Favorable effects of carotid endarterectomy on baroreflex sensitivity and cardiovascular neural modulation: a 4-month follow-up

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First published April 10, 2013; doi:10.1152/ajpregu.00078.2013.—Carotid LF/HF and LFSAP and reduced HFRR compared with rest (P < 0.02) at rest. SAP variance decreased both at rest and during tilt (P < 0.02). Before surgery, tilt did not modify the autonomic profile compared with baseline. After CEA, tilt increased LF/HF and LFSAP and reduced HFRR compared with rest (P < 0.02). Four months after CEA was performed, arterial baroreflex sensitivity was enhanced. Accordingly, the patients’ autonomic profile had shifted toward reduced cardiac and vascular sympathetic activation and enhanced cardiac vagal activity. The capability to increase cardiovascular sympathetic activation in response to orthostasis was restored. Baroreceptor sensitivity improvement might play an additional role in the more favorable outcome observed in patients after carotid surgery.

carotid endarterectomy; arterial baroreflex sensitivity; autonomic nervous system; power spectrum analysis; head-up tilt test

THE BENEFICIAL EFFECTS of carotid endarterectomy (CEA) on the recurrence rate of ischemic stroke in selected patients are well known (34) and have been mainly attributed to removal of the atherosclerotic process from the bifurcation of the internal carotid artery (34, 37). The possibility of an increase of carotid baroreflex gain after CEA might contribute to a more favorable cardiovascular prognosis. Indeed, low arterial baroreceptor-
ment, a careful clinical history and a complete physical examination were obtained. All patients received the same medical treatment before and after surgery. Clinical characteristics of the patients are summarized in Table 1. The study complies with the Declaration of Helsinki and was approved by the Ethical Committee on Human Research at the Luigi Sacco Hospital. All participants signed an individual informed consent form.

**Inclusion and exclusion criteria.** Patients scheduled to undergo CEA were eligible to be enrolled if they had unilateral carotid stenosis (contralateral carotid stenosis <30%) and were in sinus rhythm. Patients were excluded if they had a recent history (<6 mo) of myocardial infarction, stroke, or surgical medicalization. In addition, depressed left ventricular systolic function [ejection fraction (EF) < 50%], diabetes mellitus, moderate to severe chronic obstructive pulmonary disease, moderate to severe hypertension, moderate to severe chronic renal failure, significant valvular disease, and beta-blocking therapy were all considered to be exclusion criteria, as these conditions are known to determine modification of the autonomic profile and arterial baroreceptor sensitivity (16, 17, 25, 29, 31, 44, 48).

**Surgery.** Surgery was performed under general anesthesia. All patients underwent complete endarterectomy of the internal carotid artery, of the carotid sinus, or of the origin of the external carotid artery by an eversion technique with reimplantation of the internal carotid artery into the carotid sinus (6). Briefly, eversion CEA requires an oblique rather than longitudinal transection of the artery at its origin with distal excision for removal of the plaque. The oblique approach may account for a low restenosis rate, while it might be responsible for a potential loss of baroreceptor function due to transection of nerve fibers (9). On the other hand, an advantage of this approach is completely autogenous repair, as the use of a patch is not necessary. All subjects were submitted to intraoperative and postoperative angiography to confirm results.

**Protocol.** All subjects were tested in a quiet room in our clinical laboratory in the late morning. All had consumed a light, caffeine-free breakfast. Care was taken to avoid noise, and the room temperature was kept at a comfortable level. Earlier in the same morning, a 75° head-up tilt test was performed in random order. A recovery period of at least 40 min was allowed between the two tests (21, 43). The above protocol was performed the day before and 4 mo after surgery.

Data analysis. Analog data were analyzed off-line. Heart period was calculated as the time difference between two consecutive parabolic apexes [R-R interval (RR)]. The maximum arterial pressure within RR was taken as systolic arterial pressure (SAP). Software techniques for series extraction and spectral and cross-spectral analyses of RR and SAP variability and respiratory activity have been described in detail elsewhere (2, 38). Autoregressive spectral analysis provided the power of low frequency (LF, from 0.04 to 0.15 Hz) and high frequency (HF, >0.15 Hz) components of the RR and SAP series. These oscillatory components were expressed in both absolute units (ms² or mmHg²) and normalized units (nu) (48). Normalization was obtained by dividing the absolute power of each component by the total variance minus the power of the very low-frequency component.

Table 1. Patients’ individual clinical characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age, yr</th>
<th>Smoking</th>
<th>Associated Disease</th>
<th>Therapy</th>
<th>Stenosis (localization, %)</th>
<th>TIA</th>
<th>Ischemic Lesion (CT scan)</th>
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<tbody>
<tr>
<td>1*</td>
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<td>+</td>
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<td>a/e</td>
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<td>IICA85</td>
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<td>–</td>
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<td>3</td>
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<td>a/e/s</td>
<td>rICA80, rECA70</td>
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<tr>
<td>4</td>
<td>m/68</td>
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<td>HTN,CAD</td>
<td>a/t/s</td>
<td>IICA70</td>
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<td>–</td>
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<tr>
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<td>–</td>
<td>a</td>
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<td>6*</td>
<td>f/75</td>
<td>–</td>
<td>HTN,CAD</td>
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<td>–</td>
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<td>t/am</td>
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<tr>
<td>10</td>
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<td>–</td>
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<td>IICA70</td>
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<td>t</td>
<td>rCCA70</td>
<td>+</td>
<td>+</td>
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<td>HTN,CAD</td>
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<td>+</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>m/79</td>
<td>–</td>
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<td>rICA70</td>
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<td>–</td>
</tr>
<tr>
<td>17</td>
<td>m/79</td>
<td>+</td>
<td>–</td>
<td>t/e</td>
<td>rCCA80</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>f/79</td>
<td>–</td>
<td>HTN,CAD</td>
<td>a/s</td>
<td>rICA90</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>a</td>
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<td>–</td>
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<tr>
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<td>a/s</td>
<td>rICA80</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

m, Male; f, female; HTN, hypertension; CAD, coronary artery disease; a, aspirin; am, amiodipine; e, enalapril; s, statin; t, ticlopidine; l, left; r, right; I, internal; E, external; C, common; CA, carotid artery; % stenosis; TIA, transient ischemic attack; *Follow-up drop.
High-performance liquid chromatography with electrochemical detection (Bio-Rad Laboratories, München, Germany) was used to assess plasma epinephrine and norepinephrine values in venous blood samples. Samples were centrifuged at 4°C and a velocity of 3,000 relative centrifugal force (RCF) for 10 min (1, 24).

Arterial baroreflex sensitivity. Both pharmacological (BRS) and spontaneous (index α, spectral analysis) arterial baroreflex sensitivity were evaluated. BRS was obtained by using the modified Oxford technique as previously reported (21, 43). Briefly, a bolus injection of sodium nitroprusside (NTP) was administered intravenously, followed by a bolus injection of phenylephrine as soon as the NTP-induced decrease in SAP reached 30 mmHg or 60 s after the NTP injection. Three trials were completed, and each was separated by a minimum of 15 min of quiet recovery. After RR vs. SAP values derived during the period of vasoactive drug administration were plotted, the linear portion of the RR-SAP relation was identified. BRS was assessed as the slope of the regression line calculated over the linear portion of the RR-SAP relationship. The correlation coefficients between drug trials were consistently high and similar (range r = 0.81 ± 0.01 to 0.85 ± 0.01) for the three measures. The average of the slopes of the three trials was used as the estimate of BRS for each subject. The index α was computed as the square root of the ratio between LFRR and LFSAP (11). Cross-spectral analysis was exploited to check that RR and SAP series were significantly correlated at LF (i.e., coherence value > 0.5) (2).

Statistical analysis. The sample size was calculated according to the t-test formula where the difference between the means was 3 ms/mmHg and BRS variance was 10 ms²/mmHg² for each of the two groups in agreement with data obtained in age-matched hypertensive subjects (29). The chosen size of the groups (i.e., 15) allows the calculation of a t-value corresponding to a probability of type I error largely less than 0.05.

Data are expressed as means ± SD. The two-tailed Student’s t-test and two-way repeated-measures analysis of variance (Holm-Sidak test for multiple comparison, 2 factor repetition) were used to compare data before and after surgery and changes induced by head-up tilt. A P < 0.05 was considered significant.

RESULTS

Clamping time during CEA was 24 ± 7 min. No patient required treatment for significant hemodynamic instability during surgery or in the immediate postoperative period. We reported no major postoperative complications.

Fifteen patients completed both pre- and postoperative (126 ± 9 days) evaluation, as one patient was found to be in atrial fibrillation at the time of follow-up, one patient had been newly diagnosed with diabetes and another with cancer, and two patients refused the follow-up tests.

Arterial baroreflex sensitivity. Pre- and post-surgery BRS indexes, obtained in the supine position, are reported in Table 2. While both mean index α and BRS were significantly higher (P < 0.02) 4 mo after CEA, two patients showed a dramatic decrease of both arterial baroreflex sensitivity estimates (Fig. 1).

Table 2. Baroreflex sensitivity indexes before and after carotid endarterectomy

<table>
<thead>
<tr>
<th></th>
<th>PreOP</th>
<th>PostOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>α Rest, ms/mmHg</td>
<td>5.9 ± 1.2</td>
<td>9 ± 1.6*</td>
</tr>
<tr>
<td>α Tilt, ms/mmHg</td>
<td>4.8 ± 2.4</td>
<td>7.4 ± 2.5*</td>
</tr>
<tr>
<td>BRS rest, ms/mmHg</td>
<td>2.5 ± 1.1</td>
<td>5.6 ± 1.5*</td>
</tr>
</tbody>
</table>

Values are means ± SD. α, Spontaneous baroreflex sensitivity; BRS, pharmacological baroreflex sensitivity; PreOP, before carotid endarterectomy; PostOP, after carotid endarterectomy. *P < 0.02, PostOP vs. PreOP.

The mean ± SD changes of arterial baroreflex sensitivity after surgery were 3.6 ± 5.8 and 2.7 ± 3.5 ms/mmHg for the index α at rest and during tilt, respectively, and 3.2 ± 4.5 ms/mmHg for BRS. Mean variations and SD are of the same order of magnitude as those hypothesized for the calculation of the size of the group (i.e., 3 ± 3.1 ms/mmHg).

Autonomic profile. Plasma catecholamine levels, hemodynamic parameters, and heart rate variability data obtained before and after surgery are shown in Table 3. No significant differences in the hemodynamic parameters or in plasma noradrenaline and epinephrine levels were found before and after surgery. Variance of SAP was found to be decreased postoperatively, both at rest and during tilt (P < 0.02).

At rest, patients’ cardiovascular autonomic profile was remarkably modified by CEA. Indeed, LFRR nu and LF/HF significantly (P < 0.02) decreased, HFRR increased, and LFSAP declined (Table 3).

Before surgery, tilt test induced no significant changes in LF/HF, LFRR nu, HFRR, and LFSAP compared with baseline. After surgery, tilt significantly (P < 0.02) increased LF/HF and LFRR nu, decreased HFRR, and enhanced LFSAP compared with rest (Table 3).

Figure 2 shows the effects of tilt on the indexes of cardiovascular autonomic control before and after CEA. Cardiac sympathetic activity, as assessed by LFRR nu and LF/HF, and sympathetic activity directed to vessels, as assessed by LFSAP, increased.
CARDIAC VAGAL PREDOMINANCE (INCREASED HFRR) AND REDUCED CARDIAC (DECREASED LFRR NU AND LF/HF) AND VASCULAR (DECREASED LFSAP) SYMPATHETIC ACTIVITY AT REST. IN ADDITION, 4 MO AFTER CEA AFTER CAROTID ENDARTERECTOMY

DISCUSSION

The results of the present study indicate that CEA induced profound modifications of carotid baroreflex function and of cardiovascular autonomic control in patients with unilateral carotid stenosis. Indeed, arterial baroreceptor sensitivity increased, as indicated by the significant enhancement of both BRS and index α, and the patients’ autonomic profile was shifted toward a cardiac vagal predominance (increased HFRR) and reduced cardiac (decreased LFRR nu and LF/HF) and vascular (decreased LFSAP) sympathetic activity at rest. In addition, 4 mo after CEA the ability to increase the sympathetic drive to the heart and the vessels in response to the tilt test was restored. Over the short period of recording (20 min at rest and 15 min during tilt), variance of SAP was decreased after CEA.

Arterial baroreflex sensitivity before and after CEA. In keeping with previous investigations (1, 15, 18, 20, 33, 50), the patients with carotid atherosclerosis and unilateral critical stenosis in the present study were characterized by a depressed baroreflex function and overall increased sympathetic cardiovascular activity, probably due to abnormalities resulting from impaired baroreceptor afferents of the diseased area, despite the presumed integrity of the other baroreceptor regions and of the sympathetic efferent pathways (1, 15).

Importantly, a reduced arterial baroreflex sensitivity value similar to that observed in the population of our study before CEA was found to be an independent risk factor for increased cardiac mortality (8, 25–27, 31) and the onset of life-threatening arrhythmias (8, 16, 25, 26). Therefore, our results reporting an improved arterial baroreflex sensitivity after CEA suggest that carotid surgery might contribute to reducing the cardiovascular risk in these patients. An additional mechanism underlying the favorable effect on the clinical outcome is the expected long-term reduction of blood pressure variability induced by the increase of baroreflex efficiency (22, 49). In the present study the finding of an increased arterial baroreflex sensitivity after surgery may result from the reinnervation of carotid baroreceptor areas. As observed in animal studies (4), the reinnervation process is characterized by a week-based time course. A suitable period of recovery after CEA is likely to be necessary to make the effects of the neural baroreceptor reinnervation perceivable. In this context, we reasoned that a 4-mo recovery time seemed optimal to plan a baroreflex functioning follow-up. Previous heterogeneous studies have described decreased arterial baroreceptor sensitivity after CEA in the intraoperative (47) or early postsurgical (9, 19, 35) phases and either improved (18) or decreased (35) baroreceptor sensitivity in the long-term period. We hypothesize that such diverging findings might have been overcome in the present investigation by 1) increasing the homogeneity of the studied group, focusing on patients with unilateral stenosis and a narrow range of age (60–80 yr) undergoing the same endarterectomy technique, 2) including in the present study patients without significant comorbidities or

![Fig. 2. Changes of cardiovascular sympathetic indexes induced by tilt. Rest-tilt changes (Δ) of low-frequency R-R interval (LFRR) power expressed in normalized units (nu) (top), low-frequency systolic arterial pressure (LFSAP) power (middle), and low frequency-to-high frequency ratio (LFHF; bottom) before and after CEA are shown. *All 3 indexes significantly increased after CEA.](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00078.2013)
therapies known to interfere with autonomic control, and 3) choosing a follow-up period of 4 mo in order to allow a baroreceptor functional recovery (4), avoiding the situation that aging and atherosclerotic progression could act as confounders.

Of interest, the two patients who did not show an improvement of BRS and index α after CEA (see Fig. 1) showed signs of mild orthostatic hypotension, characterized by a SAP drop of 15 and 25 mmHg during tilt. This may suggest the existence of a structural dysautonomia leading to impairment of blood pressure control during orthostasis in these patients.

Future studies should address the issue of comparing different approaches for baroreflex sensitivity estimation based on spontaneous cardiovascular variability. The comparison might be particularly interesting in these patients because of the low values of arterial baroreflex sensitivity found before CEA (28).

Autonomic profile before and after CEA. The results of the present study indicated that before CEA patients with critical unilateral carotid stenosis were characterized by a predominant cardiovascular sympathetic activation and concomitant reduced cardiac vagal activity, as assessed by the high values of LF/HF and LF <i>SAP</i> and reduced HF <i>RR</i>.

Notably, a cardiovascular neural profile characterized by a sympathetic predominance and reduced cardiac vagal tone has been associated with unfavorable pathophysiological changes and adverse clinical outcomes including an increase in coronary vasoconstriction (40), worsening of left ventricular dynamics (7, 16, 17, 45), enhanced electrical instability (5, 51) promoting life-threatening arrhythmias (5, 26, 27, 30), and an overall increased cardiovascular mortality (8, 27, 30).

In our patients with carotid stenosis, the sympathetic activation attending the head-up tilt maneuver (14) was not associated with the expected increase in the spectral indexes of cardiac and vascular sympathetic modulation, LF <i>RR</i> num, LF/HF, and LF <i>SAP</i>, and decrease of HF <i>RR</i> (14, 38). Accordingly, SAP values were slightly reduced during orthostasis compared with supine position. Altered carotid arterial stiffness and local mechanical abnormalities (1, 3, 7) produced by the atherosclerotic plaque may account for the reduced responsiveness of cardiovascular autonomic control during tilt observed in our patients before surgery. Of note, 4 mo after carotid surgery, not only did the index of cardiac vagal activity HF <i>RR</i> increase but also the effects of sympathetic excitation and of vagal withdrawal induced by tilt were restored, as indicated by a significant enhancement of LF <i>RR</i> num, LF/HF, and LF <i>SAP</i> and decrease in HF <i>RR</i>.

Finally, we could not measure any relevant effect of the CEA procedure on plasma norepinephrine, which slightly increased during tilt both before and after surgery. However, norepinephrine may not reflect overall sympathetic activity, since its plasma concentration is likely to be influenced not only by its spillover into the blood but also by its systemic clearance (10) and norepinephrine transporter efficiency (41, 46).

Notably, the observed changes in the spectral indexes of cardiovascular sympathovagal activity were not attended by concomitant modifications in the mean values of heart rate and SAP. This is not surprising. In several physiological and pathologic conditions a similar pattern was previously observed. For example, at awakening patients with mild hypertension showed increased LF <i>SAP</i> without modifications in mean SAP values compared with nighttime (12). In healthy subjects, neurally mediated syncope was characterized by a remarkable change of spectral indexes of cardiac sympathovagal balance in the absence of modifications in RR (13). Taken together, these data suggest that a modification in the cardiovascular autonomic profile may not necessarily result in a change of RR and SAP. Future studies are needed to address the issue of causality between RR and SAP variability before and after CEA to better understand the SAP-RR relationship and verify whether the strength of the link improves as suggested by coherence analysis (39).

Perspectives and Significance

We found an improvement of arterial baroreflex sensitivity and of cardiovascular neural regulation in response to the tilt test 4 mo after CEA. Given that low baroreflex sensitivity is an independent risk factor for increased cardiovascular mortality and morbidity such as life-threatening arrhythmias (16, 25, 42, 44), we hypothesize that the improvement of arterial baroreflex sensitivity obtained 4 mo after CEA might contribute to account for the better prognosis previously observed in patients who underwent CEA (37). In addition, the restoration of arterial baroreflex sensitivity might determine a reduced SAP liability in the long-term period, which in turn would lead to lowered morbidity and mortality (22, 23, 49).

Our findings of a reduced SAP variance 4 mo after CEA support this hypothesis, although further follow-up on a larger number of patients is needed.

ACKNOWLEDGMENTS

We thank the patients who agreed to undergo such a demanding protocol.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


