Autonomic Function and Cerebral Autoregulation in Patients Undergoing Carotid Endarterectomy

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Background: Carotid endarterectomy (CEA) is the first-line treatment in severe carotid stenosis to prevent stroke. Because of methodological limitations, the acute impact of CEA on baroreflex function and cerebral autoregulation is not well defined and was therefore investigated by applying a novel algorithm.

Methods and Results: Systemic arterial blood pressure, ECG and respiration during metronomic breathing and Valsalva maneuver were continuously recorded in 18 patients with carotid stenosis before and after CEA, and in 10 healthy controls. Baroreflex sensitivity, frequency spectra of RR intervals and indices for cerebral autoregulation were evaluated by trigonometric regressive spectral analysis. Compared with the controls, patients had impaired baroreflex sensitivity. Baroreflex sensitivity and frequency spectra were not changed by CEA. Cerebral autoregulation of patients with carotid stenosis as calculated by phase shift was reduced compared with controls but it improved significantly after CEA. Improvement of cerebral autoregulation was independent of changes in cerebral blood flow velocity.

Conclusions: Baroreflex sensitivity and cerebral autoregulation are impaired in patients with carotid stenosis, conferring a high stroke risk. CEA improves cerebral autoregulation, but does not affect baroreflex sensitivity. For further risk reduction, interventional approaches targeting baroreflex function need to be considered. (Circ J 2010; 74: 2139–2145)

Key Words: Baroreflex sensitivity; Carotid endarterectomy; Carotid stenosis; Cerebral autoregulation; Spectral analysis

Hypertension and Circulatory Control

Original Article

Atherosclerotic carotid artery stenosis is associated with increased risk for stroke, and carotid endarterectomy (CEA) is considered superior to medical treatment for stroke prevention.1,2 Surgery takes place in the immediate vicinity of baroreceptors located in the carotid sinus. These stretch receptors are involved in the regulation of blood pressure (BP) and heart rate (HR), known as baroreflex.3 Diminished baroreflex sensitivity (BRS) impedes adequate modulation of baroreceptor activity, resulting in increased BP variability. Consequently, low BRS has been associated with long-term mortality after myocardial infarction and ischemic stroke.4,5

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Transient hemodynamic instabilities have been observed during and after carotid surgery, suggesting an affect on baroreflex.6–10 However, previous studies have yielded contrasting results, reporting decreased,11,12 stable or increased BRS13,14 after CEA. Differences in the algorithms used to calculate BRS and in operational processing may have contributed to the diversity of outcomes.

Cerebral autoregulation represents another physiological mechanism of blood flow control that is crucial for stroke prevention. It describes the ability of small cerebral arteries to maintain constant cerebral blood flow by compensating for changes in cerebral perfusion pressure.15 Cerebral autoregulation is impaired in carotid artery stenosis16–19 and is partly restored by CEA.20,21

In the present study, we aimed to verify the short-term effect of CEA on BRS using a novel statistical algorithm specifically validated for baroreflex calculation.22,23 Furthermore, we assessed cerebral autoregulation in patients with carotid artery stenosis before and after CEA.
Patients and Study Design
Pre- and postoperative neuroautonomic examinations were performed in 18 patients with carotid stenosis undergoing CEA. The decision for CEA was based on case-presentation in the vascular conference, which included vascular surgeons, neurologists, neuroradiologists and anesthesiologists. Surgery was performed under local anesthesia with the patient pressing an object in the contralateral hand for neuromonitoring.

All patients were examined by a neurologist before and after surgery. Stroke-related neurologic deficits were assessed using the stroke scale of the National Institutes of Health (NIHSS). Preoperative measurements of cerebral autoregulation and autonomic cardiovascular control were performed on the day before surgery. Postoperative measurements followed during hospitalization (ie, 3.8 ± 1.1 days post surgery). Ten healthy age-matched controls underwent the identical examination of cardiovascular function. Written informed consent was given by all patients and controls. The study was approved by the Ethics Committee of the Faculty of Medicine of Dresden, University of Technology and the study procedure performed with the Declaration of Helsinki.

Neuroautonomic Assessment
All recordings were performed in a temperature and humidity controlled specialised laboratory while the participant was supine. Continuous cardiovascular monitoring was performed using the SUEMPATHY device (Suess Medizin Technik, Aue, Germany), including a non-invasive BP monitoring CBM-7000 device (Colin Corp, Komaki, Japan). Cerebral blood flow velocity (CBFV) of the middle cerebral arteries (MCA) was measured simultaneously using a 2-MHz Doppler device (MultiDop T, DWL, Compumedics Germany GmbH, Singen, Germany). The Doppler probes were held in position by an adjustable head-strap. The MCA were insonated via the transtemporal bone window adjusted to a depth of 54 mm. In case of insufficient signal quality the insonation depth was adjusted accordingly, ranging between 52 and 58 mm. The insonation depth was kept constant for the pre- and postoperative measurements.

After an equilibration period of 20 min, resting BP, HR and CBFV were recorded followed by deep metronomic breathing with 6 cycles per minute for 3 min. Controlled breathing evokes highly coherent changes in BP and HR at a certain frequency, predominantly reflecting cardiovascular function. Following recovery, the Valsalva maneuver was performed twice. To evoke an intrathoracic pressure of 40 mmHg, the participant was instructed to take a large tidal breath and then to forcefully exhale for 15 s against an incompletely closed valve connected to an aneroid pressure gauge. Intrathoracic pressure was recorded during the maneuver. The hemodynamic response to the sudden, transient increase in intrathoracic and intra-abdominal pressure during Valsalva results in dynamic changes of cerebrovascular resistance mediated by autoregulatory mechanisms.

Data Analysis
Cerebral autoregulation was assessed using the Valsalva Index AI-IV and phase shift during metronomic breathing. The AI-IV quotient was derived from the CBFV and systolic BP data obtained in phases I and IV of the Valsalva maneuver. The mean of the AI-IV indexes was calculated from both maneuvers. Phase shift, defined as the latency of CBFV oscillations following oscillations in BP, was analyzed using trigonometric regressive spectral (TRS) analysis (MTRS, ANS Consult Freital, Germany). As depicted in Figure 1 the interval between markers 1 and 2 indicates the phase shift. The specification is given in angular dimensions, where 360° equates to a full wave length. A diminished phase shift represents a retarded reaction of cerebral vasomotion to changes in arterial BP. In general, higher values for both AI-IV and phase shift represent better autoregulation.

TRS was also used to determine the spectrum of oscillations from continuously monitored systolic BP and RR intervals and to calculate BRS. TRS provides a pure physiological spectrum using statistical methods to minimize the variance of a process. The EuroBavar Study demonstrated a good agreement of BRS calculated by trigonometric spectral analysis with that obtained by other techniques. BRS reflects the ability of the autonomic nervous system to respond to BP changes. Spectral analysis allows for quantification of cardiovascular regulation by assessing spontaneous oscillations in RR interval. Two main spectral bands are usually considered: High-frequency oscillations of the HR (spectral band between 0.15 and 0.4 Hz) relate to respiratory sinus arrhythmia and therefore to parasympathetic cardiovascular tone. The other oscillation of interest is in the low-frequency range (spectral band between 0.04 and 0.15 Hz). Low-frequency oscillations of HR are thought to reflect the baroreflex-mediated adjustments to the sinus node, which involve both sympathetic and parasympathetic influences. Thus, the LF/HF-quotient is referred to as a marker of sympathetic input.

Statistical Analysis
The SPSS software package version 16.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all statistical computations. Data are presented as mean ± SD. Gaussian distribution was verified by Kolmogorov-Smirnov test. Student’s t-test for paired data was used to compare pre- and postoperative measurements. Associations between changes in variables before and after CEA were analyzed by Pearson correlation. Differences were considered significant when P < 0.05.
The clinical characteristics of all study participants are shown in Table 1. Four patients suffered mild peripheral facial nerve paresis after surgery, which resulted in an elevated postoperative stroke score calculated by NIHSS. Although diffusion-weighted magnetic resonance imaging of the brains was not performed, clinical signs of cerebral ischemia were absent in all these patients. Antihypertensive medication was extended in 6 patients after the operation; however, patients did not show any episodes of severe hypo- or hypertension after surgery. Clinical signs of cerebral hyperperfusion syndrome were not observed. Control subjects did not have a history of neurological or cardiovascular events. However, 3 controls were hypertensive.

Resting hemodynamic parameters are presented in Table 2. In patients, systolic BP had decreased and HR had increased postoperatively. There was also a tendency towards a lower diastolic BP after surgery. The ipsilateral CBFV had increased while the contralateral CBFV remained unchanged after carotid surgery. Patients and controls did not differ with regard to hemodynamic measures at any time, except for a higher HR in patients after surgery compared with controls.

As depicted in Figure 2, spontaneous BRS was unaffected by surgery in patients (before CEA: 4.07±7.95 mmHg/ms, after CEA: 4.73±4.37 mmHg/ms; P=0.698). Likewise, low-frequency and high-frequency powers of the RR interval and the ratio thereof remained unchanged (before CEA: LF 27.8±14.4; HF 16.8±13.7; LF/HF 3.5±4.7; after CEA: LF 26.8±13.7; HF 20.0±15.9; LF/HF 3.3±3.3) (Figure 2). BRS was significantly reduced in patients before surgery compared with controls (7.95±4.48 mmHg/ms). This difference could not be verified after surgery (P=0.079). Patients had a higher LF/HF ratio after surgery compared with controls while low- and high-frequency powers were not significantly different between patients and controls.

Parameters of cerebral autoregulation are illustrated in Figure 3. Before surgery, the AI-IV ratio and the phase shift during metronomic breathing were significantly reduced at the stenotic side. Phase shift significantly improved at the ipsilateral side after surgery while the AI-IV ratio did not change. However, a tendency towards higher values on the ipsilateral side was observed postoperatively. Changes of cerebral autoregulation indices did not correlate with changes in cerebral blood flow (r=0.218, P=0.420).

### Results

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### Discussion

CEA is indicated in patients with significant carotid stenosis, but because this invasive procedure is adjacent to baroreceptors it has been suggested to affect baroreceptor function. As previous results were inconsistent we attempted to assess the effect of CEA on baroreflex function and cerebral auto-regulation using a novel algorithm for evaluation. Our results clearly indicate that patients with significant stenosis have impaired BRS when compared with healthy controls. Neither CEA, carotid endarterectomy; NIHSS, National Institutes of Health stroke scale; ACE, angiotensin-converting enzyme.
**Figure 2.** Baroreflex sensitivity (BRS) and spectral bands of RR interval at rest in patients before and after carotid endarterectomy and in controls. Data are presented as mean and SEM.

**Figure 3.** Cerebral autoregulation during Valsalva maneuver (AI-IV) and metronomic breathing (phase shift) in patients before and after carotid endarterectomy and in controls. Data are presented as mean and SEM.
BRS nor autonomic input to the heart was affected by invasive CEA. We also revealed impaired cerebral autoregulation during experimentally evoked BP changes in the hemisphere affected by carotid stenosis. Intriguingly, cerebral autoregulation had significantly improved after carotid surgery. Of 18 patients, 4 suffered peripheral facial nerve pareses. Although this is a frequent but transient complication of CEA the incidence in our study was higher, but the impairment less severe, compared with previous studies investigating larger patient samples.\textsuperscript{31–34} However, it must be noted that the incidence of facial nerve pareses varied greatly between the studies.

Although most of the present patients were regularly treated by drugs thought to exert favorable effects on BRS, the baroreflex gain of patients was severely reduced compared with controls and remained low after surgery.\textsuperscript{1,11,14} A diminished BRS has also been reported by other studies investigating patients with carotid stenosis.\textsuperscript{37,38} It has been speculated that the low BRS is a result of decreased arterial distensibility in the affected region,\textsuperscript{36} but as we did not observe any improvement in BRS after CEA this hypothesis may not fully apply or only in the case of a direct and severe effect of sites of baroreceptor location. Intriguingly, a previous study reported reduced BRS only in bilateral carotid stenosis, but not in unilateral disease.\textsuperscript{38} There was also no association between BRS and the degree of stenosis in the present study, so it may be assumed that a reduced BRS in carotid stenosis rather reflects the severity of underlying metabolic or hemodynamic derangement than the extent of lesions in the carotid segment itself. Nevertheless, a direct effect of atherosclerosis on baroreceptor functionality cannot be ruled out.

Previous studies evaluating the effect of CEA on baroreflex function have yielded conflicting results, ranging from improvement to no effects to improvement.\textsuperscript{11–14} Our findings, therefore, support the notion that CEA does not affect baroreceptors. However, this statement has to be critically revised because the power to detect significant differences was limited by the small sample size. Contrasting our findings, Nouraei et al\textsuperscript{11} observed a deterioration of BRS after CEA. It needs to be emphasized that the investigators performed CEA under general anesthesia, which is particularly important because anesthetics such as isoflurane as used by Nouraei et al have been described as affecting BRS.\textsuperscript{39} Additionally, the investigators applied an intraluminal rub-test during surgery to stimulate baroreceptors. This invasive procedure may have adversely affected on baroreflex function and, hence, may falsely imply adverse effects of surgery. Furthermore, the timing of BRS assessment may be critically for study comparisons because hemodynamic instability has been reported in the first 6 h postoperatively.\textsuperscript{40} In particular, an inflammatory or prothrombotic response in consequence of surgery may evoke transient changes in BRS and cerebral autoregulation.\textsuperscript{41} Long-term follow-up measurements are, therefore, less confounded by immediate humoral effects of CEA and may better reflect the hemodynamic influence of abrogation of vascular obstruction. Nevertheless, any changes in state of health during the first days after surgery are of utmost clinical importance for clinicians and patients, because a decision about dismissal from hospital is made on that basis.

Because we observed significant changes in systolic BP and HR after surgery one might argue that these changes reflect alterations in baroreflex function. This assumption seems rather unlikely though, because frequency analysis of the RR intervals represents a highly sensitive and accurate method for BRS determination. Changes in sympathetic or parasympathetic activity would have resulted in frequency shifts of HR oscillations. Although the LF/HF ratio had increased after surgery relative to the controls, no differences were noted compared with pre-surgery measurements in patients. Therefore, it seems plausible that these hemodynamic changes are likely a consequence of a tightened antihypertensive regimen post-surgery. This may also explain the increased HR in patients after surgery compared with controls.

Methodological differences should certainly be taken into account when comparing autonomic and cardiovascular measures between studies. Previous studies applied fast Fourier transformation (FFT) for spectral analysis. This method is of limited reliability because it requires equidistant values, which cannot be generated from the RR intervals. The validated algorithm of TRS\textsuperscript{22} we were applying uses statistic elements to cope with the stochastic nature of time-varying signals, like RR intervals. During the analysis, data are broken down into short segments and shifted beat by beat allowing for temporal determination of frequency and amplitude. In each segment, maximal variance reduction is achieved by fitting appropriate sinusoidal oscillations via statistical regression. These sinusoidal oscillations represent real oscillations of pure physiological origin. Unlike TRS, FFT generates solely mathematical oscillations that are less suitable for analysis of RR intervals.\textsuperscript{42}

Except for a reduced BRS, our patients with carotid stenosis exhibited impaired cerebral autoregulation, which improved after CEA. These observations are in line with previously published results by Telman and Reinhard.\textsuperscript{18,20,21} It may be argued that abrogation of carotid artery stenosis-evoked cerebral hypoperfusion by CEA is critically involved in the improvement of cerebral autoregulation. However, the improvement of autoregulation was independent of changes in cerebral blood flow indicating differential mechanistic and etiological effects of CEA on cerebral function and hemodynamics. Although we used 2 different methods for evaluation of cerebral autoregulation, only phase shift, but not Tieck’s AI-IV index, indicated functional improvements after surgery. This finding is of high clinical importance because a dysfunctional cerebral autoregulation increases the risk of stroke and of ipsilateral ischemic events.\textsuperscript{17} It has also been shown that the risk of stroke during and 1 month after carotid surgery is increased, with concomitant impaired cerebral autoregulation.\textsuperscript{43} Therefore, improvement of cerebral autoregulation as observed in our study may indicate a reduced stroke risk.

**Study Limitations**

There are some methodological limitations regarding determination of cerebral autoregulation in our study, which need consideration. The Valsalva maneuver is often hampered by the patient’s difficulty in maintaining a transmural pressure of 40 mmHg, leading to underestimation of the AI-IV index. Furthermore, the AI-IV index has not yet been applied for determination of changes in cerebral autoregulation after invasive vascular intervention, so the sensitivity of the index may be limited. Phase shift derived from metronomic breathing seems a more reliable measure for cerebral autoregulation, because it is easy to perform and induces less dramatic hemodynamic alterations. A recent study using phase shift also detected favorable effects of PTA on cerebral autoregulation.\textsuperscript{44} Therefore, phase shift rather than the Valsalva maneuver and Tieck’s AI-IV index may be the method of choice for future studies examining cerebral autoregulation.

In conclusion, CEA did not affect BRS and autonomic
function in patients with carotid stenosis, but significantly improved impaired cerebral autoregulation. These findings are of high psychosomatic, as well as clinical importance. Firstly, a patient’s fear of carotid surgery may affect process quality and vital status during surgery. Secondly, improvement of cerebral autoregulation may confer a reduced risk for future ischemic events and stroke. Thirdly, for further risk reduction, a correction of deranged BRS should be considered in patients after CEA and could be achieved by targeted pharmacological intervention through direct effects on baroreceptors or through correction of hemodynamic disturbances.

Acknowledgments
This work was supported by the Dresden University Technology, School of Medicine Carl Gustav Carus, Dresden, Germany. We thank all participants for their cooperation.

Disclosures/Conflict of Interest
L. Mense, M. Reimann, H. Rüdiger, G. Gahn and H. Hentschel report no disclosures.

H. Reichmann serves on scientific advisory boards, receives speaker honoraria, and/or receives funding for travel from Cephalon, Novartis, TEVA, Lundbeck, GlaxoSmithKline, Boehringer Ingelheim, Schering/Bayer HealthCare, UCB/Schwarz Pharma, Desitin, Pfizer, and Solvay. T. Ziemssen has received speaker honoraria from Biogen Idec, Sanofi-Aventis, MerckSerono, Novartis, Teva, and Bayer Healthcare; he serves as a consultant for Teva, Novartis, and Bayer HealthCare; and receives research support from the Roland Ernst Foundation.

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