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ORIGINAL COMMUNICATION

Cerebral dysautoregulation and the risk of ischemic events in occlusive carotid artery disease

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Abstract Dynamic cerebral autoregulation assessed from blood pressure transients can be considerably impaired in severe internal carotid artery (ICA) obstruction. It is unknown whether impaired autoregulation indicates an increased risk of subsequent ischemic events in this situation. 165 patients with ICA stenosis (>70 %) or occlusion were prospectively followed until anterior circulation stroke, transient ischemic attack, carotid recanalization without prior event, death or study end. Transcranial Doppler sonography was used to determine autoregulation in both middle cerebral arteries from spontaneous blood pressure fluctuations (correlation coefficient indices Dx and Mx) and respiratory-induced 0.1 Hz oscillations (phase). Standard CO_2 reactivity (CO_2R) was additionally assessed. All indices were classified as impaired vs. preserved according to reference values from 79 age-matched controls. During median follow-up of 24.5 months, there were 16 ischemic events over ipsilateral sides. Competing risk analysis revealed a significant predictive effect on ipsilateral ischemic events for impaired Dx (rate ratio 8.2 [95 % confidence interval 1.7–39], $p = 0.0079$), phase (5.0 [2–13], $p = 0.0007$) and CO_2R (9.4 [2.2–40], $p = 0.0025$). Restricting analysis to severe stenosis alone (n = 103), only impaired phase (rate ratio 8.6 [1.6–45], $p = 0.01$) remained as a significant predictor. In a continuous statistical model, only Dx and Mx were significant predictors of ischemic events ($p = 0.012$ and $p = 0.016$). In conclusion, impaired dynamic cerebral autoregulation indicates an increased risk of subsequent ischemic events in severe obstructive ICA disease. Its clinical application might thus be of help in identifying higher risk patients.

Key words cerebral autoregulation · CO_2 reactivity · carotid artery stenosis · cerebral ischemia · transcranial Doppler sonography

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Introduction

Poor collateral flow in severe carotid artery stenosis or occlusion leads to vasodilation of cerebral arterioles and potential impairment of the autoregulatory reserve. Episodes with low blood pressure and consequent cerebral hypoperfusion may then be either directly associated with ischemic brain insults or with reduced washout of emboli and thereby increase the risk for apparent stroke due to arterial embolism [1].

Such a state of poor hemodynamic compensation may be identified by an impaired dilatory reserve capacity of cerebral arterioles, increased cerebral blood volume or, if severe, by detecting an increased oxygen extraction fraction with positron emission tomography [2]. A broader clinical application of hemodynamic assessment in carotid obstruction, however, necessitates non-invasive and inexpensive methods readily available in an outpatient clinic. Prospective studies using transcranial Doppler sonography and CO_2 as a testing vasodilator showed a predictive role of an exhausted dilatory capacity for ischemic events in carotid stenosis and occlusion [3–5].

Cerebral autoregulation, being the classic intrinsic mechanism of maintaining stable cerebral blood flow, may be the most natural measure of hemodynamic integrity. Traditionally, clinical assessment of autoregulatory ability was considered as difficult because of the need of inducing possibly harmful blood pressure changes. Over the last few years, the concept of dynamic autoregulation has evolved using smaller blood pressure transients, either induced by, e.g., thigh cuff deflation or occurring spontaneously [6–8]. Such dynamic indices indicate considerably impaired autoregulation in severe carotid artery obstruction, improve rapidly after carotid recanalization and correlate only moderately with CO_2 reactivity [9, 10]. Their clinical impact, however, in terms of a prospective association with ischemic events in carotid artery obstruction has not been studied so far.

We aimed to investigate whether different measures of dynamic cerebral autoregulation are actually able to indicate the risk of ischemic events in severe carotid artery stenosis or occlusion.

Methods

Patients

A total of 165 patients presenting at our local outpatient department with stenosis of at least 70% or occlusion of the proximal internal carotid artery were prospectively followed up. Carotid artery stenosis or occlusion was determined according to standard protocol [11]. Exclusion criteria were an absent transtemporal bone window for sonography, severe stenosis of the middle cerebral artery on transcranial Doppler sonography, clinical symptoms due to the stenosis or occlusion within the preceding 7 days, present atrial fibrillation and scheduled carotid revascularization as indicated by treating physicians. Patient recruitment was not based on results from previous tests other than those stated above. Sampling into the study was not consecutive. The study was approved by the local Ethics Committee and patients gave informed consent to participate. Datasets used in earlier methodological studies on dynamic cerebral autoregulation were derived partially from baseline autoregulatory measurements of patients followed-up in the present study [12, 13].

At study entry, all patients underwent a careful history review of previous cerebral ischemic events, their medication and vascular risk factors. Patients were followed until a spontaneous ischemic event ascribed to the anterior circulation, death, revascularization despite asymptomatic stenosis, or study end.

Follow-up investigations were performed on a regular basis. Four patients were lost to further follow-up after at least one follow-up visit. All patients maintained the medical treatment corresponding to their vascular disease and risk factors, including antithrombotic, antihypertensive, antidiabetic and cholesterol-lowering agents. Detailed information was obtained for all endpoints by trained investigators by consulting patients and treating physicians. When assessing the presence of clinical events, study investigators were blinded to the autoregulation data of individual patients. Of primary interest for the study were ischemic events (TIA, stroke) that may be predicted on the basis of autoregulation data. TIA was defined as neurological deficits lasting for less than 24 hours, stroke for symptoms of > 24 h duration. A retinal ischemic event was defined as a typical history of amaurosis fugax or retinal artery occlusion. Death of patient and recanalization without prior ischemic event were further clinical endpoints not of primary interest.

Hemodynamic measurements

Cerebral blood flow velocity (CBFV) was measured in both middle cerebral arteries (MCA) by transcranial Doppler sonography (DWL, Germany). Continuous non-invasive ABP recording was achieved via a servo-controlled finger plethysmograph (Finapres, USA). End-tidal CO_2 partial pressure was measured in mmHg with an infrared capnometer (Datex, Finland) during nasal expiration. After stable baseline values had been established, a data segment of 10 minutes was recorded with the patients breathing spontaneously in a supine position with 50° inclination of the upper body. After detailed instruction, sinusoidal oscillations in ABP and CBFV were then elicited by paced breathing at a rate of 6/min (i.e., 5-s periods of in- and expiration) for 180 s. Finally, CO_2 reactivity (CO_2R) was assessed via inhalation of room air mixed with 7% CO_2 for 90–120 seconds.

Autoregulation analysis

Dynamic cerebral autoregulation was assessed by two previously-described methods (illustrated in Fig. 1 and 2) [13–15]:

Correlation coefficient index

The rationale behind this method is that a higher correlation between time-averaged ABP and CBFV indicates increasing dependency of CBFV on ABP and thus decreasing autoregulatory ability. Thereby, diastolic and mean values of ABP and CBFV were first averaged over three seconds to reject pulse waves and most respiratory waves. Successively, 20 consecutive averaged values were used to calculate Pearson's correlation coefficient of diastolic and mean ABP and CBFV for 1-min periods of the time series (Fig. 1). The sets of 1-min correlation coefficients were then averaged over the 10-min period yielding the autoregulatory indices Dx (based on diastolic values of CBFV and ABP) and Mx (mean values), respectively.

Cross-spectral (transfer function) analysis

The power spectra SABP and SCBFV were estimated by transforming the time series of ABP and CBFV to the frequency domain via discrete

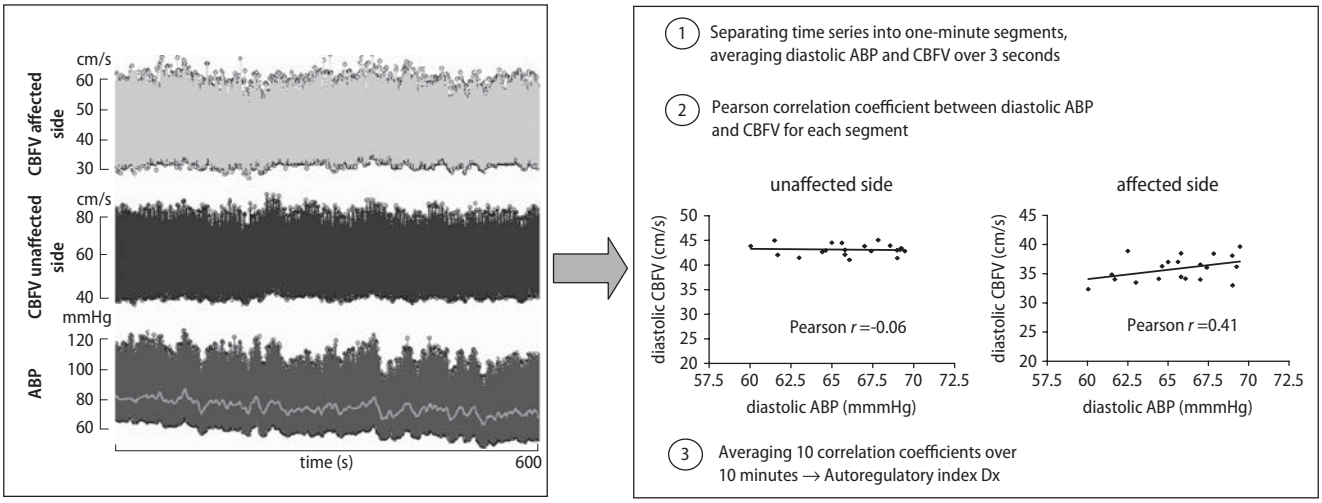

Fig. 1 The correlation coefficient index method for assessment of cerebral autoregulation. A 57-year-old patient with occlusion of the right ICA. Correlation coefficient index calculated from a 10-min time series of spontaneous fluctuations. The absent correlation between diastolic ABP and CBFV over the unaffected side reflects preserved autoregulation; the positive correlation over the affected side indicates impaired autoregulation. Using mean ABP and CBFV would result in the index Mx

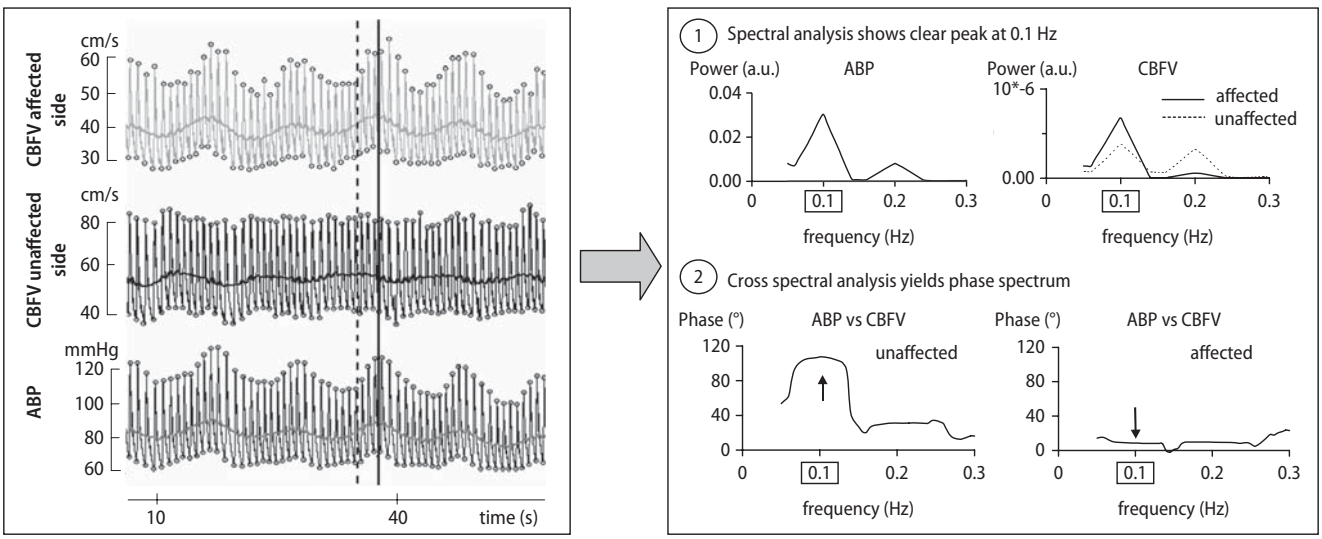

Fig. 2 Phase shift analysis of respiratory induced hemodynamic oscillations. Same patient as in Fig. 1. Breathing at 6/min induces clear oscillations of ABP and CBFV at 0.1 Hz. CBFV over the unaffected side shows intact autoregulation with fast and early 'counter' regulation of the repetitive falls and rises during oscillating ABP leading to a phase shift (dotted line vs bold line). This phase shift is quantified by cross-spectral analysis (also termed transfer function analysis) at 0.1 Hz (arrows). In case of autoregulatory impairment (affected side), this reaction is delayed or absent resulting in a low phase

Fourier transformation. Smoothing the respective periodograms resulted in the power spectra and cross spectra estimates. The cross spectra contains information on the phase spectra. The phase shift is a measure of the extent to which each frequency component of the CBFV time series leads the ABP time series (Fig. 2). In the present study, the phase shift was uniformly extracted at the 0.1 Hz frequency induced by regular breathing at 6/min [14].

Standard CO_2-reactivity (in %/mmHg) was also determined by dividing the maximum percentage increase of mean CBFV during hypercapnia (averaged over one respiratory cycle) by the absolute increase of P_{ETCO2} (in mmHg).

Reference values of autoregulation

To define impaired autoregulation, data from previously-measured 79 older persons with mean age 63 years (standard deviation = 9) without any carotid obstruction on duplex scan and with no history of cerebrovascular disease were analyzed. According to the 5th percentile limit of the autoregulation measurements obtained in this reference group, an affected side of the presently studied patients was classified as impaired if Dx ≥ 0.24, or Mx ≥ 0.46, or phase ≤ 20.6°. Similarly, for standard CO_2 reactivity, a cut-off value for severely impaired ('exhausted') reactivity was set at 2 standard deviations below the mean of the reference group (≤ 0.7 %/mmHg). This cut-off is in agreement with those of previous studies [3, 17].

Statistical analysis

The measurements of Dx, Mx, phase, and CO_2R were considered independently as predictors of ischemic events ipsilateral to the severely stenosed or occluded side. The event time was defined as the duration from the time-origin until the first occurrence of one of the competing endpoints, or until the end of the study period if no event occurred.

For the main analysis, only ipsilateral events were considered. In patients with severe stenosis (> 70 %) on both sides, we randomly defined one side as the study side ('ipsilateral'). Kappa statistics for agreement were used to compare the prognostic indices on ipsilateral sides at baseline. Comparability of patients at their individual time-origin was achieved by adjusting the analysis for the following potential confounders: age, sex, hypertension, diabetes, degree of stenosis ipsilateral and contralateral, and history of prior ischemic events over affected sides. A feature of a longitudinal study is that competing events may interfere with the ischemic events of interest (here it is considered that the ischemic event risk changes due to carotid artery recanalization and that the risk is zero when the patient died due to other reasons). Standard statistical techniques like Cox regression analysis might therefore overestimate the true rate of events in this situation. To control for these effects we used a proportional hazards regression analysis in a competing risk model [17]. Thereby, in a sensitivity analysis, we allowed each of the predictors (Dx, phase, Mx and CO_2R) to be entered with the continuous measurements. Then, simple prognostic indices (impaired vs. non-impaired) were considered. To predict ischemic events on the basis of baseline measurements, the Aalen-Johansen estimator was used within the strata defined by various prognostic indices. Predicted probabilities of an ischemic event between the time origin and time t are supplied by 95 % confidence limits. Analysis of variance (ANOVA) was used to detect a potential interference of antihypertensive medications with autoregulatory values and CO_2 reactivity over ipsilateral sides controlling for the degree of stenosis.

Table 1 Baseline characteristics

	n = 165
Age, y (SD)	66 (8)
Male, n (%)	141 (85)
Female, n (%)	24 (15)
Internal carotid artery obstruction	
Ipsilateral mean degree, % (SD)	90 (11)
Contralateral mean degree, % (SD)	40 (36)
Ipsilateral severe stenosis, n (%)	103 (62)
Ipsilateral ICA occlusion, n (%)	62 (38)
Prior ischemic event over ipsilateral side, n (%)	56 (34)
Median delay to study inclusion, months	5.3
Range, min, months	0.3
Range, max, months	218
Pharmacological treatment	
Platelet inhibitor, n (%)	122 (74)
Anticoagulation, n (%)	40 (24)
Antihypertensive, n (%)	134 (81)
Statin, n (%)	91 (55)
History of vascular risk factors/disease	
Hypertension, n (%)	139 (84)
Diabetes, n (%)	35 (21)
Hypercholesterolemia, n (%)	120 (73)
Current smoking, n (%)	30 (18)
Coronary heart disease, n (%)	66 (40)

Internal carotid artery (ICA) obstruction represents pooled values over all study sides, comprising on ipsilateral sides n = 103 patients with severe stenosis and n = 62 patients with occlusion. Antihypertensive treatment consisted of monotherapy or various combinations of: angiotensin converting enzyme inhibitors (n = 73 patients on that medication), angiotensin type I receptor blockers (n = 14), beta blockers (n = 84), diuretics (n = 55), calcium antagonists (n = 35) or others (n = 10). *SD* standard deviation

Results

Patient follow-up

Baseline characteristics of the 165 enrolled patients are given in Table 1. The median follow-up period was 24.5 months (range 1 to 51 months). Between one and six follow-up visits per patient were recorded with the mean first visit 12.2 months after the time origin. There were 21 ischemic events ascribed to the anterior circulation (8 TIAs, 3 minor strokes, 3 major anterior circulation strokes, and 7 retinal ischemic events). Of these events 16 occurred over the defined study sides ipsilateral to the severe stenosis or occlusion (5 TIAs, 2 minor strokes, 2 major strokes, and 7 retinal ischemic events). In addition, two events (1 TIA and 1 stroke) occurred in the posterior circulation. One additional retinal ischemic event occurring during carotid bulb compression by a Doppler probe was not considered an independent ischemic event for analysis. Two patients suffered spontaneous intracranial hemorrhage ipsilateral to the study side, one of them died. Two other patients died from non-cerebral reasons. In five asymptomatic patients carotid endarterectomy was performed on the study side after a mean of 23.2 months of follow-up with patients and treating physicians being unaware of any autoregulation data.

Baseline autoregulatory data

Due to measurement artifacts, phase was not available in 14 patients, Dx in 13 and CO_2R in 4. Regular breathing for phase analysis could not be sufficiently performed by 12 patients (7 %). Table 2 shows the distribution of autoregulatory data and their level of agreement. ANOVA showed a significant increase of CO_2R in patients with angiotensin type I receptor blocker medication ($p = 0.0074$). No significant effect was found for other antihypertensive medications and autoregulatory parameters.

Regression analysis of ischemic events

Rate ratios for the prognostic indices and confounding variables are given in Table 3.

The analysis of patients with stenosis ≥70 % alone (n = 103 patients eligible, n = 11 ipsilateral ischemic events) yielded still significant results for phase (rate ratio 8.6 [1.6–45], $p = 0.0107$), while CO_2R (8.4 [0.95–73], $p = 0.0555$) and Dx (5.9 [0.82–42], $p = 0.0778$) just missed statistical significance. A second sensitivity analysis in severe stenosis and occlusion, using the continuous measurements without cut-off values, showed that Dx ($p = 0.012$) and also Mx ($p = 0.016$) were significant predictors, while CO_2R and phase were not.

Table 2 Distribution of autoregulatory indices and levels of agreement over affected study sides

	Dx	Mx	phase	CO_2R
Preserved (n)	87	79	96	128
Impaired (n)	65	73	43	33
Kappa values				
vs CO_2R	0.23*	0.12	0.40**	–
vs phase	0.32**	0.34**	–	–
vs Mx	0.50**	–	–	–

Level of significance for kappa values. * p < 0.01; ** p < 0.001

Table 3 Proportional hazards regression analysis

	Rate ration (95 % CI)	Level of significance (*p*)
Autoregulatory indices		
Dx impaired	8.2 (1.7–39)	0.0079
Mx impaired	2.5 (0.76–8)	0.1308
Phase impaired	5.0 (2–13)	0.0007
CO_2R impaired	9.4 (2.2–40)	0.0025
Confounders		
Age	1 (0.97–1.1)	0.2948
Female gender	0.33 (0.092–1.2)	0.0897
Hypertension	0.92 (0.22–3.8)	0.9089
Diabetes	0.48 (0.099–2.3)	0.3626
Degree of ipsilateral stenosis	0.99 (0.95–1)	0.7036
Degree of contralateral stenosis	0.99 (0.97–1)	0.0975
Previous ipsilateral symptoms	1.9 (0.7–5.1)	0.2059

Rate ratios for TIA or stroke ipsilateral to the study side (severe ICA stenosis or occlusion) were calculated using a competing risk model. Rate ratios for the single prognostic indices were adjusted for confounding. The rate ratios for the confounders were obtained by fitting a model without prognostic indices. *CI* confidence interval

Prediction of ischemic events

The estimated cumulative incidences of ipsilateral ischemic events in severe ICA stenosis or occlusion are shown in Fig. 3. The predicted probabilities of any ipsilateral ischemic event after 12, 24 and 36 months are given in Table 4 for all methods. Overall, both the autoregulatory indices Dx and phase indicated a high probability of ischemic events in the impaired group over time. The same was observed for CO_2R.

Table 4 Predicted probabilities of ipsilateral TIA or stroke

	Probability in % (95 % confidence interval)		
	12 months	24 months	36 months
Dx normal	2.4 (0.0–5.6)	2.4 (0.0–5.6)	2.4 (0.0–5.6)
Dx impaired	4.8 (0.0–10.1)	10.0 (2.4–17.5)	18.3 (5.1–31.6)
Mx normal	5.4 (0.2–10.6)	5.4 (0.2–10.6)	5.4 (0.2–10.6)
Mx impaired	1.4 (0.0–4.1)	6.1 (0.3–11.9)	14.0 (2.1–26.0)
Phase normal	2.1 (0.0–5.1)	7.7 (0.5–15.0)	7.7 (0.5–15.0)
Phase impaired	12.2 (2.2–22.2)	22.6 (7.9–37.3)	22.6 (7.9–37.3)
CO_2R normal	3.2 (0.1–6.2)	4.3 (0.6–8.0)	8.2 (1.8–14.6)
CO_2R impaired	9.9 (0.0–20.5)	26.3 (9.2–43.3)	26.3 (9.2–43.3)

Predicted probabilities for TIA or stroke ipsilateral to the study side (severe ICA stenosis or occlusion) using the Aalen-Johansen estimator not adjusted for confounding

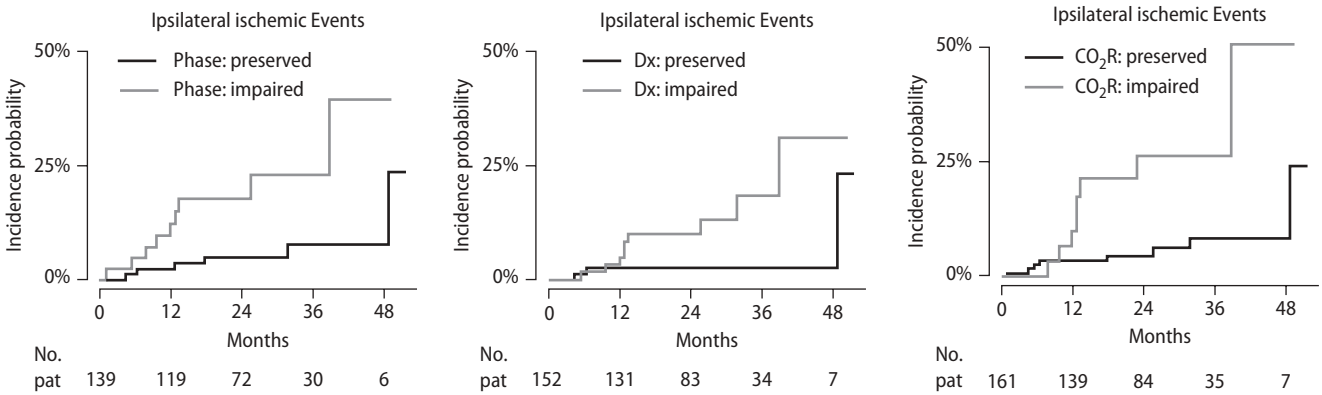

Fig. 3 Plots of estimated cumulative incidence. Ipsilateral ischemic events (TIA or stroke) for the categorized autoregulatory indices (phase and Dx) and CO_2 reactivity (CO_2R) in severe ICA stenosis and occlusion. The numbers of patients that were still in the study are shown below the figures

Discussion

In the present prospective study, values of impaired dynamic cerebral autoregulation were significantly associated with subsequent ischemic events in patients with internal carotid artery stenosis or occlusion.

Applied autoregulatory methods

We used two completely non-invasive dynamic autoregulation approaches. The phase shift between ABP and CBFV oscillations distinctly reflects dynamic properties of autoregulation (as explained in Fig. 2). While this phase can also be estimated from spontaneous oscillations of longer time series, it seems more practical and time-sparing to ask the patient to induce slow oscillations by regular slow breathing. This also guarantees a clear frequency peak at which phase can be determined in all patients and thus effects a better reproducibility [12]. The limitation to this method is that it requires patient cooperation and that regular breathing can not be sufficiently performed in approximately 5 to 10 % of patients due to respiratory apraxia, lung disease or language barriers.

The correlation coefficient method is a simple time-domain based method quantifying the degree of correlation (i.e., dependence) of CBFV fluctuations with those of ABP. This approach is well examined for monitoring sedated and ventilated patients with traumatic brain injury, where it demonstrated a specific prognostic value [18]. Its main limitation in an outpatient setting is that the original application of the method required longer data recording. However, already with 10 minutes of data recording in awake patients reliable results could be obtained [13].

Predictive value of cerebral dysautoregulation

Since the mid 1990s, dynamic cerebral autoregulation in carotid artery obstruction has been intensively studied [4, 19–21]. So far, only retrospective analyses showed that patients with previous symptoms were more likely to have dysfunction of autoregulation in terms of a poorer phase but not poorer Dx values [13]. The present study found that impaired dynamic autoregulation is in fact prospectively related to an increased rate of subsequent ischemic events in carotid artery stenosis and occlusion. Restricting the analysis to stenosis alone with a lower statistical power still resulted in significant results for phase. Using a continuous statistical model without thresholds, increasing Dx remained a significant predictor, while decreasing phase (and CO_2R) was not significant anymore. Interestingly, also the autoregulation index Mx was significant when considered as a continuous measure rather than comparing it with a threshold value, suggesting its value in continuous gauging of cerebral autoregulation [18].

The role of CO_2 reactivity

Impaired CO_2 reactivity predicted ischemic events in asymptomatic carotid stenosis or occlusion and also in recently symptomatic stenosis [4, 5, 16]. In groups with mixed symptomatic or asymptomatic carotid occlusion, poor CO_2R was also significantly associated with ischemic events [3, 22], while in recently symptomatic patients only it was not [23].

The present results confirm a high predictive value of an exhausted CO_2R in a mixed group of severe stenosis and occlusion. The predetermined strict cut-off point for CO_2R (2 standard deviations below the mean) assured a threshold value of exhausted reactivity corresponding well to those of previous studies [3, 16]. The fair level of agreement in detecting impaired states between autoregulation and CO_2R might be explained by the uneven distribution into 'impaired' and 'preserved' states. However, also CO_2R and phase with their more similar proportions of 'impaired' states only showed a fair to moderate agreement. Impaired autoregulation and CO_2R thus still reflect different aspects of hemodynamic impairment and may identify different subsets of high-risk patients.

The difference in rate ratios between various autoregulatory parameters and CO_2R should not be overinterpreted because of the large confidence intervals. Overall, the ratios of impaired dynamic autoregulatory measures are comparable to that of CO_2R.

Interestingly, a significant positive interaction was observed between angiotensin type I receptor blocker medication and CO_2R at baseline. Such an association was not found for any dynamic autoregulatory measure. Angiotensin receptor blockers exhibit a beneficial role in secondary prophylaxis after stroke beyond pure reduction of blood pressure [24]. Improvement of the lower limit of cerebral autoregulation by an angiotensin receptor blocker has been shown in animals [25]. The present post hoc findings should be interpreted with caution since this study was not intended to analyze a specific effect of antihypertensive treatment on cerebral hemodynamics or clinical course in carotid artery disease. They may, however, stipulate future research on the specific vasoprotective role of angiotensin receptor blockers particularly in obstructive cerebrovascular disease.

Study limitations

This study is a mono-center pilot investigation with an expectable small overall number of ischemic endpoints.

The outcome measure thus included not only completed strokes but also the more frequent transient hemispheric and retinal ischemic attacks. The latter two both strongly depend on the patients' awareness. Since both patients and investigators were blinded to autoregulation data, a systematic interference with the effective distribution of events depending on autoregulatory disturbance is unlikely. The limitation, however, that the risk for disabling clinical events cannot be established by the present sample size still remains valid.

The overall low mortality rate in the observed group and the low rate of major strokes indicate the presence of a selection bias. Patients were recruited from our outpatient clinic having a known carotid obstruction often for years, and, since coronary disease usually precedes carotid disease, many of them had treated coronary heart disease. Therefore, our sample contains more pretreated patients with chronic vascular disease while patients with previously undiagnosed unstable vascular disease are underrepresented.

A confounding effect of including both previously asymptomatic patients and symptomatic patients into one study has been discussed [2, 23], because in primary asymptomatic patients the risk of stroke is low and the CO_2 reactivity and autoregulatory capacity usually higher. We therefore introduced the presence of previous symptoms as a confounder into the statistical model which proved not to be significant. Note that the mean latency between previous ipsilateral symptoms and study inclusion was more than 5 months, a period after which the ischemic risk approximates that of asymptomatic patients defeating an overall benefit of carotid recanalization [26].

Finally, a statistically strong correlation between dysautoregulation and cerebral ischemic events may be scientifically correct, but may not be useful for identification of individual high risk patients. The results obtained here (Table 4) indicate that autoregulatory parameters are useful for predicting outcome. However, to guide clinical management the prognostic indices should also include conventional risk factors. For such a complex risk prediction a larger study is needed.

Clinical implications

Assuming a routine clinical situation, there are two established functional TCD tests for identifying high risk patients with carotid stenosis so far: 1) Detection of microemboli originating from carotid plaques by transcranial Doppler sonography [27, 28]. 2) Detection of impaired vasodilatory reserve capacity assessed by inhalation of CO_2, breath-holding or application of acetazolamide.

The present study suggests the concept of dynamic cerebral autoregulation as a further possible predictor. The principal pathological link of increased stroke risk with dysautoregulation seems to be that patients with exhausted ipsilateral autoregulation are prone to transient hypoperfusion and that emboli occurring from time to time are less well cleared or washed-out in this situation [29]. The detection of microemboli and dysautoregulation may thus measure different aspects of a common final pathway. It would be ideal to merge both the assessment of microembolic activity and dysautoregulation into one measurement protocol in a larger cohort study. Actually, slow oscillations containing autoregulatory information (e.g., assessed by Dx) already occur during detection of microemboli and future studies may combine both approaches at the same time. To strengthen the clinical role of functional TCD tests in carotid obstruction an intervention study in patients with poor autoregulation is needed.

Conclusions

Measures of impaired dynamic autoregulation are prospectively associated with ischemic events in patients with obstructive carotid artery disease. Their clinical application might thus be of help in identifying higher risk patients.

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