: 167–176.

Vernieri F, Pasqualetti P, Matteis M, et al. Effect of collateral blood flow and cerebral vasomotor reactivity on the outcome of carotid artery occlusion. Stroke 2001;32:1552–1558.

Visser GH, van Huffelen AC, Wieneke GH, Eikelboom BC. Bilateral increase in CO2 reactivity after unilateral carotid endarterectomy. Stroke 1997;28:899–905.

von Reutern G, von Büdingen HJ. Ultrasound diagnosis of cerebrovascular disease. Stuttgart: Thieme, 1993.

White RP, Markus HS. Impaired dynamic cerebral autoregulation in carotid artery stenosis. Stroke 1997;28:1340–1344.

Young WL, Prohovnik I, Ornstein E, Ostapkovich N, Matteo RS. Cerebral blood flow reactivity to changes in carbon dioxide calculated using end-tidal versus arterial tensions. J Cereb Blood Flow Metab 1998;11:1031–1035.

Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. Am J Physiol 1998;274:H233–H241.