

Effect of Carotid Endarterectomy or Stenting on Impairment of Dynamic Cerebral Autoregulation

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Background and Purpose—Analysis of dynamic cerebral autoregulation (DCA) from spontaneous blood pressure fluctuations might contribute to prognosis of severe internal carotid artery stenosis, but its response to carotid recanalization has not been investigated so far. This study investigates the effect of carotid endarterectomy or stenting on various DCA parameters.

Methods—In 58 patients with severe unilateral stenosis undergoing carotid endarterectomy (n=41) or stenting (n=17), cerebral blood flow velocity (CBFV, transcranial Doppler) and arterial blood pressure (ABP, Finapres method) were recorded over 10 minutes before and on average 3 days after carotid recanalization. Nineteen patients were additionally examined after 7 months. Correlations between diastolic and mean ABP and CBFV fluctuations were averaged to form the correlation coefficient indices (diastolic [Dx] and mean values [Mx]). Transfer function parameters (low-frequency phase and high-frequency gain between ABP and CBFV oscillations) were calculated over the same 10 minutes. CO₂ reactivity was assessed via inhalation of 7% CO₂.

Results—Before recanalization, all DCA parameters were clearly impaired ipsilaterally compared with contralateral sides. Phase, Dx, and Mx indicated early normalization of DCA after both endarterectomy and stenting. By multiple regression, the degree of DCA improvement was highly significantly related to the extent of impairment before recanalization. No significant change in DCA was found at follow-up. Ipsilateral gain and CO₂ reactivity increased significantly less after endarterectomy than after stenting ($P<0.05$).

Conclusions—Dynamic cerebral dysautoregulation in patients with severe carotid obstruction is readily and completely remedied by carotid recanalization. (*Stroke*. 2004;35:1381-1387.)

Key Words: internal carotid artery stenosis ■ carotid endarterectomy ■ carotid angioplasty, stent-protected ■ autoregulation, cerebral ■ transcranial Doppler sonography

The extent of cerebral hemodynamic impairment plays an increasingly important role in the decision of whether or not to operate on internal carotid artery (ICA) stenosis, especially in asymptomatic patients.¹ Cerebral autoregulation is an intrinsic protective mechanism guaranteeing hemodynamic integrity of cerebral circulation. Evaluation of the classical upper and lower limits of the cerebral autoregulatory plateau requires considerable manipulation of arterial blood pressure (ABP), making the method invasive and potentially harmful for patients with critical carotid stenosis. Therefore, attention has more and more been directed toward “dynamic” cerebral autoregulation (DCA) testing, particularly using spontaneously occurring blood pressure fluctuations.^{2,3} In patients with severe carotid stenosis, both frequency (transfer function) and time domain (correlation coefficient) methods have demonstrated a clear impairment of DCA capacity over affected compared with unaffected contralateral sides.^{4–6}

However, it has not been studied so far whether parameters of DCA calculated from spontaneous blood pressure fluctuations are altered at all after recanalization of the occluded vessel. Previous studies using CO₂-reactivity tests showed a reconstitution of impaired CO₂ reactivity after carotid endarterectomy (CEA).^{7–9} Furthermore, DCA calculated from sudden drops in blood pressure after deflation of leg cuffs showed significant improvement after carotid recanalization.¹⁰

This clinical study in patients with severe unilateral carotid obstruction investigates the effect of CEA or stent-protected angioplasty of the carotid artery (SPAC) on various DCA parameters derived from spontaneous blood pressure fluctuations.

Subjects and Methods

A series of 58 patients with severe unilateral stenosis ($\geq 70\%$) of the ICA undergoing CEA (n=41) or SPAC (n=17) was investigated

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11±9 (mean, SD) days before and 3±2 days after the procedure within our routine cerebrovascular workup program for carotid stenosis patients (including assessment of CO₂ reactivity). Nineteen patients were additionally studied 7±3 months after CEA or SPAC. A complete routine neurosonological examination including extracranial and intracranial color-coded Doppler sonography was performed before each measurement (HDI 3500/5000, ATL). Grading of stenosis was performed using Doppler velocities in combination with B-mode imaging according to standard criteria.¹¹ Fifty-two patients had previous retinal or hemispheric ischemic events (transient ischemic attack or minor stroke) at a median of 21 days before the first autoregulation measurement (range 3 to 200 days), 6 were clinically asymptomatic. Two patients experienced a minor stroke during the recanalizing procedure, and none of the patients undergoing follow-up measurement had new ischemic events. Exclusion criteria for the present analysis comprised inability to obtain stable Doppler signals (due to an absent temporal bone window or noncompliance of patients; n=8), atrial fibrillation (n=3), intolerance of 7% CO₂ inhalation (n=1), and unsuccessful carotid recanalization (n=4). Moderate residual stenosis (n=2) was not regarded as an exclusion criterion.

Assessment of DCA and CO₂ Reactivity

DCA was analyzed from the baseline recorded before CO₂-reactivity testing. The Local Ethics Committee had approved the completely noninvasive DCA assessment protocol. Measurements were performed with subjects in a supine position with 50° inclination of the upper body. Cerebral blood flow velocity (CBFV) was measured in both middle cerebral arteries (MCA) by insonation through the temporal bone window with 2 MHz transducers attached to a headband (DWL-Multidop-X, Sippligen). Continuous noninvasive ABP recording was achieved via a servo-controlled finger plethysmograph (Finapres 2300, Ohmeda) with the subject's right hand positioned at heart level. End-tidal CO₂ partial pressure (P_{ETCO₂}) was measured in mm Hg with an infrared capnometer (Normocap, Datex) during nasal expiration. P_{ETCO₂} values were shown to correlate closely with intraarterial CO₂ values.¹² After stable values had been established, the servo mechanism of the Finapres device was turned off and a baseline data segment of 10 minutes was recorded with the patients breathing spontaneously. Thereafter, a standard CO₂-reactivity test with inhalation of room air mixed with 7% CO₂ was performed.

The raw data were recorded with a data-acquisition software package (TurboLab v4.3, Bressner Electronic) at a sampling rate of 100 Hz. Further analysis was performed via custom-written software developed in house.

Correlation Coefficient Analysis

Correlation coefficient analysis was done according to several investigations of M.C. and colleagues^{3,13} and a recent work of our group.⁶ The steps of calculation were as follows: (1) diastolic values of ABP and CBFV were averaged over 3 seconds; (2) 20 consecutive 3 second values were used to calculate Pearson's correlation coefficient between diastolic ABP and CBFV for 1 minute periods of the 10 minute time series; and (3) the sets of resulting 10 1-minute correlation coefficients were averaged yielding the diastolic correlation coefficient index (Dx). Likewise, calculation with mean ABP and CBFV yielded the mean index (Mx). Using systolic values (index Sx) came out less reliably⁶ and was therefore not considered in the present analysis.

Transfer Function Analysis

We have described this method in more detail previously.^{14,15} Briefly, the power spectra *S* of ABP (*S*_{ABP}) and CBFV (*S*_{CBFV}) and the cross spectrum CS were estimated by transforming the time series of ABP and CBFV to the frequency domain via discrete Fourier transformation. Smoothing the respective periodograms resulted in the power spectra and CS estimates. With the smoothing used (triangular window of half-width 8 frequency bins), the coherence

$$\text{Coh}(f) = \frac{|\text{CS}(f)|}{\sqrt{S_{\text{ABP}}(f)S_{\text{CBFV}}(f)}}$$

(normalized modulus of CS) is significant at the 95% level if it exceeds 0.49. The phase spectrum $\phi(f)$ is the argument of the cross spectrum and is defined over

$$\text{CS}(f) = |\text{CS}(f)| \exp(i\phi(f))$$

The gain can be interpreted as the regression coefficient of CBFV on ABP:

$$G(f) = \frac{|\text{CS}(f)|}{S_{\text{ABP}}(f)}$$

Phase shift in the low-frequency range (LF phase, 0.06 to 0.12 Hz) and gain in the high-frequency range (HF gain, 0.20 to 0.30 Hz) were extracted according to previously described rules, the most important of which is to select a point of high coherence within the respective frequency range.¹⁴ LF phase and HF gain proved to be the most meaningful parameters when using the transfer function approach for spontaneous oscillations of ABP and CBFV.^{14,16} For more details regarding calculation of dynamic cerebral autoregulation indices please refer to <http://www.fdm.uni-freiburg.de/groups/timeseries/stroke/>.

Calculation of CO₂ Reactivity

CO₂ reactivity (in %/mm Hg) was determined by dividing the maximum percentage increase of mean CBFV during hypercapnia (averaged over 1 respiratory cycle) by the absolute increase of P_{ETCO₂} (in mm Hg).

Statistical Analysis

Calculation of intra- and interindividual differences and correlations was performed using nonparametric tests (Kruskal-Wallis, Mann-Whitney, Wilcoxon, Spearman's rank coefficient). In case of multiple testing, we used the closed test principle to control the multiple significance level. Multiple linear regression modeling was applied to control the improvement of autoregulatory parameters by recanalization (difference post-pre) for various confounding factors (in order of inclusion to the model: prerecanalization values, blood pressure, and P_{ETCO₂} difference post-pre recanalization, age, sex, degree of stenosis before recanalization; when comparing procedures, the type of recanalization [CEA versus SPAC] was entered first). All analyses were performed using standard statistic software (SAS v8.02, SAS Institute Inc). A probability value of <0.05 was considered statistically significant. Data are reported as mean±SD.

Results

DCA analysis before and after CEA is illustrated in a single patient in Figure 1. General hemodynamic parameters during autoregulation analysis are given in Table 1.

Both autoregulatory parameters of transfer function analysis (LF phase and HF gain) and correlation coefficient indices (Dx, Mx) showed clearly poorer autoregulation values before the procedure compared with contralateral sides (Figure 2). Patients with a stenosis degree of ≥90% had poorer ipsilateral values for phase, Dx, and Mx than patients with a degree of 75% to 89% (*P*<0.05). After recanalization of the obstructed ICA, autoregulatory parameters improved markedly, reaching values of contralateral unaffected sides. Conventional CO₂ reactivity was also improved by the recanalization, but values on the affected side did not completely reach that of unaffected sides (Figure 2). Correlation coefficient analysis showed that the ipsilateral degree of autoregulatory improvement was highly significantly related to autoregulatory values before recanalization (Figure 3). Mul-

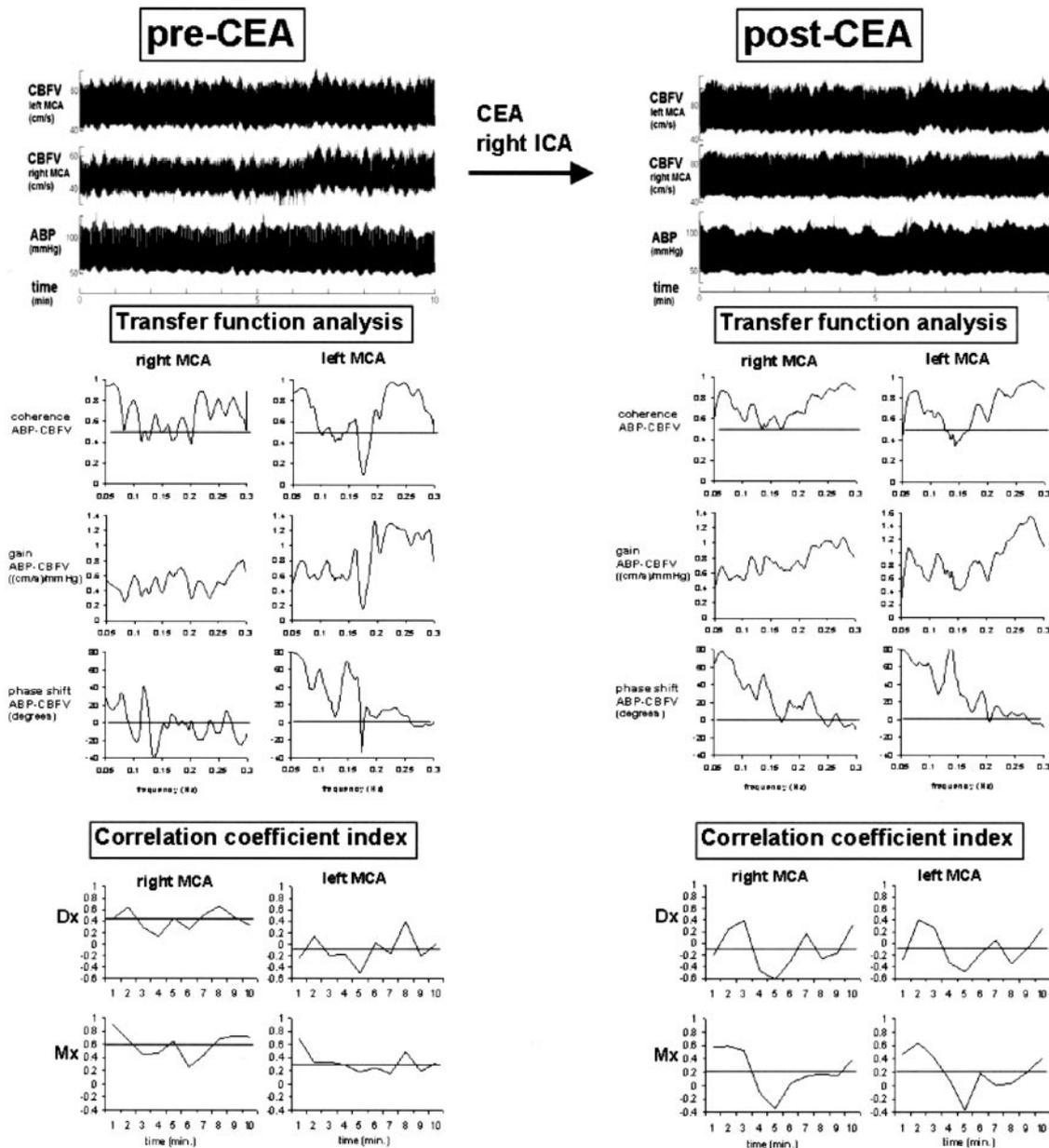


Figure 1. A 52-year-old man with 90% stenosis of the right ICA. Raw data and applied methods of dynamic autoregulation analysis from spontaneous oscillations in ABP and CBFV are illustrated before and 4 days after CEA. Transfer function analysis: Note the normalization of the phase spectrum (right MCA) around 0.1 Hz after CEA with restored high-pass filter properties (ie, decreasing phase shift at higher frequencies). Gain was analyzed at 0.25 Hz. Note the lacking high-pass filter properties of the gain spectrum over the affected side preoperatively, leading to a clear side-to-side difference at this frequency, and its normalization postoperatively. Correlation coefficient analysis: The consecutive 1 minute correlation coefficients were averaged over 10 minutes to form the respective indices Dx and Mx (illustrated by the horizontal lines). Note the high positive correlation of diastolic and mean CBFV with respective values of ABP on the affected right side before CEA and the clear reduction of this dependency postoperatively.

multiple linear regression confirmed these results ($P < 0.001$ for all parameters except for HF gain: $P < 0.01$), and no other significant covariates could be found except for age positively relating to post-HF gain ($P = 0.02$). The observed contralateral increase in HF gain was also significantly related to age ($P = 0.01$) and prevalues ($P = 0.008$).

Analyzing CEA and SPAC separately, both procedures resulted in significant improvement of cerebral autoregulatory parameters. CO_2 reactivity and HF gain of transfer function were significantly lower post-CEA than post-SPAC even after controlling for various covariates (Table 2).

At follow-up, no significant changes in any parameters were found (Figure 4).

Discussion

DCA parameters have been previously demonstrated to be significantly reduced in patients with severe ICA stenosis.^{4,10,17} Impaired DCA might be prognostic for ipsilateral stroke in asymptomatic severe carotid stenosis, as shown for other parameters of hemodynamic impairment.^{1,18} Routine assessment of DCA could thus become a promising tool in selecting patients at highest risk from stroke for carotid

TABLE 1. General Hemodynamic Parameters Averaged Over the 10-Minute Recording for Autoregulation Analysis

n=58	Pre-CEA/SPAC	Post-CEA/SPAC	Significances Pre-Post
Arterial blood pressure (mm Hg)			
Systolic	106.8±20.8	98.3±19.8	P=0.004
Diastolic	57.8±12.7	52.9±11.4	P=0.001
Mean	73.9±13.8	67.4±12.7	P<0.001
Heart rate (beats/min)	68.7±11.3	72.4±12.5	P=0.019
Endtidal PCO ₂ (mm Hg)	38.7±3.7	39.8±4.9	P=0.021
Mean CBFV (cm/s)			
Ipsilateral	43.0*±8.1	53.5±11.5	P<0.001
Contralateral	52.5±10.2	54.9±10.4	NS

*P<0.001 between ipsi-lateral and contralateral cerebral blood flow velocity CBFV in the MCA.

recanalization. However, if carotid recanalization is to be the method of choice to intervene in this group of poor DCA, it should first be demonstrated that this intervention actually improves the impaired DCA. Our study indeed demonstrates that DCA parameters derived from spontaneous blood pressure fluctuations effectively improve over affected sides by carotid recanalization.

Methodological Aspects

Assessment of DCA from spontaneous blood pressure fluctuations is attractive because it does not require any external blood pressure manipulation. ABP and P_{ETCO₂} values during the 10-minute periods analyzed in the present study differed significantly before and after carotid recanalization. Relative hypotension post-CEA has been observed previously and might be attributed to restituted flow at the carotid sinus baroreceptor site.^{19,20} However, the ABP changes observed in our study are overall comparatively small and multiple regression modeling of the present data could not demonstrate a significant influence on restoration of cerebral autoregulatory parameters. It is thus unlikely that these factors have critically influenced the autoregulatory changes observed after carotid recanalization.

Major clinical limitations for the transfer function approach lie in the lack of coherence in ≈10% of patients mostly in the LF range. Furthermore, there is no common standard from which to extract the phase and gain in the respective frequency range. We chose the point of maximum coherence in accord with other authors.¹⁶ Reproducibility of transfer function autoregulatory parameters with the phase extraction rules we use is moderate to good with better values for HF gain than LF phase.¹⁴

The correlation coefficient index approach has been predominantly applied to patients with traumatic brain injury.²¹ It correlates significantly with static cerebral autoregulation measurements and evolved as a potential marker for clinical outcome of head-injured patients.^{22,23} Recently, this method was also successfully applied to patients with carotid stenosis, yielding significant side-to-side differences for correlation indices of Dx and Mx but not for Sx.⁶

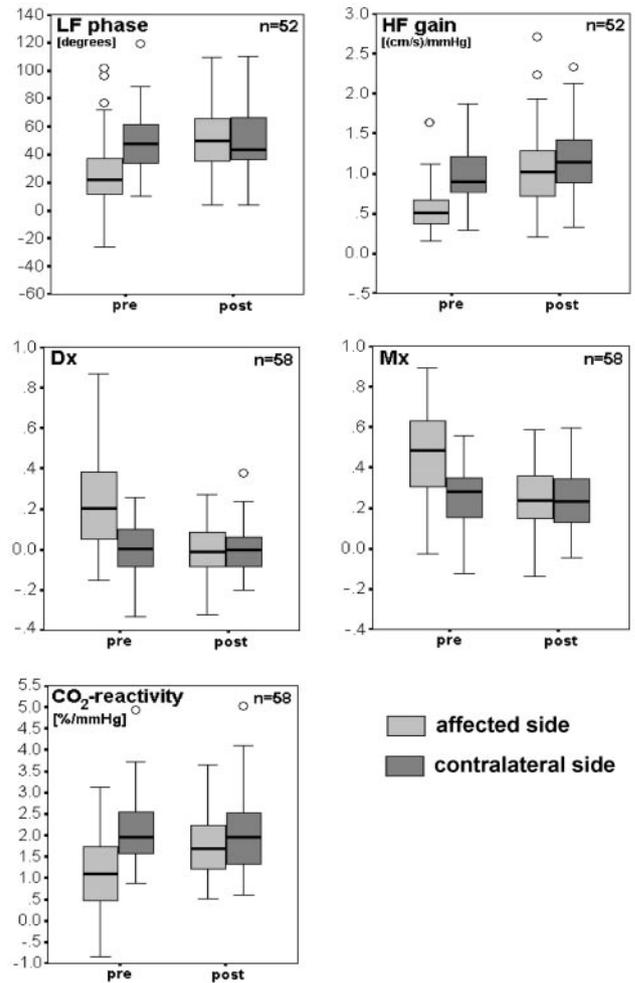


Figure 2. Box plots illustrating the effect of CEA/SPAC on DCA. Autoregulatory parameters of transfer function analysis (n=52, 6 patients excluded due to insignificant coherence). Parameters of the correlation coefficient method (n=58): Dx and Mx. All parameters showed before recanalization (pre) highly significant side-to-side differences (P<0.001) and a highly significant improvement after recanalization (post) over affected sides (P<0.001). For HF gain, contralateral sides also showed a significant increase (P<0.05) after recanalization. Comparing side-to-side differences, the values on affected sides after CEA/SPAC were still significantly poorer for HF gain (P=0.008) and CO₂ reactivity (P=0.036).

Cerebral Autoregulation and Carotid Recanalization

The literature on this topic is sparse. DCA has been analyzed by the cuff deflation technique in 8 patients 1 month after CEA or angioplasty and found to be normalized.¹⁰ Studies on larger collectives have not been performed so far, nor has the time course of cerebral autoregulatory improvement been assessed.

Both the correlation coefficients Dx and Mx decreased clearly and early after carotid recanalization. This indicates a decreasing dependence of CBFV from ABP changes and thus restored cerebral autoregulation, confirming the pathophysiological soundness of the correlation coefficient method as a measure for cerebral autoregulation.

The phase shift between CBFV and ABP with CBFV oscillations leading that of ABP in an LF range ≈0.1 Hz is

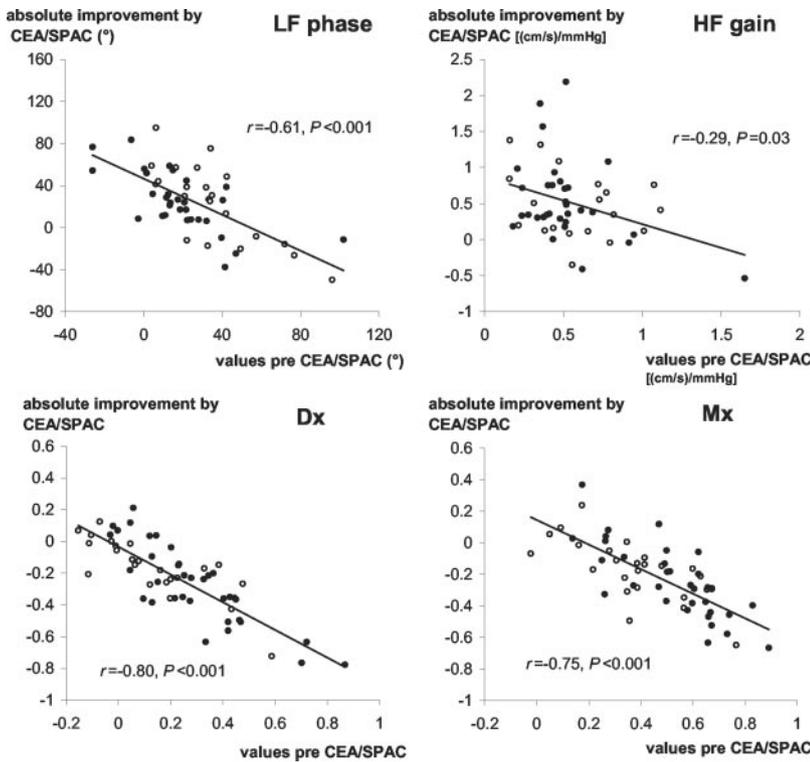


Figure 3. Correlation analysis (Spearman) to illustrate relationship between the prerecanalization autoregulatory impairment and absolute autoregulatory improvement after CEA/SPAC. ○, prerecanalization stenosis degree of 75% to 89%; ●, 90% to 99% (see Results).

the main parameter of the transfer function analysis approach. It has its natural meaning in that the delay of the cerebrovascular resistance reaction to ABP changes and its coupling to CBFV physiologically amounts to ≈2.5 to 3 seconds, thus leading to counterregulation of CBFV consistently earlier than the turning points in repetitive 5-second periods of decrease and increase of ABP occurring during the 0.1 Hz oscillations.^{24,25} The interpretation of gain, which has been statically linked to autoregulatory dampening in the ampli-

tude range, is less well understood, particularly because we can observe the clearly lower gain on affected sides with severe carotid stenosis and under hypercapnia.^{14,24} Inability of dilated arterioles to actively achieve diameter changes may play a role for the lower dynamic gain of transfer function observed in poorer hemodynamic states.²⁶ On the other hand, a rapidly and clearly elevated dynamic gain, as observed after carotid recanalization in the present study for both MCA sides, might be associated with (transient) impaired damp-

TABLE 2. Results Separated by the Kind of Recanalizing Treatment

	CEA		SPAC		Significances CEA vs SPAC effect
	Pre	Post	Pre	Post	
Correlation coefficient indices (n=41 vs 17)					
Dx ipsilateral	0.24±0.22	-0.02±0.14***	0.17±0.22	0.03±0.12*	NS
Dx contralateral	0.00±0.13	-0.02±0.12	0.04±0.12	0.03±0.09	NS
Mx ipsilateral	0.47±0.21	0.24±0.15***	0.44±0.21	0.26±0.16*	NS
Mx contralateral	0.26±0.15	0.23±0.16	0.26±0.17	0.27±0.12	NS
Transfer function analysis (n=38 vs 14)					
LF phase ipsilateral (°)	25.7±21.3	47.6±22.0***	25.6±33.7	57.1±27.0*	NS
LF phase contralateral	48.3±23.4	51.1±20.3	51.3±17.4	51.9±27.4	NS
HF gain ipsilateral ((cm/s)/mm Hg)	0.52±0.22	0.96±0.51***	0.61±0.40	1.31±0.38**	P=0.038
HF gain contralateral	0.99±0.36	1.14±0.43*#	0.93±0.35	1.25±0.44*	NS
CO ₂ -reactivity (%/mm Hg) (n=41 vs 17)					
Ipsilateral	1.11±0.89	1.65±0.72**	1.20±0.76	2.09±0.71**	P=0.033
Contralateral	2.07±0.74	1.99±0.94##	2.12±0.55	2.10±0.83	NS

*P<0.05, **P<0.01, ***P<0.001 between pre- and post-values. #P<0.05, ##P<0.01 between ipsi- and contralateral sides for post-values. Significances between CEA vs SPAC effect represent P-values of multiple regression analysis which was used to control for various covariates (see Methods), of which pre-values (P<0.01 for all parameters) and for HF gain also age (P=0.042) were significant. The n for different parameters varies because of exclusion of 6 patients from transfer function analysis due to insignificant coherence.

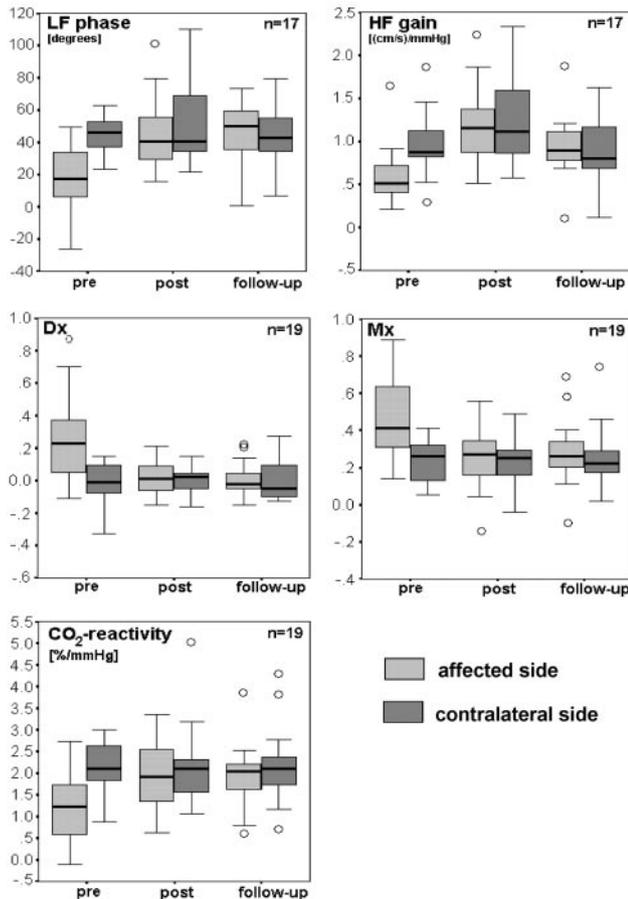


Figure 4. Time course of cerebral autoregulation after CEA/SPAC. Follow-up represents a measurement 7 ± 3 months after recanalization of the ICA. No significant changes were observed between post and follow-up. Comparing the course between CEA ($n=12/10$) and SPAC ($n=7$), also no significant differences could be found. The n for different methods varies because of exclusion of 2 patients from transfer function analysis due to insignificant coherence.

ening of blood pressure peaks. This might pose an interesting pathophysiological link to the genesis of hyperperfusion syndrome or postendarterectomy hypertensive encephalopathy.²⁷ Clinically, however, none of the present patients studied suffered from such a condition. In addition, it remains an interesting question whether the significant relation of age with the bilateral HF gain increase after recanalization observed in the present study makes older patients generally more vulnerable for postrecanalization encephalopathy.

For all autoregulatory parameters, the degree of improvement highly correlated with the extent of preprocedural impairment. This shows that patients with poor autoregulation profit most from the recanalizing procedure and that even virtually abolished autoregulation is completely restored by carotid recanalization. Poor autoregulation values are usually observed in patients with a higher degree of stenosis and particularly with insufficient collateral compensation.²⁸

Comparison Between CEA and SPAC and Comparison With CO_2 Reactivity

For DCA parameters, no significant difference was found between procedures except for HF gain. Generally, the aim of

the present observational analysis was not to compare CEA with SPAC, but rather to look for any essential effect of carotid recanalization on impairment of DCA. When comparing our results for CEA versus SPAC, it should be borne in mind that our study was not randomized in this respect. However, the higher HF gain after SPAC remained significant after controlling for covariates by multiple regression modeling. The present results might indicate a specific disturbance of gain in the cerebral hemodynamic system post-SPAC in the presence of otherwise undisturbed cerebral pressure autoregulation. Future prospective studies are needed to clarify this interesting aspect and its potential role for the genesis of a special post-SPAC encephalopathy.

Previous studies analyzing the hemodynamic effects of carotid recanalization usually focused on vasomotor reactivity as a surrogate for arteriolar dysfunction.^{8,29,30} Generally, improvement of vasomotor reactivity was found in patients with poor hemodynamic states pre-CEA. In our study, unlike DCA parameters, CO_2 reactivity was still significantly lower than contralateral sides early postoperatively. Contrary to previous studies, we could not detect a slight improvement occurring also on contralateral sides.^{29,30}

Analyzing CEA and SPAC patients separately, it became clear that mainly patients undergoing CEA showed incomplete restoration of CO_2 reactivity. Previously, no relevant difference in CO_2 reactivity between patients undergoing CEA and angioplasty had been found after 1 month.³⁰ A general discrepancy between CO_2 reactivity and DCA may be interpreted in that assessment of CO_2 reactivity is a "static" method (ie, measurement of CBFV at 2 static levels of P_{ETCO_2}). Therefore, lower CO_2 reactivity may indicate that cerebral arterioles are still slightly dilated after the recanalization, but are perfectly reactive in their current "working point," as indicated by full recovery of DCA. Whether transient hypoperfusion during carotid clamping may play a role for this effect that seems to occur only after CEA remains open because no CBFV measurements during surgery have been performed in the present study. A general effect (eg, of anesthesia) is unlikely because of unaltered contralateral values in CEA patients.

Effect of Time on Hemodynamic Improvement After CEA

The main findings are that DCA improves early after CEA or SPAC and that no relevant changes occur at follow-up. This is in line with the early improvement of impaired cerebral hemodynamics as assessed by perfusion MRI and CO_2 reactivity, which have been described recently.³¹ Changes of HF gain imply a certain overshoot directly after the procedure (Figure 4). However, this did not reach significance when controlling for a multiple significance level.

Conclusions

Dynamic cerebral dysautoregulation in patients with severe carotid obstruction is readily and completely remedied by CEA or SPAC. In contrast, conventional CO_2 reactivity does not completely improve early after CEA, but does so after SPAC. This study encourages further investigations on cere-

bral dysautoregulation to prospectively identify patients with eminent risk of stroke.

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