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Cerebral Autoregulation in Carotid Artery Occlusive Disease Assessed From Spontaneous Blood Pressure Fluctuations by the Correlation Coefficient Index

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Background and Purpose—Estimation of dynamic cerebral autoregulation from spontaneous fluctuations of arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) is an attractive monitoring option for cerebral hemodynamic impairment. We evaluated the correlation coefficient index method in patients with severe obstructive carotid disease and compared it with transfer function analysis (frequency domain approach to cerebral autoregulation) and CO_2 vasomotor reactivity.

Methods—In 139 patients with severe unilateral carotid stenosis (≥70%) or occlusion, CBFV (transcranial Doppler) and ABP (Finapres method) were recorded over 10 minutes. Correlations between systolic pressure, diastolic pressure, and mean ABP and CBFV oscillations over 1-minute epochs were averaged over 10 minutes to form the correlation coefficient indexes (Sx, Dx, Mx, respectively). Transfer function parameters (phase shift and gain between ABP and CBFV oscillations) were determined from the entire 10-minute period. CO_2 reactivity was assessed by inhalation of 7% CO_2.

Results—The correlation indexes Dx and Mx were significantly higher ipsilateral to stenosis and increased with degree of stenosis, indicating increasing dependence of CBFV on ABP and thus impairment of cerebral autoregulation. Dx and Mx correlated moderately but highly significantly with transfer function parameters and CO_2 reactivity and showed a good level of agreement in detecting pathological values. Patients with a small variance of the 1-minute source correlations of Dx and Mx showed clearly better correlation values. Transfer function parameters and CO_2 reactivity but not Dx and Mx were significantly poorer in patients with symptomatic stenosis or occlusion.

Conclusions—The potential of the correlation coefficient indexes Dx and Mx in detecting hemodynamic impairment in patients with carotid stenosis is comparable to that of transfer function analysis and CO_2 reactivity testing. In future, a combination of various hemodynamic tests might help to identify patients at risk for ischemic events.

Key Words: autoregulation ■ carbon dioxide ■ carotid stenosis

Cerebrovascular pressure autoregulation is a protective intrinsic control mechanism of the cerebral circulation that keeps cerebral blood flow independent from systemic changes in blood pressure.[1] In clinical states associated with chronic hemodynamic compromise such as obstructive carotid artery disease, detection of impaired cerebral autoregulation might help to identify patients at risk from stroke as shown for cerebrovascular reserve capacity.[2,3]

Clinical assessment of cerebral autoregulation is based on various concepts. Over many years, the upper and lower arterial blood pressure (ABP) limits of autoregulatory maintenance of cerebral blood flow were assessed, requiring considerable manipulation of ABP. Over the last decade, the high temporal resolution of transcranial Doppler sonography allowed analysis of the amplitude and time latencies of the cerebral blood flow velocity (CBFV) response to rapid but relatively small changes in ABP (dynamic cerebral autoregulation).[4] Reliable and repeatable noninvasive induction of ABP changes, however, proved difficult. Over the last years, attention has therefore been directed toward analyzing physiologically occurring ABP changes without the need for any external manipulation.

Two main approaches to analyzing dynamic cerebral autoregulation from such spontaneous ABP fluctuations have been used so far. The first one works in the frequency domain. Via transfer function analysis, the phase shift and gain between spontaneous (or respiratory-induced) oscillations of ABP and CBFV are calculated.[5] Mainly, a positive

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TABLE 1. Results of Various Cerebral Autoregulatory Parameters and CO_2 Reactivity in Different Groups of Stenosis

	Degree of Stenosis					
	A, 70–79% (N=40), Unilateral	B, 80–89% (n=21), Unilateral	C, 90–99% (N=56), Unilateral	D, 100% (n=22), Unilateral	Significances, Ipsi- vs Contralateral	Intergroup
Correlation coefficient indices						
Sx ipsilateral	0.28±0.18	0.34±0.16	0.33±0.19	0.32±0.25	A,B†, C*	NS
Sx contralateral	0.21±0.21	0.26±0.13	0.22±0.19	0.29±0.21		NS
Dx ipsilateral	0.08±0.16	0.15±0.14	0.25±0.19	0.26±0.24	A,B,C‡, D†	A-C‡, A-D†
Dx contralateral	0.01±0.15	0.00±0.15	0.01±0.13	0.11±0.22		NS
Mx ipsilateral	0.35±0.18	0.45±0.11	0.51±0.18	0.51±0.21	A,B,C‡, D†	A-C‡, A-D†
Mx contralateral	0.27±0.17	0.28±0.11	0.30±0.17	0.39±0.17		NS
Transfer function analysis						
LF phase ipsilateral (°)	38.8±22.2	34.9±24.5	20.4±24.5	19.0±25.8	A,B†, C,D‡	A-C‡, A-D†
LF phase contralateral	44.8±20.8	55.9±25.5	44.8±27.9	39.6±20.5		
HF gain ipsilateral (cm/s) · mm Hg^{-1}	0.75±0.27	0.63±0.26	0.59±0.28	0.49±0.28	A,C‡, B,D†	A-D‡, A-C†
HF gain contralateral	0.97±0.34	0.97±0.47	1.03±0.34	0.87±0.35		
CO_2-reactivity						
Ipsilateral (cm/s) · mm Hg^{-1}	1.92±0.78	1.32±0.86	1.06±0.70	1.17±1.09	A,B†, C,D‡	A-C‡, A-B†, A-D†
Contralateral	2.16±0.78	1.97±0.73	1.95±0.66	2.34±0.80		

*$P<0.05$; †$P<0.01$; ‡$P<0.001$

phase shift between ABP and CBFV oscillations (ie, CBFV oscillations precede ABP oscillations) was interpreted as intact cerebral autoregulation according to a high-pass filter model of the cerebral autoregulatory feedback control system.[6,7] Both transfer function phase and gain were found to be reduced in patients with carotid artery stenosis.[6,8,9]

The second approach works in the time domain. Its rationale is based on the classic assumption of independence of cerebral blood flow from a wide range of ABP or cerebral perfusion pressure (autoregulatory plateau). Thus, quite simply, a correlation index of ≈0 indicates functioning autoregulation, whereas a correlation index of ≈1 denotes impaired autoregulation. This method has been largely validated in sedated patients suffering from traumatic brain injury, correlating well with static cerebral autoregulation and clinical outcome.[10–12] Little is known so far, however, of its applicability to other, nonsedated patient groups. Furthermore, the correlation coefficient index method has never been compared with the transfer function analysis approach or, in a larger series, with the conventional assessment of CO_2 reserve capacity.

This study aims (1) to evaluate the correlation coefficient index method in patients with severe carotid artery stenosis or occlusion and (2) to compare this approach with results from transfer function analysis and CO_2 reactivity testing.

Patients and Methods

We studied 150 patients (mean age, 67±8 years; 18 women) with severe unilateral stenosis (≥70%) or occlusion of the internal carotid artery (ICA). Exclusion criteria included an insufficient temporal bone window, relevant stenosis of the middle cerebral artery (MCA), current atrial fibrillation, and >4 ventricular extra beats per minute. Grading of stenosis was performed by use of Doppler velocities combined with B-mode imaging.[13] Medium-grade, hemodynamically insignificant contralateral stenosis (50% to 69%) was present in 29 patients. Patients considered for final analysis were assigned to different groups on the basis of degree of ipsilateral ICA stenosis (Table 1). Carotid stenosis or occlusion was defined as clinically symptomatic if hemispheric or retinal ischemic symptoms (transient ischemic attack or stroke) ipsilateral to the affected side had occurred during the previous 2 years.

Measurements were performed with subjects in a supine position with 45° inclination of the upper body. CBFV was measured in both MCAs by insonation through the temporal bone window with 2-MHz transducers (Multidop-X4, DWL). Continuous noninvasive ABP recording was achieved via a servocontrolled finger plethysmograph (Finapres 2300, Ohmeda) with the subject's right hand positioned at heart level. End-tidal CO_2 partial pressure (P_{ETCO_2}) was measured with an infrared capnometer (Normocap, Datex) during nasal expiration. After stable baseline values had been established, a data segment of 10 minutes was recorded with the patient breathing spontaneously. ABP, heart rate, and P_{ETCO_2} levels, determined at the beginning and end of this period, did not show substantial differences between the different groups. CO_2 reactivity was assessed via inhalation of room air mixed with 7% CO_2.

All parameters were recorded online at a sampling rate of 100 Hz and further analyzed with custom-written software developed in house. The mean length of analyzed time series of spontaneous oscillations of ABP and CBFV was 565±65 seconds.

Correlation Coefficient Analysis

This analysis was done according to several investigations (M.C. and colleagues) that showed that fluctuations on a long time scale in CBFV are more or less correlated with fluctuations in ABP.[12,14] To quantify the degree of correlation, Pearson's correlation coefficient was used. In the first step, mean, systolic, and diastolic values of ABP and CBFV were averaged over 3-second periods. Then, 20 consecutive 3-second averages of mean, systolic, and diastolic ABP and CBFV were used to calculate single Pearson's correlation coefficients (ie, for every 1-minute period; see Figure 1). Finally, the collected 1-minute systolic, diastolic, and mean correlation coefficients were averaged over the whole measurement period and labeled as the autoregulatory indexes Mx, Sx, and Dx, respectively. These 3 indexes thus mirror the averaged grade of correlation of systolic,

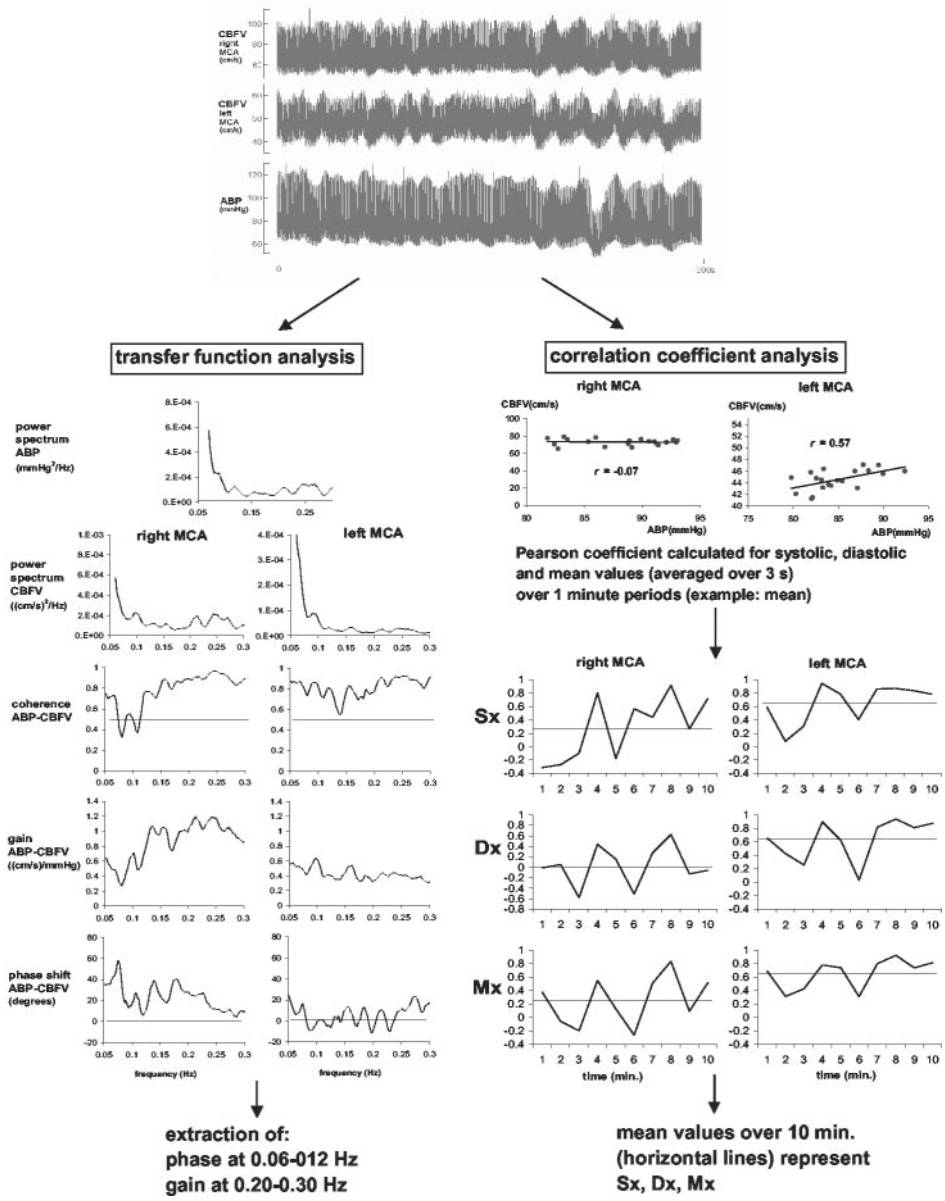

Figure 1. A 59-year-old woman with occlusion of the left ICA. Transfer function analysis: A frequency of ≈0.065 Hz was selected for phase extraction on both sides. Phase shift was clearly reduced on the affected left side. Gain was analyzed at 0.25 Hz. Note the lacking high-pass filter properties of the gain spectrum over the affected side, leading to a clear side-to-side difference at this frequency. Correlation coefficient analysis: In the upper tracings, an example of a 1-minute period is shown. Note the dependency of CBFV on ABP over the affected left side (positive Pearson coefficient). Average of 10 correlation coefficients over 10 minutes was calculated as Sx, Dx, and Mx. Note the consistently higher mean value (horizontal lines) on the affected side, but also the variability of the single correlation coefficients over the analyzed 10-minute period.

diastolic, and mean ABP and CBFV fluctuations. For data sets not ending with a whole 1-minute period (eg, total eligible length of 9.8 minutes), the last period was also allowed for calculation if it was >0.5 minutes.

Various prefiltering of the data for reduction of spectral noise (>0.05 Hz, >0.15 Hz), other lengths of the primary data segments (5 or 10 seconds instead of 3 seconds), and the use of a moving window for calculation of the correlation coefficients did not yield better results in terms of intergroup differences and variances. For reasons of simplicity, we therefore present results of data analyzed without prefiltering and moving window calculation.

Transfer Function Analysis

We have described this method in detail elsewhere.[15,16] In short, the periodograms and cross-periodogram of ABP and CBFV were computed by discrete Fourier transform, and the auto-spectra and cross-spectrum were estimated by smoothing the respective periodograms with a triangular window.[16] The coherence spectrum is defined as the normalized modulus of the cross-spectrum; the phase spectrum is the argument of the (complex-valued) cross-spectrum. Finally, the gain is essentially the regression coefficient of CBFV on ABP.

The coherence at any frequency is a number between 0 and 1, where 0 indicates no linear relationship and 1 indicates perfect linear dependence of the signals at the given frequency. With the smoothing we used, the coherence is significant (at the 95% level) if it is >0.49. If the coherence is not significantly different from 0, the phase spectrum cannot be used for analysis, because under the hypothesis of zero coherence, the phase spectrum is uniformly distributed over the interval $[-\pi, \pi]$.[17] For estimation of the cerebral

autoregulatory capacity, a low-frequency range (LF, 0.06 to 0.12 Hz) and a high-frequency range (HF, 0.20 to 0.30 Hz) were analyzed. The applied rules for phase extraction are described elsewhere.[15,18] Briefly, an area within the target frequency range that showed a maximum coherence of CBFV and ABP oscillations for both MCA sides and was not affected by discontinuities in the estimated phase spectrum was selected. We concentrated on the phase shift between ABP and CBFV oscillations in the LF range and the gain between ABP and CBFV oscillations in the HF range. These were the most meaningful parameters in previous studies.[8,15]

We included 139 patients in the final analysis. We excluded 11 data sets because of a lack of significant coherence of spontaneous oscillations in the LF band.

Assessment of CO_2 Reactivity

This assessment was done by dividing the maximum percentage increase of CBFV during hypercapnia (averaged over 1 respiratory cycle) by the absolute increase in P_{ETCO_2} (in mm Hg).

Statistical Analysis

Statistical analysis of intraindividual and interindividual differences and correlations was carried out with nonparametric tests (Kruskal-Wallis, Wilcoxon, Spearman's rank coefficient). We used the closed test principle to control the multiple significance level taken in the case of multiple testing for differences among the 4 groups. A value of $P<0.05$ was considered statistically significant. Data are reported as mean±SD.

For calculating the level of agreement (LA) between methods of detection of pathological values, cutoff values for the pathological range of affected sides were defined as poorer than the 10% quantile of the unaffected sides (Mx, ≥0.51; Dx, >0.22; LF phase, ≤18°; HF gain, ≤0.61 (cm/s) · mm Hg^{-1}; CO_2 reactivity, ≤1.24%/mm Hg). Then, the LA for affected sides was calculated as the portion of those patients classified identically by both methods.

Results

Figure 1 illustrates raw data and application of autoregulation analysis.

Correlation Coefficient Autoregulatory Indexes Mx, Sx, and Dx in Different Groups of Stenosis

A clear side-to-side difference was found in unilateral stenosis ≥80% for the autoregulatory indexes Dx and Mx but not for Sx (Table 1 and Figure 2). In addition, in terms of intergroup differences, the autoregulatory indexes Mx and Dx proved to be more useful than Sx. For Mx, differentiation between different degrees of stenosis was most pronounced between groups A and B; groups C and D tended to have poorer values. A similar trend was observed for the autoregulatory index Dx.

Comparison of the Correlation Coefficient Autoregulatory Indexes With Autoregulatory Indexes Derived From Transfer Function Analysis and CO_2 Reactivity

Moderate but highly significant correlations were found between autoregulatory indexes Dx and Mx and the phase shift and gain of transfer function analysis. Significant correlations were also found when Dx and Mx were compared with conventional CO_2 vasomotor reactivity (Table 2 and Figure 3). Between-group differences and within-group variances of the autoregulatory indexes Dx and Mx were generally comparable with those of conventional CO_2 reactivity (Figure 2). The LA in detection of pathological values with transfer function parameters was moderate to good (Dx with phase/gain, 0.61/0.64; Mx with phase/gain, 0.60/0.63). The LA between Dx/Mx and CO_2 reactivity was 0.69/0.68. For comparison, the LA between phase/gain and CO_2 reactivity was 0.66/0.51. No significant correlation between any cerebral autoregulatory parameter and average P_{ETCO_2} during the spontaneous breathing period was found.

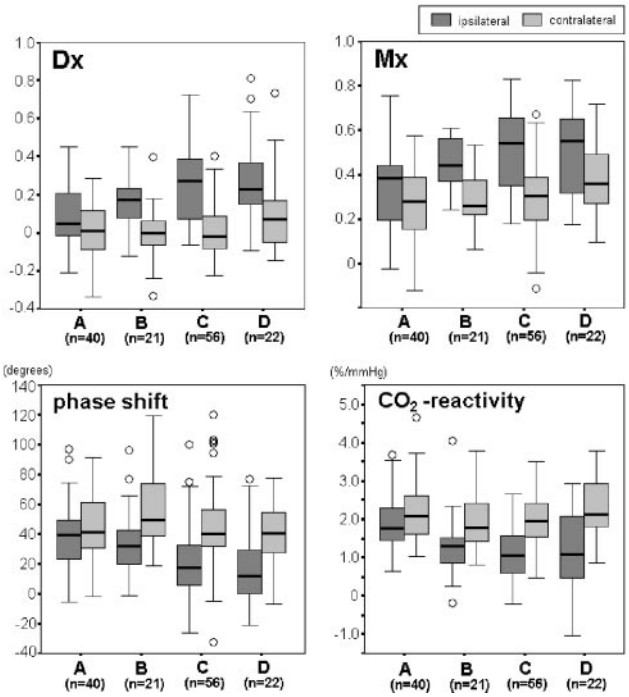

Figure 2. Box plots of autoregulation parameters in different groups of ICA stenosis. ○, Denotes exceeding values (>1.5 box length). Significances and definition of groups A through D are given in Table 1.

Methodological Aspects of Calculating the Correlation Coefficient Indexes

The absolute standard deviations of the subsequent source correlation values (SCSD) averaged for calculation of the respective autoregulatory indexes Sx, Mx, and Dx were slightly smaller over affected sides (significant only for Mx, $P<0.001$). There was a slight but highly significant trend toward lower SCSD for Dx and Mx compared with Sx ($P<0.001$). A significant inverse correlation between SCSD and the respective autoregulatory indexes Sx and Mx but not Dx was found (r, up to −0.52; $P<0.001$). Analysis of the correlation coefficient indexes from the lowest and highest quartile of SCSD separately shows clearly better correlations with transfer function parameters and CO_2 reactivity for the lowest quartile of SCSD (Table 2).

To assess the influence of various lengths of measurement periods on Mx and Dx, values calculated from data segments shorter than the full 10-minute period were correlated with those from the full period. It turned out that Mx and Dx values calculated from data segments up from a duration of 4 minutes showed a high and stable correlation ($r>0.84$) with values calculated from the full period.

Relation to Clinical Status

The mean degree of stenosis was only slightly higher in symptomatic patients (90±8% versus 86±9%, $P=0.014$).

TABLE 2. Results of Correlation Analysis

All Sides (n=278) Quartiles (n=70)	Versus LF phase *r*	*P*	Versus HF gain *r*	*P*	Versus CO_2 Reactivity *r*	*P*
Sx, all sides	−0.37	<0.001	−0.09	NS	−0.24	<0.001
Sx, low-quartile SCSD	−0.31	0.009	0.01	NS	−0.26	0.027
Sx, high-quartile SCSD	−0.35	0.003	0.04	NS	0.10	NS
Dx, all sides	−0.40	<0.001	−0.33	<0.001	−0.38	<0.001
Dx, low-quartile SCSD	−0.47	<0.001	−0.52	<0.001	−0.45	<0.001
Dx, high-quartile SCSD	−0.25	0.036	−0.14	NS	−0.34	0.005
Mx, all sides	−0.39	<0.001	−0.30	<0.001	−0.34	<0.001
Mx, low-quartile SCSD	−0.59	<0.001	−0.46	<0.001	−0.49	<0.001
Mx, high-quartile SCSD	−0.13	NS	−0.33	0.006	−0.13	NS
LF phase					0.39	<0.001
HF gain					0.25	<0.001

The correlation coefficient autoregulatory parameters showed no significant difference between clinically symptomatic and asymptomatic patients, whereas transfer function parameters and CO_2 reactivity differed significantly between these 2 groups (Figure 4). Analyzing the quartile of patients with the lowest SCSD did not result in significant improvement in differentiation between asymptomatic and symptomatic patients for the correlation coefficient index method.

Discussion

Best treatment strategies for patients with severe ICA stenosis or occlusion are under debate. Large trials have shown that there is only a small overall benefit of carotid endarterectomy in patients with asymptomatic stenosis, whereas extra-intracranial bypass surgery for carotid occlusion was of no benefit even in symptomatic patients.[19,20] However, the fact that association of severe carotid stenosis or occlusion with chronic cerebral hemodynamic compromise bears a considerably increased risk of stroke has become more evident over the last years.[2,3,21] Therefore, routine characterization of the cerebral hemodynamic status might become increasingly important in the therapeutic management of patients with carotid stenosis or occlusion by identifying those patients at highest risk of stroke. In the present study, we showed that estimating the cerebral autoregulatory capacity from spontaneous fluctuations in ABP is an attractive, completely noninvasive option for assessing intrinsic cerebral hemodynamics.

Methodological Aspects

The correlation coefficient index method has evolved as a method for continuous, noninvasive monitoring of cerebral autoregulation over the last decade.[11,12] The main methodological problem of the correlation coefficient index approach in our series was the strong variation of the 1-minute source correlation coefficients (Figure 1). Already in previous studies analyzing long-term recordings over hours in head-injured patients, a considerable variation of the source correlation coefficients could be observed.[12] In these investigations, at least 30-minute averaging of Mx has been recommended to filter out random fluctuations of ABP and CBFV. We found that with a data assessment length of 4 minutes, the absolute Mx and Dx values did not relevantly differ from the 10-minute period. The length of data assessment might therefore not be the only relevant factor. The extent of variation in the 1-minute source correlations (SCSD) substantially influenced absolute correlation coefficient index values and correlation with other methods. Thus, the SCSD might reflect the extent of signal noise and random fluctuations of ABP and CBFV as a critical parameter for calculation of the correlation coefficient indexes.

In contrast to previous studies applying the correlation coefficient index method in head-injured patients, the autoregulatory index Dx appeared to be more useful than Sx in our patients. This can be explained by the possible disturbance of diastolic cerebral blood flow resulting from a high intracranial pressure in brain-injury patients, rendering the autoregulatory index Dx unreliable.

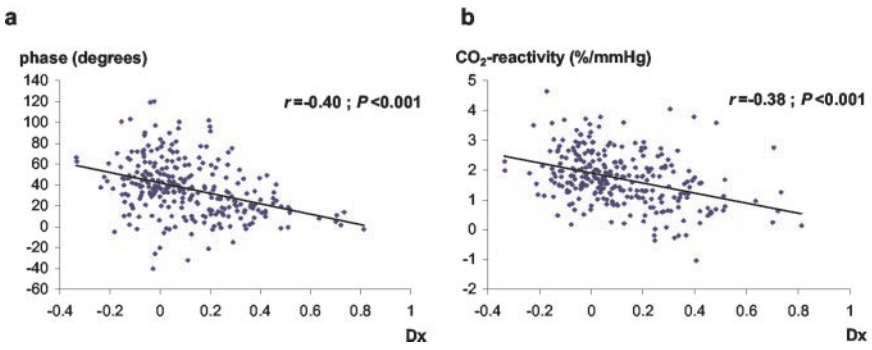

Figure 3. Illustrative scatterplots (n=278 MCA sides). a, Autoregulatory index Dx with phase shift of transfer function; b, Autoregulatory index Dx with CO_2 reactivity.

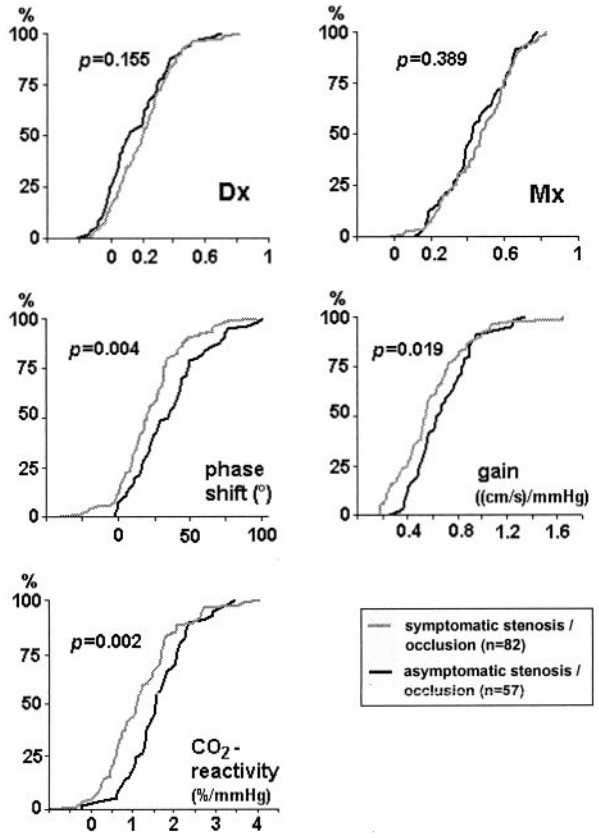

Figure 4. Cumulative distribution of autoregulatory parameters and CO_2 reactivity with regard to the presence or absence of previous clinical symptoms ipsilateral to the affected ICA side (symptomatic vs asymptomatic stenosis). Note that, for Dx and Mx, smaller values indicate better autoregulation, whereas for the remaining parameters, smaller values indicate a poorer state. Probability values indicate significances between symptomatic and asymptomatic patients.

Application to Patients With Obstructive Carotid Disease

The increase in the indexes Mx and Dx with increasing degree of stenosis indicates an increasing dependence of CBFV on ABP and thus impairment of cerebral autoregulation. The lack of difference between preocclusive stenosis and occlusion may be explained by the lacking hemodynamic difference between these 2 states. We also found a considerable overlap among different degrees of stenosis, which was also observed for parameters of transfer function analysis and CO_2 reactivity. This overlap is based on the fact that not only the degree of stenosis but also the quality of intracranial collateral flow compensation determine the extent of hemodynamic compromise.[22]

Comparison With Transfer Function Analysis

From a basic physiological point of view, the correlation coefficient indexes might be related to the phase shift calculated from transfer function analysis. Translating the phase shift into the time domain, a phase shift toward 0 means no relevant time delay between slow oscillations of ABP and CBFV. This should result in a higher positive correlation between these signals and thus a higher correlation coefficient index.[14,23] Indeed, we found a moderate to good LA in detecting pathological values by both methods and a moderate overall correlation.

The gain of the transfer function between ABP and CBFV oscillations is principally more difficult to interpret. As observed previously, absolute values of transfer function gain were significantly smaller for affected ICA sides, decreasing further with increasing degree of stenosis.[8,15,24,25] This does not necessarily indicate a more intact autoregulatory damping effect of ABP amplitude changes. It might rather be interpreted as the inability of achieving active autoregulatory diameter changes in (sub)maximally dilated cerebral arterioles, leading to reduced CBFV amplitude oscillations.[24] However, the real interpretation of the gain as an autoregulatory parameter remains unresolved, and correlations with other established autoregulatory tests have not yet been performed. However, our study does show a highly significant negative correlation and a good LA in detecting pathological values between the autoregulatory indexes Mx and Dx and transfer function gain, supporting in principle the pathophysiological significance of this parameter. The correlation of gain with CO_2 reactivity was better in a previous study.[8] Reasons for this difference remain unclear; probably the different HF ranges (0.15 to 0.40 Hz versus 0.20 to 0.30 Hz in our study) might play a role.

Overall, a clear superiority of either transfer function analysis or the correlation coefficient approach regarding correlation and agreement with CO_2 reactivity and side-to-side and intergroup differences could not be found.

Comparison With CO_2 Vasomotor Reactivity

Measuring the cerebrovascular reserve capacity is the most widely established method for assessing cerebral hemodynamic compromise in patients with obstructive carotid disease so far.[21] It is based on the assumption that reflex vasodilation occurs with reduced poststenotic perfusion pressure and that further vasodilation as a reaction to a stimulus such as CO_2 or acetazolamide is hence reduced. This has been found to be of prognostic relevance with regard to future cerebral ischemic events.[2,3] Our study confirmed this ability by the significant difference between symptomatic and asymptomatic patients. Absolute correlations between Dx and Mx and CO_2 reactivity were only moderate. On the other hand, we could show a comparatively good LA in detecting pathological values between the autoregulatory indexes Dx and Mx and CO_2 reactivity. Although the cerebral autoregulatory system has a more complex nature by involving intrinsic sensing of blood flow and controlling of cerebral arterioles, a principal pathophysiological relationship between both methods, which do have cerebral arterioles as a common effector organ, might thus exist.

Comparison With Clinical Status

We found that previously symptomatic patients have significantly poorer cerebral autoregulation as calculated from transfer function analysis of spontaneous blood pressure oscillations. This has not been reported yet and supports the probable prognostic value of autoregulatory parameters for cerebral ischemic events. Correlation coefficient parameters,

however, did not differ significantly between symptomatic and asymptomatic stenosis. This might point to a better pathophysiological validity of transfer function analysis and CO_2 reactivity regarding detection of clinically relevant hemodynamic impairment in terms of ischemic events. However, prospective studies will have to evaluate this topic.

Conclusions

The correlation coefficient method as a measure of cerebral autoregulation in chronic obstructive carotid artery disease has a power to detect hemodynamic impairment comparable to that of the conventional CO_2 reactivity test and transfer function analysis. We suggest introducing this approach and transfer function analysis to hemodynamic testing in patients with carotid artery disease.

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