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**LONGTERM PERIPHERAL BAROREFLEX AND CHEMOREFLEX FUNCTION
AFTER
BILATERAL EVERSION CAROTID ENDARTERECTOMY**

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INTRODUCTION

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Carotid endarterectomy (CEA) is the treatment of choice for the prevention of stroke in patients affected with symptomatic and/or high-grade carotid stenosis ^{1,2,3}. However, controversies persist regarding the optimal surgical technique to reduce perioperative complications and improve clinical outcome.

The “eversion” CEA (e-CEA) was originally described in 1959 ⁴ and involves transection of the distal common carotid artery (CCA) and plaque removal by turning inside out both the internal (ICA) and the external carotid artery (ECA) (Figure 1a). However, this technique may not allow a full visualization of the distal end point of the endarterectomy. As a consequence, its wide acceptance in common surgical practice was reached only 30 years later with the introduction of a modified method ⁵ that entails the transection of the ICA at its origin at the carotid bulb and eversion of the ICA only over the atherosclerotic plaque (Figure 1b). The e-CEA is particularly useful in patients with some elongation with kinking or coiling of the ICA because it allows the correction of arterial redundancy performed by reanastomosing the ICA more proximally to the common carotid artery. Also, it is associated with reduced clamping times and low restenosis rates because sutures are placed at the widest part of the artery, and avoids the use of prosthetic material ¹⁰.

A number of studies, including few randomized trials ^{6,7,8,9,10}, have compared clinical results following e-CEA with those obtained with standard CEA (s-CEA), that is performed through a longitudinal arteriotomy of the ICA (Figure 2). No significant differences were found between the two modalities in terms of perioperative stroke, myocardial infarction or death, early carotid occlusion, local complications and carotid restenosis during follow-up. However, Mehta *et al.*¹¹ reported an increased risk of

postoperative hypertension in patients submitted to e-CEA compared to those operated on with the s-CEA technique. The Authors attributed such phenomenon to a possible direct iatrogenic damage to the carotid sinus fibers occurring during dissection and exposure of the proximal ICA at the bulb and its oblique circumferential incision. Notably, postoperative hemodynamic instability in patients undergoing CEA is associated with increased cardiovascular morbidity and mortality ^{12,13}.

The long-term effect of e-CEA on carotid baroreceptors (CB) and on peripheral chemoreceptors (PC) located in the carotid bodies in close proximity to the former has never been previously investigated. Interestingly, recent studies on patients with histologically demonstrated complete carotid sinus denervation as a result of bilateral carotid body tumor resection (bCBTR), showed that in humans, in contrast to what observed in experimental models, the lack of CB is not completely compensated by aortic and cardiopulmonary baroreceptors ¹⁴. In particular, CB denervation results in a persistent decrease in vagal and sympathetic baroreflex sensitivity and an increase in blood pressure variability ¹⁵. These findings have practical implications also because reduced baroreceptors sensitivity has a prognostic relevance being associated with the occurrence of ventricular arrhythmias and sudden cardiac death in patients with myocardial infarction ¹⁶. Furthermore, bCBTR was found to be associated with a peripheral chemoreflex failure that entails the abolition of the ventilatory response to hypoxia ¹⁵.

The aim of this study is to assess the long-term effect of e-CEA on arterial baroreflex and peripheral chemoreflex function in humans, as assessed in patients submitted to bilateral e-CEA to eliminate the background noise from contralateral

carotid sinus fibers. Also, we will investigate whether such patients may represent a human model of carotid sinus denervation.

FIGURE 1a. The original eversion carotid endarterectomy.

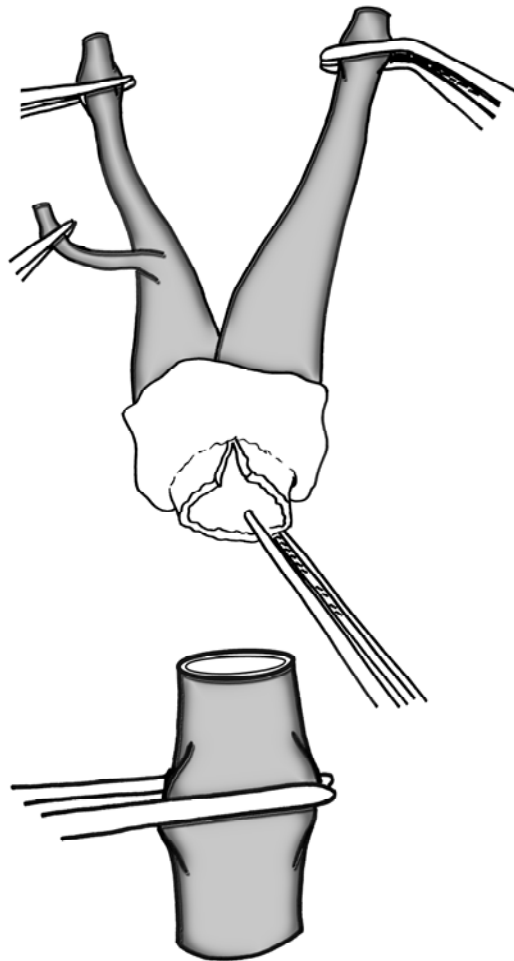


FIGURE 1b. The modified version of eversion carotid endarterectomy employed in the study.

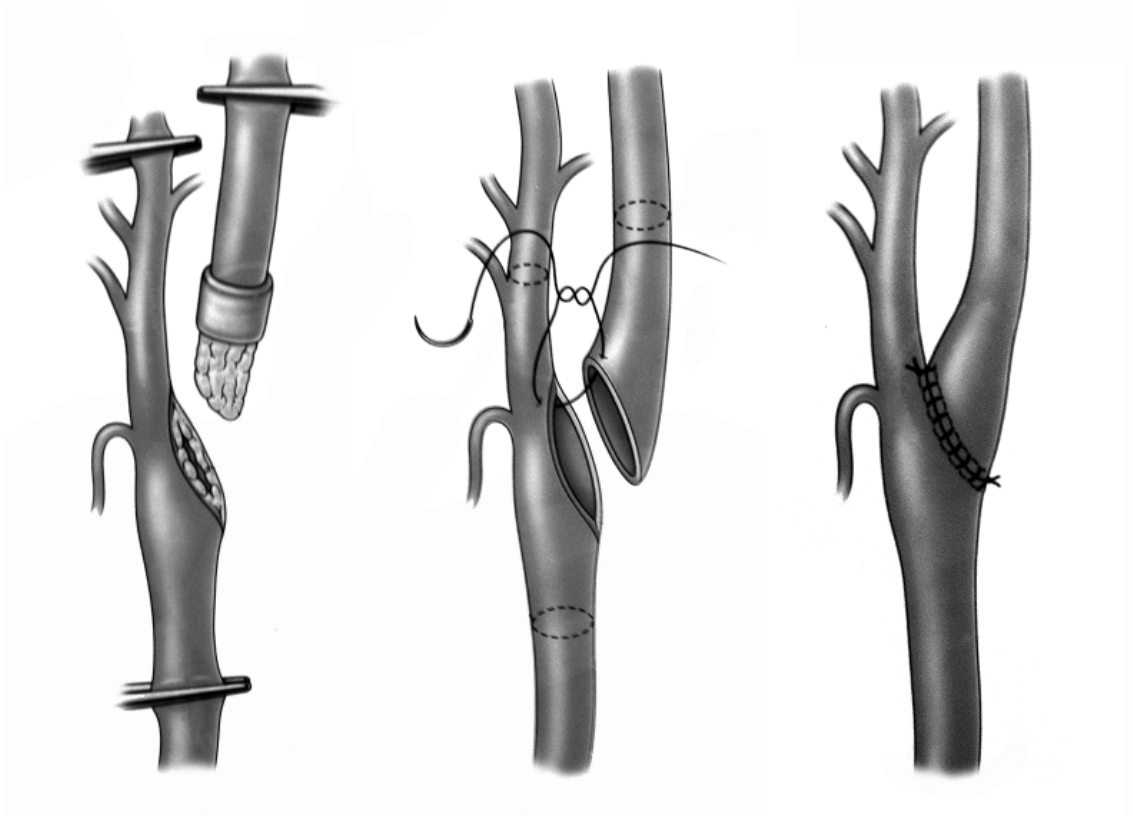
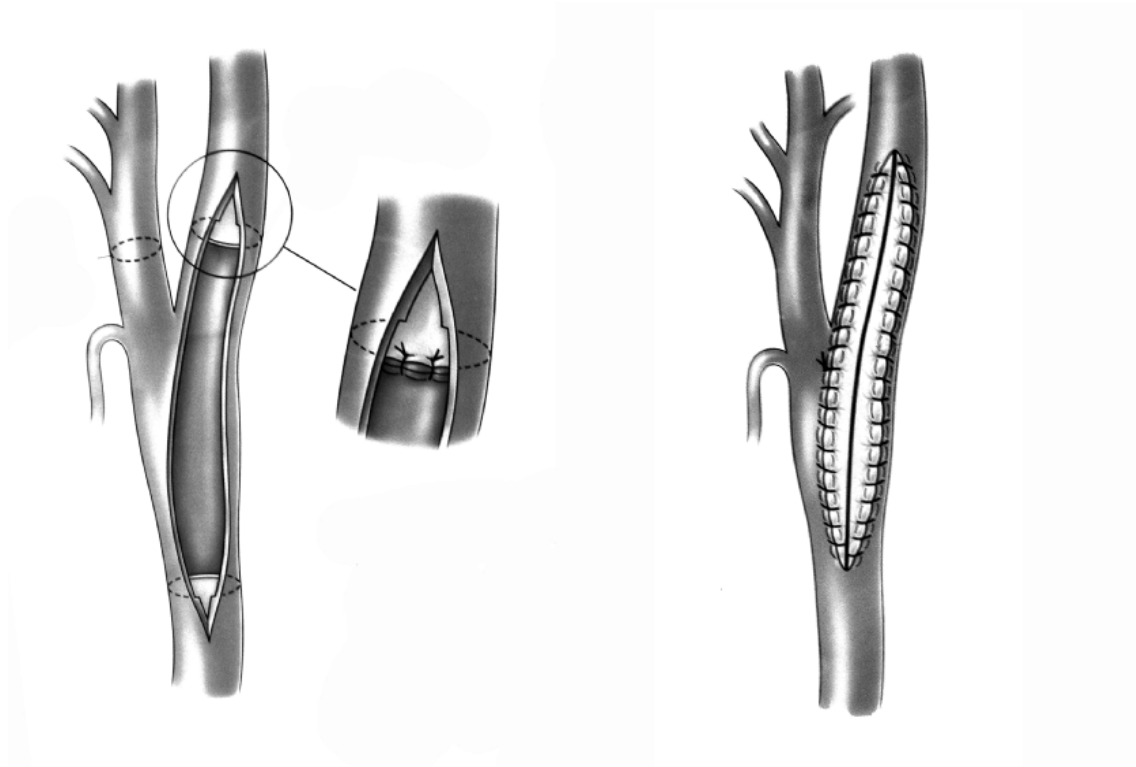


FIGURE 2. The standard technique for carotid endarterectomy with patch angioplasty.



METHODS

METHODS

A retrospective review was conducted on a prospectively compiled computerized database of 3128 CEAs performed on 2617 patients at our Center between January 2001 and March 2006. During this period, a total of 292 patients who had bilateral carotid stenosis $\geq 70\%$ at the time of the first admission underwent staged bilateral CEAs. Of these, 93 patients had staged bilateral e-CEAs, 126 staged bilateral s-CEAs and 73 had different procedures on each carotid.

CEAs were performed with either the eversion or the standard technique with routine Dacron patching in all cases regardless of ICA diameter. Preoperative diagnostic work-up and anesthetic and surgical management were previously described in detail¹⁷.

The study inclusion criteria were bilateral CEA with the same technique on both sides and an uneventful postoperative course after both procedures. Exclusion criteria were: age >70 years, diabetes mellitus, chronic pulmonary disease, symptomatic ischemic cardiac disease or medical therapy with b-blockers, cardiac arrhythmia, permanent neurologic deficits or an abnormal preoperative cerebral CT scan, carotid restenosis and previous neck or chest surgery or irradiation.

Perioperative systolic blood pressure (SBP) and heart rate (HR) values up to 24 hours after surgery were retrospectively collected by means of charts review. Quantification of hemodynamic variability was calculated according to Sternbach *et al.*¹⁸ as a fraction of the preoperative baseline value and expressed as a percentage according to the following equation: $(\text{HR or SBP max} - \text{HR or SBP min}) / \text{HR or SBP baseline} \times 100$.

Selected patients were divided in two groups based on operative technique, i.e. bilateral e-CEA or bilateral s-CEA, and underwent noninvasive assessment of

baroreflex and chemoreflex function after discontinuation of antihypertensive medication and restrain from smoking and from alcohol and caffeine assumption for 48 hours. Young and aged-matched healthy subjects were also recruited and submitted to the same tests under the same conditions to provide reference values for comparison with patients. Health was judged by standard clinical evaluation, *ad hoc* carotid duplex scanning, EKG and medical history.

Internal Review Board approval and patients informed consent were obtained.

Surgical technique¹¹

In the s-CEA, after systemic heparinization, the common (CCA), external (ECA), and internal ICA carotid arteries are clamped and a longitudinal arteriotomy is made in the CCA and extended to the ICA, distal to the end of the atherosclerotic plaque. The endarterectomy is then performed, followed by distal intimal endpoint tacking sutures whenever indicated, and closure of the arteriotomy using a synthetic or biological patch. In the e-CEA, the CCA, ECA, and ICA are exposed as in the standard technique. However, the proximal ICA at the carotid bifurcation is mobilized circumferentially to facilitate its transection from the CCA at the carotid bulb. During this approach, carotid sinus nerve fibers derived from the glossopharyngeal nerve and innervating the carotid body within the adventitia of the proximal ICA are divided. After systemic heparinization and clamping of the carotid vessels, the ICA is obliquely transected at the carotid bulb and everted over the atherosclerotic plaque. After completion of the endarterectomy, the everted ICA is brought down to its normal anatomic position and reanastomosed to the distal CCA or more proximally in case of kinking or coiling of the ICA.

Cardiovascular reflex tests

Heart rate reflexes occur within seconds of a perturbation, and beat-to-beat heart rate analysis comes from analysis of EKG. Standard precordial placements of the recording electrodes were used. Patients were assessed by 4 tests: Lying-to-standing (LS) Orthostatic hypotension (OH) Deep breathing (DB), and Valsalva Maneuver (VM). Investigations were performed in a room with an ambient temperature of 22°C to 24°C.

Lying-to-standing. Studying the heart rate changes to standing (30:15 ratio was calculated dividing R-R interval at the 30th beat by the R-R interval at the 15th beat) is indicated in testing the integrity of parasympathetic cholinergic cardiovagal function. In to gravitational changes from upright posture, standing induces an exercise reflex and mechanical squeeze on both venous capacitance and arterial resistance vessels. These changes stimulate the baroreceptors, and there ensues a pronounced neurally mediated reflex, which decreases sympathetic outflow, releases vasoconstrictor tone, decreases total peripheral resistance by up to 40% and drops blood pressure by up to 20 mmHg. These changes last 6-8 s.

Orthostatic hypotension. Studying blood pressure changes to standing is indicated in testing the integrity of the sympathetic adrenergic function. Orthostatic hypotension is a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure. Blood pressure was measured with the patient supine, and after at 30, 60, 90, 120 and 180 s after standing following 3 min of recumbency.

Deep breathing. Studying heart rate variation with respirations is indicated in testing the integrity of the parasympathetic cholinergic (cardiovagal) function. Inspiration increases heart rate, and expiration decreases it. The patient breathed deeply at six

breaths per min for 1 min, while the heart rate was recorded by EKG. The maximum and minimum R-R intervals during each breathing cycle were measured and converted to beats per min. Each test was repeated three times and the mean value was calculated. The mean difference between maximum and minimum heart rate was calculated.

Valsalva maneuver. Testing heart rate changes during the Valsalva maneuver (Valsalva ratio) is indicated in testing the integrity of parasympathetic cholinergic function. The patient blew through a mouthpiece attached to a manometer, maintaining 40 mmHg pressure for 15 s under continuous EKG monitoring. The Valsalva ratio was calculated dividing the longest R-R interval after strain release by the shortest R-R interval during the strain period.

Spectral analysis of heart rate and blood pressure variability

Cardiovascular signals were acquired by a Micromed Myoquick SystemPLUS 4 channel digital polygraph (Micromed s.r.l., Mogliano Veneto (TV), Italy). EKG was recorded with two electrodes placed on the patient's thorax, breathing pattern (PNG) was recorded by a piezoelectric thoracometer and finger arterial blood pressure (BP) was continuously monitored by a Ohmeda Finapres 2300 system (model 5, TNO-BioMedical Instrumentation, Ohmeda, Englewood (CO), USA) connected to the Micromed system. For each patient, EKG, PNG and BP were concurrently recorded during two different epochs: (1) resting (e.g. the patient lying horizontal on a bed); (2) standing (e.g. the patient changed to the orthostatic position). Each epoch lasted at least 5 min.

Acquisition parameters were Band pass prefilter: 0.7-70 Hz (EKG channel), DC-70 Hz (PNG and BP channels), sampling frequency: 256 Hz, coding: 12 bits.

A purposely-developed software (Heartscope, ver.1.6, A.M.P.S. llc, New York, USA) was used to identify the peak of R wave on EKG, the systolic arterial blood pressure (SAP), bursts of Muscle Sympathetic Nerve Activity (MSNA), and respiratory rate (RESP). The software constructs automatically time series of RR intervals, SAP, MSNA and RESP, with low operator-analysis interaction. Spontaneous variability of RR interval, SAP, MSNA and RESP were characterized by means of power spectral analysis using an autoregressive algorithm on all recorded parameters¹⁹. In short, from beat-to-beat variability series of adequate length and stationarity (usually 250-350 beats), the software calculated simple statistics and the best autoregressive estimate of the power spectral density. The powers and frequencies of the low (0.03-0.14 Hz) and the high (0.15-0.5 Hz) frequency spectral components (LF and HF, respectively), expressed in normalized units, were computed as the percent ratio of the absolute power of either HF or LF to the total power, less the Very Low Frequency (VLF) component, according to the following formula $P_{LF[nu]} = [(P_{LF[ms]}^2) / (VAR_{RR[ms]}^2 - V_{LF[ms]}^2)] \times 100$, where $P_{LF[nu]}$ = LF powers in normalized unit; VAR = tot variance; and VLF = very low frequency component < 0.03 Hz; similar normalization was performed for HF powers. LF/HF of RR interval variability power ratio was also computed²⁰. The total power (TP) of RR and SAP variabilities were also calculated¹⁹.

Cross spectral analysis was used to determine whether there was a stable relationship between RR and SAP series (significance coherence > 0.5). Cross-spectral analysis was performed by means of bivariate autoregressive identification²¹ and was used to compute a squared coherence function, K^2 and phase relationship, Ph. K^2 was defined as the square cross-spectrum amplitude normalized by the product of the spectra of the two signals. Ph was defined as the phase of the cross-spectrum. K^2 is a measure

of the statistical link between RR and SAP series at any given frequency and ranges between 1 (perfect correlation) and 0 (perfect uncorrelation). Ph is a measure of the phase shift between two oscillations at the same frequency detected in both RR and SAP series (negative values indicate that RR series lags behind SAP series at that specific frequency). In this study, coherence values 0.5 were considered significant²². LFK² and HFK² were derived as the maximum of K² inside the LF and HF bands, respectively. LFPPh and HFPPh were defined as the phase in correspondence of LFK² and HFK², respectively.

The baroreflex gain was evaluated on the SAP and RR spontaneous variabilities. The following methods were used: 1) the sequence method that evaluates in the plane (RR, SAP) the gain of short spontaneous sequences characterized by simultaneous increase or decrease of both variables (indicated as BRS in the following); 2) the spectral method that calculates the baroreflex sensitivity as the average of the sum of the squared root of the ratio between the RR and SAP powers in both the LF and the HF bands (indicated as α index)²³; 3) the XAR method, that is the exogenous autoregressive causal linear parametric model²⁴; 4) the gains of the autoregressive transfer function between RR and SAP variabilities, computed at LF and HF. This computation provides critical values describing the stability of the SAP-RR relationship, as squared coherence (K²) and phase (Ph). LFPPh is usually more negative (i.e. SAP precedes RR) than HFPPh²³.

Reference groups (Table 1) of young healthy subjects (young controls, n=15, age 33±6, Body Mass Index=22.88±2.95 Kg/m²) and aged healthy subjects (old controls, n=21, age 66±10, Body Mass Index= 27.65±5.32 Kg/m²) were also recruited and

submitted to the same tests under the same conditions to provide reference values for comparison with patients.

Statistical analysis:

Significance of differences was estimated with GLM Mixed Model, with post hoc contrasts. Additional tests included, as appropriate, 1W ANOVA and T-test. Computations were performed with a commercial statistical package SPSS/PC+ 13.0 (SPSS Inc, Chicago, Ill) for Windows (Microsoft, Redmond, Wash).

Peripheral chemoreflex function

The ventilatory response to oxygen is the measurement of the increase or decrease in the minute ventilation (\dot{V}_E) caused by breathing various concentrations of oxygen under isocapnic conditions ($\text{PaCO}_2 = 40 \text{ mmHg}$). The change in ventilation may be recorded in relation to changes in PaO_2 or haemoglobin oxygen saturation as monitored by pulse oximetry. This test investigates peripheral chemoreflex sensitivity which may be altered in a number of conditions and may be associated with a selective potentiation of autonomic and hemodynamic responses.

The ventilatory response to hypoxia was assessed in 21 patients at least 3 months after undergoing carotid artery endarterectomy by patch (n=10) or eversion (n=11) technique. The control group consisted of 12 healthy volunteers. Classic rebreathing tests were performed at sea level at 21°C and 60% relative humidity. The subjects were asked to refrain from smoking and drinking caffeinated beverages for at least 2 h before the experiment. The ventilatory response to decreasing concentrations of oxygen under isocapnic conditions was measured using an open circuit technique. The subjects were seated comfortably breathing through pneumotachograph and non-rebreathing valve

(Hans Rudolph) connected to a 50 l Douglas bag containing a gas mixture of 23% oxygen, 4% carbon dioxide and balance nitrogen regulated by separate rotameters. Tidal volume, breathing frequency, fractional inspired and end-tidal concentrations of oxygen and carbon dioxide were monitored breath by breath using a metabolic cart (Vmax, Sensor Medics, Yorba Linda California, USA). Oxygen saturation was continuously monitored via a pulse oximeter (9600 Nonin, Philadelphia, USA) connected to the metabolic cart via an analog/digital interface permitting a breath by breath record of oxygen saturation and heart rate. After allowing the subjects to reach a steady state, baseline measurements were taken followed by a standard step test was performed. Stepwise decrements in oxygen concentrations (from 20% to 10%) were performed allowing the subjects to reach steady state at every concentration. Carbon dioxide was added as necessary in order to maintain a steady end-tidal carbon dioxide concentration. The chemoreflex sensitivity to hypoxia was obtained from the slopes of the linear regression of minute ventilation vs S_{aO_2} .

RESULTS

RESULTS

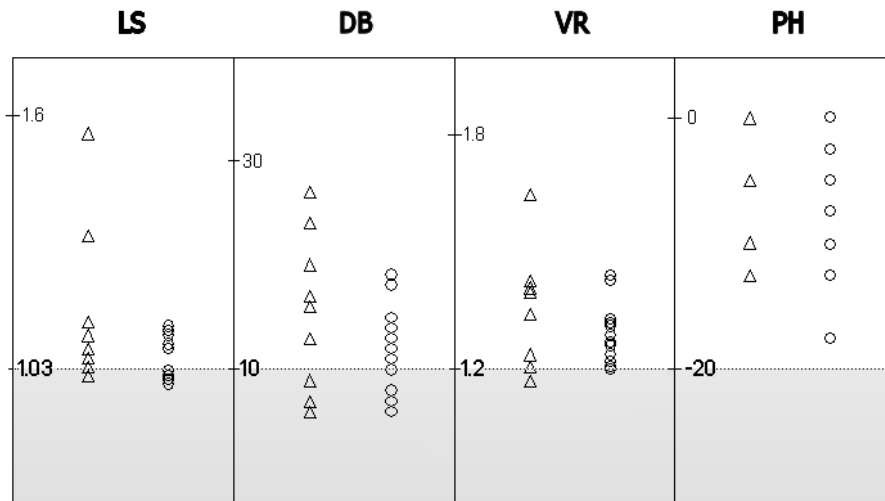
A total of 29 patients (16 males, age 62.4 ± 8.0 years) were enrolled. Twenty-eight were studied retrospectively and one was evaluated prospectively and longitudinally. Overall, 13 patients had undergone bilateral e-CEA (44.8%) and 16 bilateral s-CEA (55.2%) with a mean interval between the procedures of 62 ± 56 days. Hemodynamic variability was not different between the groups (HR variability (%): 30.7 ± 16.8 vs 25.4 ± 16.9 , $p=0.4$; SBP variability (%): 36.2 ± 13.5 vs 30.6 ± 13.7 , $p=0.3$).

After a mean interval of 24 ± 17 months from the last CEA, sixteen patients (55.2%) completed both baroreflex and chemoreflex function tests. Thirteen patients (44.8%), due to lack of compliance or fatigue, underwent only either baroreflex ($n=8$) or chemoreflex function evaluation ($n=5$).

Cardiovascular reflex tests

No patient showed signs or symptoms of autonomic dysfunction, including labile hypertension, tachycardia, palpitations, headache, inappropriate diaphoresis, pallor or flushing. The results of standard cardiovascular autonomic test are shown in Figure 3. Among the e-CEA patients, 3 had a DB pathologic test, whereas in the s-CEA group, 5 had a DB pathologic test, and only one of them had also a pathologic LS test. Overall, 8 patients had a DB test below normal values, but all of them were older than 50 years, and had a VR within normal limits. Hence, the DB results must be considered biased by the patients age. In conclusion, our results showed no evidence of autonomic dysfunction in any of the enrolled patients.

FIGURE 3. Results of standard cardiovascular autonomic test in the e-CEA (Δ) and in the s-CEA (o) groups. Normal values for each test are represented on white background.



LS, Lying-to-Standing; **DB**, Deep Breathing; **VR**, Valsalva Ratio; **PH**, Postural (Orthostatic) Hypotension.

Spectral analysis of heart rate and blood pressure variability

Rest

Table 2A provides summary data on short term cardiovascular variabilities. Monovariate data showed marked, and expected, differences between young and old controls in absolute values of RR variability such as $RR\sigma^2$, and, as a corollary, absolute powers of LF_{RR} and HF_{RR} . No difference was observed in normalized powers of RR variability. Old controls and patients did not differ.

Systolic arterial pressure was greater in old controls, as compared to young controls, but, again, patients did not differ from old controls. Likewise (Table 2B) bivariate data expressing different aspects of spontaneous baroreflex regulations of heart period, demonstrated a marked age related impairment, as documented by reductions in the frequency domain α index, in the time domain BRS and in model derived XAR, as well as in the LF and HF gains. Notably, within the obvious reduction in baroreflex functions observed in patients, a slight, but significantly higher value was observed in e-CEA, as compared to s-CEA.

Regarding differences between groups on bivariate parameters, a depressed K^2 function, both at LF and HF, should be pointed out in all controls (similar to patients) as compared to young controls.

Active Stand

As expected, in young and old controls standing up was associated to reduced RR and to a shift of the RR spectral profile in favor of the LF component. Likewise, an increase was also observed in LF_{SAP} . Overall these changes suggest sympathetic activation.

SAP remained unchanged and, notably, was not reduced upon standing in patients, who, however, did not manifest. Significant increases in spectral markers of sympathetic excitation (Fig. R1) of note is that, also in standing (Table 3B) residual baroreflex performance appeared better maintained in e-CEA (as suggested by greater values of BRS and LF gain). Also in standing K^2 tended to be more elevated in young controls.

Peripheral chemoreflex function

The control group was slightly younger than the patch group (mean age 46.4 ± 18.3 years compared with 54.6 ± 11.7 and 61.8 ± 8.2 for the eversion and patch groups respectively, ($P=0.03$ compared with patch, oneway ANOVA with LSD correction for multiple comparisons). There was also a male predominance in the control group (males =10) compared with both patch (n=7) and eversion (n=5).

In all subjects ventilation (\dot{V}_E) and oximetry data fitted a linear regression model with r values > 0.8 . Oneway analysis of variance showed a significantly higher slope both for $\Delta V_E/\Delta SaO_2$ in controls compared with both patient groups which were not different from each other (-1.37 ± 0.33 compared with -0.33 ± 0.08 and -0.29 ± 0.13 l/min/%SaO₂, $p<0.05$, Fig.). Similar results were observed for and $\Delta V_E/\Delta PetO_2$ (-0.20 ± 0.1 versus -0.01 ± 0.0 and -0.07 ± 0.02 l/min/mmHg, $p<0.05$).

A regression model using treatment, age, baseline FiCO₂ and minimum SaO₂ achieved showed only treatment as a significant factor in explaining the variance in minute ventilation ($R^2= 25\%$).

FIGURE 4. Slopes of the linear regression of minute ventilation vs Sao2%.

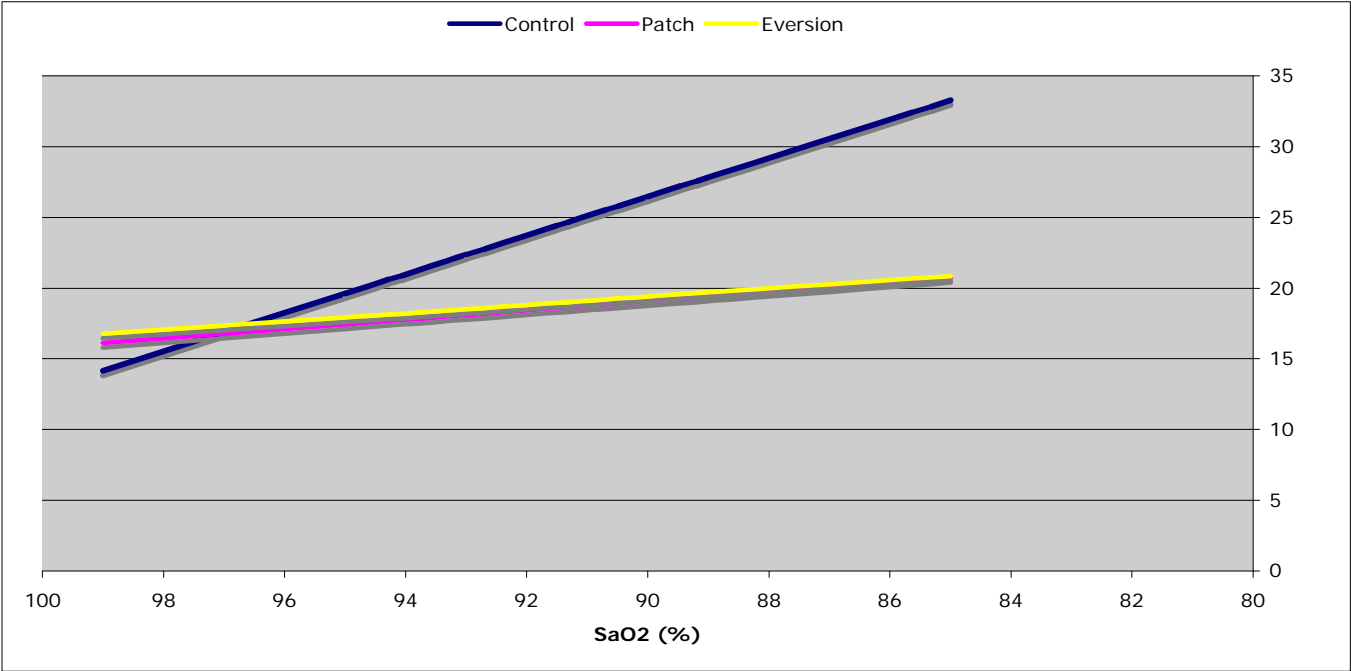
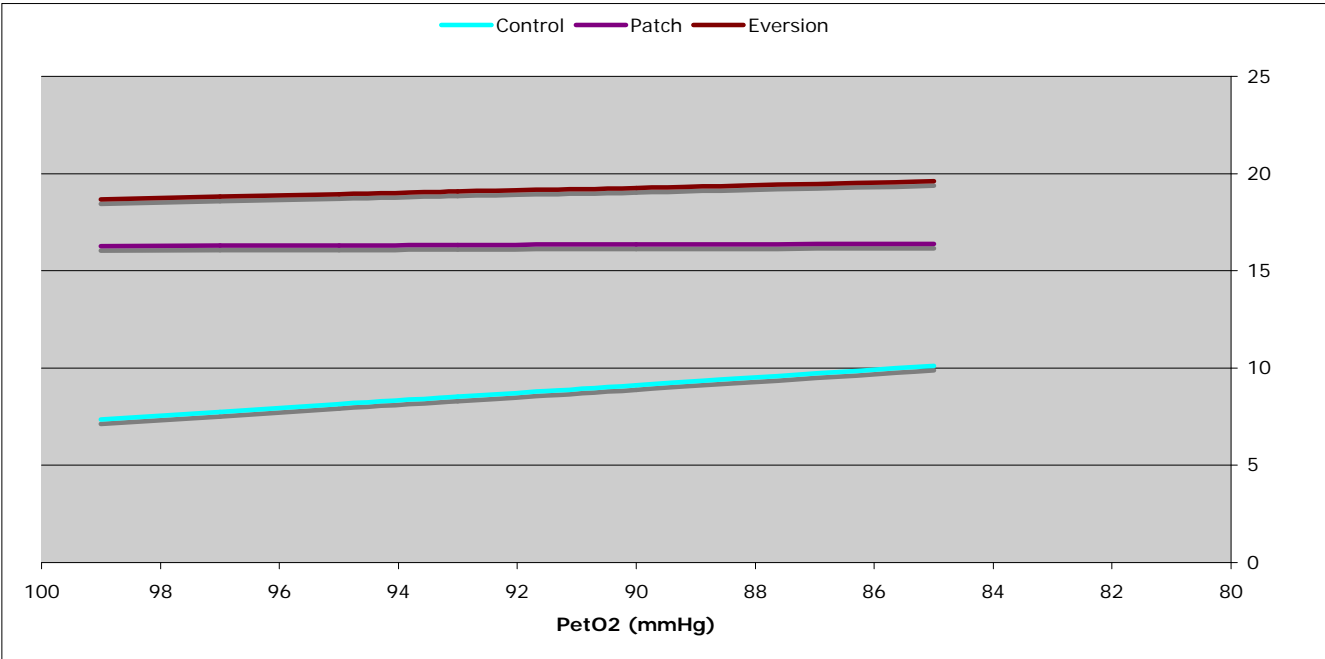


FIGURE 5. Slopes of the linear regression of minute ventilation vs PetO2 mmHg.



DISCUSSION

Discussion

Baroreflex and chemoreflex mechanisms play an important part in the dynamic adjustments of circulation and ventilation. Carotid sinus baroreceptors lie in close proximity to the peripheral chemoreceptors of the carotid bodies, and the afferent signals from the former and the latter travel up the carotid sinus nerve to join with the glossopharyngeal nerve towards the brainstem ¹⁵.

In the late 1920s, Hering and Koch were the first to recognize the reflex nature of changes in heart rate and blood pressure evoked by external massage of the neck ¹⁵. The afferents were tracked as nerve endings at the carotid bifurcation ^{25,26}. The arterial baroreflex buffers abrupt transients of blood pressure and originates from stretch sensitive receptors in the arterial wall of the carotid sinus and the aortic arch and large vessels of the thorax ^{27,28}. Afferent fibers from carotid sinus baroreceptors join the glossopharyngeal nerve (ninth cranial nerve) and project to the nucleus tractus solitarius in the dorsal medulla, which in turn projects to efferent cardiovascular neurones in the medulla. In addition to carotid baroreceptors, stretch-sensitive baroreceptors are also located in the aortic arch, heart and large pulmonary vessels. The extra-carotid baroreceptors transmit their afferent information along with the vagal nerves to the same brain stem nuclei. The efferent limbs of the baroreflex loop consist of sympathetic and parasympathetic fibres to the heart as well as to blood vessels.

Adjustment of respiration in response to alterations in levels of oxygen, carbon dioxide and hydrogen ions in the body fluids are mediated by a complex interplay between central and peripheral chemoreceptors ^{15,29}. The peripheral arterial chemoreceptors, located in the carotid and aortic bodies, are responsible for the immediate ventilatory and arterial pressure increments during acute hypoxia. Apart

from hypoxaemia, peripheral chemoreceptors play a minor role in the sensing of changes in arterial carbon dioxide tension (PCO_2) and pH. Carotid and aortic bodies are supplied with sensory fibres, which course through carotid sinus/glossopharyngeal and vagus nerve respectively towards medullary centres, including the nucleus tractus solitarius³⁰ Central chemoreceptive areas located at the rostral ventrolateral medulla respond to changes in the hydrogen ion concentration in the interstitial fluid in the brain and are chiefly responsible for ventilatory and circulatory adjustments during hypercapnia and chronic disturbances of acid–base balance.

Chronic failure of the baroreflex due to bilateral carotid denervation was firstly described in 1993 as a separate clinical syndrome, characterized by a limited blood pressure buffering capacity against excessive rises or falls in response to emotional and physical stimuli³¹. The underlying causes of baroreflex failure included the familial paraganglioma syndrome, neck surgery or radiation therapy for pharyngeal carcinoma, bilateral lesions of the nucleus tractus solitarius, and surgical section of the glossopharyngeal nerves; in two patients the cause was unknown³¹. Symptoms and signs included headache, palpitations, diaphoresis and pale flushing. They bear a strong resemblance to those of a pheochromocytoma. In baroreflex failure, disinhibition of central activation of efferent sympathetic pathways arises from the absence of tonic inhibitory baroreceptor input to the vasomotor centres of the brainstem³². Apart from volatile hypertension, which is most common, baroreflex failure has a broad spectrum of other clinical presentations including predominant hypotension, orthostatic tachycardia and intolerance and malignant vagotonia with severe bradycardia, depending on the extent of baroreceptor denervation and concomitant destruction of

autonomic structures^{33,34}. Centrally acting sympatholytic agents like clonidine may reduce the frequency and severity of the attacks.

Bilateral denervation or removal of carotid body chemoreceptors mainly derived from studies in small numbers of patients who underwent bilateral resection of healthy carotid bodies as an experimental treatment of bronchial asthma or chronic obstructive pulmonary disease³⁵. All the observations obtained in these settings, however, are in fact biased by the possible confounding chronic pulmonary disease, which itself alters chemoreflex function³⁶. More recently, peripheral chemoreflex function was eventually assessed in patients who had undergone bilateral carotid body tumour resection and were free of pulmonary disease³⁷.

Overall, peripheral chemoreflex failure was found to cause a permanent abolition of ventilatory responsiveness to hypoxia under normocapnic conditions. A small residual hypoxic response may be present during simultaneous hypercapnia. In addition, the condition causes a 20–30% decrease in CO₂ sensitivity. Long-term resting hypoventilation and hypercapnia may occur. The impairment of chemoreflex function is less severe following unilateral than after bilateral carotid body resection. These observations emphasize the importance of carotid relative to aortic chemoreceptor function in humans. The aortic bodies have a minor role in the modulation of spontaneous respiratory activity, but may generate a discernible response when their gain is amplified by hypercapnia¹⁵.

Baroreflex and chemoreflex function after CEA have been previously investigated, but the eversion technique has never been addressed. Also, conflicting results have been reported in the literature due to patient selection and methods for

baroreflex testing. Wade et al.³⁸ studied in 8 patients before and after bilateral CEA showing no baroreflex consistent change as a result of surgery. On the other hand, peripheral chemoreflex function, which depends on the integrity of the same afferent innervation as carotid baroreceptors, was markedly impaired by bilateral CEA. In contrast to these findings, Vanmaele et al.³⁹ did not observe any loss of chemoreceptor function after bilateral CEA. As far as unilateral CEA is concerned, Tyden et al.⁴⁰ showed an intraoperative increase in baroreflex sensitivity following removal of the atherosclerotic plaque. Hirschl et al.⁴¹ reported a differential effect of CE on baroreflex function in hyper- and normotensive subjects, with sensitivity increased in hypertensives.

Suggested mechanisms of attenuated baroreflex sensitivity by CEA include trauma to the carotid sinus baroreceptors or to the carotid sinus nerve⁴² and a decrease in wall distensibility due to surgery-induced periarterial fibrosis⁴³. On the other hand, removal of an atherosclerotic plaque may have a beneficial effect on baroreflex function by means of changes in the mechanical properties of the carotid sinus arterial wall and reintegration of baroreceptor areas into circulatory regulation⁴². Another important determinant of the net effect of unilateral CE on functional baroreflex integrity is the compensatory ability of the residual aortic and contralateral carotid baroreceptors. Compensation by residual baroreceptors probably accounts for the fact that severe and acute baroreflex failure resolves within days to weeks in most cases^{31,14}. After unilateral CE, compensation by the contralateral carotid baroreceptors may be limited by atherosclerotic changes of the nonoperated carotid artery. In atherosclerosis, distensibility of the carotid sinus vessel wall and sensitivity of baroreceptors are reduced^{44,45}.

In order to eliminate the background noise from contralateral carotid sinus fibers, in order study we employed a model of bilateral eversion CEA. Even though this was the purpose, it is noteworthy that in our experience patients with bilateral significant carotid stenosis at the time of the first hospital admission and scheduled for staged bilateral CEA account for 11.1% of the total population submitted to CEA ¹⁷. Also, disease progression in contralateral asymptomatic ICAs after CEA is relatively common in patients with a diseased ICA, with a risk at 10 years of undergoing a contralateral CEA of 8.8%. ⁴⁶.

Overall, we demonstrated that bilateral e-CEA does not imply a carotid sinus denervation. All patients were asymptomatic and had a residual baroreflex and chemoreflex function, in contrast to those submitted to bilateral carotid body tumor resection ¹⁴. As a result of some expected degree of iatrogenic damage, such performance was lower than that of controls. Interestingly though, baroreflex performance appeared better maintained in e-CEA than in s-CEA. This may be related to the changes in the elastic properties of the carotid sinus vascular wall, as the patch is more rigid than the endarterectomized carotid wall that remains in the e-CEA. Finally, these data have relevant clinical implication in the assessment and treatment of the frequent hemodynamic disturbances associated with carotid angioplasty stenting ⁴⁷, a procedure that has yet to be demonstrated as safe and effective like CEA.

References

¹ North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effects of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med.* 1991; 325: 445-453.

² Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA.* 1995; 273: 1421-1428.

³ Young B, Moore WS, Robertson JT, Toole JF, Ernst CB, Cohen SN, Broderick JP, Dempsey RJ, Hosking JD. An analysis of perioperative surgical mortality and morbidity in the asymptomatic carotid atherosclerosis study. *Asymptomatic Carotid Atherosclerosis Study. Stroke.* 1996; 12: 2216-2224.

⁴ Crawford ES, DeBakey M, Fields WS, Morris GC Jr, Cooley DA. Surgical considerations in the treatment of cerebral arterial insufficiency; scientific exhibit. *Postgrad Med.* 1959; 26: 227-237.

⁵ Raithel D, Kasprzak PM. The eversion technique for carotid endarterectomy. A new technique. In: Greenhalgh RM, Hollier LH (eds): *Surgery for stroke.* London, UK, WB Saunders, 1993, 183-193.

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- ⁶ Vanmaele RG, Van Schil PE, DeMaeseneer MG, Meese G, Lehert P, Van Look RF. Division-endarterectomy-anastomosis of the internal carotid artery: a prospective randomized comparative study. *Cardiovasc Surg.* 1994; 2: 573-581.
- ⁷ Balzer K, Guds I, Heger J, Jahnel B. Conventional thrombendarterectomy with carotid patch plasty vs. eversion endarterectomy: technique, indications and results. *Zentralbl Chir.* 2000; 125: 228-238.
- ⁸ Ballotta E, Renon L, Da Giau G, Toniato A, Baracchini C, Abbruzzese E, Saladini M, Moscardò P. A prospective randomized study on bilateral carotid endarterectomy: patching versus eversion. *Ann Surg.* 2000; 232: 119-125.
- ⁹ Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A. Carotid endarterectomy with patch closure versus carotid eversion endarterectomy and reimplantation: a prospective randomized study. *Surgery.* 1999; 125: 271-279.
- ¹⁰ Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G, Palombo D, Peinetti F, Spartera C, Stancanelli V, Vecchiati E. Eversion versus conventional carotid endarterectomy: late results of a prospective multicenter randomized trial. *J Vasc Surg.* 2000; 31(1 Pt 1): 19-30.
- ¹¹ Mehta M, Rahmani O, Dietzek AM, Mecenas J, Scher LA, Friedman SG, Safa T, Ohki T, Veith FJ. Eversion technique increases the risk for post-carotid endarterectomy hypertension. *J Vasc Surg.* 2001; 34: 839-845.

-
- ¹² Wong JH, Findlay JM, Suarez-Almazor ME. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. *Neurosurgery*. 1997; 41: 35-41.
- ¹³ Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. *Surgery*. 1980; 88: 575-80.
- ¹⁴ Smit AA, Timmers HJ, Wieling W, Wagenaar M, Marres HA, Lenders JW, van Montfrans GA, Karemaker JM. Long-term effects of carotid sinus denervation on arterial blood pressure in humans. *Circulation*. 2002; 105: 1329-35.
- ¹⁵ Timmers HJ, Wieling W, Karemaker JM, Lenders JW. Denervation of carotid baro- and chemoreceptors in humans. *J Physiol*. 2003; 553(Pt 1):3-11.
- ¹⁶ La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet*. 1998; 351(9101): 478-84.
- ¹⁷ Marrocco-Trischitta MM, Melissano G, Kahlberg A, Setacci F, Abeni D, Chiesa R. Increased incidence of cerebral clamping ischemia during early contralateral carotid endarterectomy. *J Vasc Surg*. 2006; 43: 1155-61.
- ¹⁸ Sternbach Y, Illig KA, Zhang R, Shortell CK, Rhodes JM, Davies MG, et al. Hemodynamic benefits of regional anesthesia for carotid endarterectomy. *J Vasc Surg*. 2002;35:333-9.

-
- ¹⁹ Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. *Circ Res.* 1986; 58:178-193.
- ²⁰ Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension.* 2005; 46:1201-1206.
- ²¹ Cerutti C, Baselli G, Civardi S, Liberati D, Lombardi F, Malliani A, Pagani M. Spectral and cross-spectral analysis of heart rate and arterial blood pressure variability signals. *Comps Biomed Res.* 1986; 19:520-534.
- ²² Rowell LB, O'Leary DS. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol.* 1990; 69:407-418.
- ²³ Pagani M, Somers VK, Furlan R, Dell'Orto S, Conway J, Baselli G, Cerutti S, Sleight P, Malliani A. Changes in Autonomic Regulation Induced by Physical Training in Mild Hypertension. *Hypertension.* 1988; 12:600-610.
- ²⁴ Porta A, Baselli G, Rimoldi O, Malliani A, Pagani M. Assessing baroreflex gain from spontaneous variability in conscious dogs: role of causality and respiration. *Am J Physiol.* 2000; 279:H2558-H2567.

-
- ²⁵ Hering HE. Die Karotissinusreflexe auf Herz und Gefasse. Dresden: Steinkopff, 1927.
- ²⁶ Koch E. Die reflektorische Selbststeuerung des Kreislaufs. Dresden: Steinkopff, 1931.
- ²⁷ Persson PB, Kirchheim HR. In: Persson PB, Kirchheim HR (eds). Baroreceptor reflexes: integrative functions and clinical aspects. Berlin: Springer-Verlag, 1991.
- ²⁸ Eckberg DL, Sleight P. Hypertension. Human baroreflexes in health and disease. Oxford: Clarendon Press, 1992:327-45.
- ²⁹ O'Regan RG & Majcherczyk S. Role of peripheral chemoreceptors and central chemosensitivity in the regulation of respiration and circulation. *J Exp Biol* 1982; 100, 23–40.
- ³⁰ Felder RB & Mifflin SB. Baroreceptor and chemoreceptor afferent processing in the solitary tract nucleus. In *Nucleus of the Solitary Tract*, ed. Barraco IRA, pp. 169–185. 2003 CRC Press, Boca Raton.
- ³¹ Robertson D, Hollister AS, Biaggioni I, Netterville JL, Mosqueda Garcia R, Robertson RM. The diagnosis and treatment of baroreflex failure. *N Engl J Med* 1993; 329,1449–1455.

³² Persson PB. Modulation of cardiovascular control mechanisms and their interaction. *Physiol Rev* 1996; 76, 193–244.

³³ Ketch T, Biaggioni I, Robertson R & Robertson D (). Four faces of baroreflex failure: hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation* 2002; 105, 2518–2523.

³⁴ Jordan J, Shannon JR, Black BK, Costa F, Ertl AC, Furlan R, Biaggioni I, Robertson D. Malignant vagotonia due to selective baroreflex failure. *Hypertension* 1997; 30, 1072–1077.

³⁵ Whipp BJ & Ward SA. Physiologic changes following bilateral carotid-body resection in patients with chronic obstructive pulmonary disease. *Chest* 1992; 101, 656–661.

³⁶ Godfrey S, Edwards RH T, Copland GM, Gross PL Chemosensitivity in normal subjects, athletes, and patients with chronic airways obstruction. *J Appl Physiol* 1971; 30, 193–199.

³⁷ Timmers HJ LM, Karemaker JM, Wieling W, Marres HA, Folgering, HThM, Lenders JW. Baroreflex and chemoreflex function after bilateral carotid body tumor resection. *J Hypertens* 2003; 21, 591–599.

-
- ³⁸ Wade JG, Larson CP, Jr, Hickey RF, Ehrenfeld WK, Severinghaus JW. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. *N Engl J Med* 1970; 282:823–829.
- ³⁹ Vanmaele RG, De Backer WA, Willemsen MJ, Van Schil PE, De Maeseneer MG, Van Look RF, Bosmans EJ. Hypoxic ventilatory response and carotid endarterectomy. *Eur J Vasc Surg* 1992; 6(3):241-4.
- ⁴⁰ Tyden G, Samnegard H, Thulin L, Muhrbeck O. Effect of carotid endarterectomy on baroreflex sensitivity in man. Intraoperative studies. *Acta Chir Scand* 1980; Suppl 500:67–69.
- ⁴¹ Hirschl M, Hirschl MM, Magometchnigg D, Liebisch B, Wagner O, Fux B, Kundi M. Arterial baroreflex sensitivity and blood pressure variabilities before and after carotid surgery. *Klin Wochenschr* 1991; 69:763–768.
- ⁴² Angell James JE, Lumley JS. The effects of carotid endarterectomy on the mechanical properties of the carotid sinus and carotid sinus nerve activity in atherosclerotic patients. *Br J Surg* 1974; 61:805–810.
- ⁴³ French BN, Rewcastle NB. Sequential morphological changes at the site of carotid endarterectomy. *J Neurosurg* 1974; 41:745–754.

-
- ⁴⁴ Randall OS, Esler MD, Bulloch EG, Maisel AS, Ellis CN, Zweifler AJ, Julius S. Relationship of age and blood pressure to baroreflex sensitivity and arterial compliance in man. *Clin Sci Mol Med* 1976; Suppl 3:357s-360s.
- ⁴⁵ Sleight P. Neurophysiology of the carotid sinus receptors in normal and hypertensive animals and man. *Cardiology* 1976; 61 suppl 1:31-45.
- ⁴⁶ Ballotta E, Da Giau G, Meneghetti G, Barbon B, Militello C, Baracchini C. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prospective study. *J Vasc Surg*. 2007 Mar;45(3):516-22.
- ⁴⁷ Cieri E, De Rango P, Maccaroni MR, Spaccatini A, Caso V, Cao P. Is haemodynamic depression during carotid stenting a predictor of peri-procedural complications? *Eur J Vasc Endovasc Surg*. 2008 Apr;35(4):399-404

Table 1 - Study population

		Young controls	Old controls	e-CEA	s-CEA	ANOVA
Number		15	21	8	11	
Age	Year	33±6	66±10	62±11	65±6	0.001 * † ‡
Gender	m-f	8-7	11-10	2-6	7-4	
BMI	Kg/m ²	22.88±2.95	27.88±4.70	28.05±2.69	27.55±4.27	
SAP	mmHg	119±14	140±16	153±18	143±13	0.001 * † ‡
DAP	mmHg	70±9	73±7	86±7	82±9	0.001 † ‡ †† ††
Heart Rate	b/min	62.4±9.5	61.4±9.8	70.9±11.8	66.9±9.2	

Abbreviations: BMI=Body Mass Index, SAP=Systolic Arterial Pressure, DAP=Diastolic Arterial Pressure.

Significant differences: YOUNG controls vs OLD controls *, YOUNG controls vs e-CEA †, YOUNG controls vs s-CEA ‡, OLD controls vs e-CEA ††, OLD controls vs s-CEA ††, e-CEA vs s-CEA §.

Table 2A - Summary statistics of RR and SAP variability at REST

Measure units		YOUNG controls		OLD controls		e-CEA		s-CEA		ANOVA
		Average	SEM	Average	SEM	Average	SEM	Average	SEM	
RR	msec	981.51±36.75		996.35 ± 36.71		946.18 ± 45.08		855.03 ± 36.89		
RR σ^2	msec ²	3770.24±1038.90		850.59 ± 152.36		823.49 ± 240.93		616.11 ± 160.73		0.001 * † ‡
RR LFa	msec ²	1460.26±624.88		120.74 ± 18.35		174.82 ± 48.86		102.09 ± 37.86		0.012 * † ‡
RR HFa	msec ²	785.45±126.34		262.72 ± 100.33		208.16 ± 74.57		115.17 ± 36.63		0.001 * † ‡
RR LFn _u	nu	53.89±3.87		43.20 ± 5.74		41.89 ± 8.81		41.82 ± 7.75		
RR HF _u	nu	43.68±3.72		48.39 ± 5.84		49.46 ± 9.05		48.32 ± 8.27		
RR LF/HF	-	1.51±0.26		2.02 ± 0.59		1.75 ± 0.88		1.75 ± 0.60		
SAP	mmHg	117.31±3.35		137.22 ± 4.46		142.61 ± 3.59		146.82 ± 6.10		0.001 * † ‡
SAP σ^2	msec ²	38.43±8.64		30.17 ± 5.28		20.28 ± 7.04		26.15 ± 4.62		
SAP LFa	mmHg ²	9.60±3.26		4.29 ± 0.99		3.62 ± 1.05		2.92 ± 0.94		
SAP HFa	mmHg ²	2.78±0.69		4.61 ± 1.53		2.90 ± 1.04		4.80 ± 1.62		
RESP HF	mHz	258.07±10.25		263.33 ± 10.40		258.38 ± 14.30		289.45 ± 13.96		

Abbreviations: SEM=Standard Error, σ^2 =variance, LF=Low Frequency, HF=High Frequency, a=Absolute Units, nu=Normalized Unit, SAP=Systolic Arterial Pressure, RESP=Respiration.

Significant differences: YOUNG controls vs OLD controls *, YOUNG controls vs e-CEA †, YOUNG controls vs s-CEA ‡, OLD controls vs e-CEA ††, OLD controls vs s-CEA ‡‡, e-CEA vs s-CEA §.

Table 2B - Summary statistics of bivariate analysis of RR and SAP variability at REST

	Measure units	Normali Young		Normali OLD		e-CEA		s-CEA		ANOVA
		Average	SEM	Average	SEM	Average	SEM	Average	SEM	
Alpha	msec/mmHg	17.08±1.67		8.04±0.81		8.93 ± 1.66		6.41 ± 1.42		0.001 * † ‡
BRS	msec/mmHg	19.93±2.45		7.75±1.24		13.85 ± 5.14		4.93 ± 1.15		0.001 * ‡ §
XAR	msec/mmHg	5.36±0.85		1.99±0.98		2.00 ± 0.94		0.55 ± 0.34		0.008 * † ‡
RR-SAP LF	mHz	101.91±5.01		71.59±5.46		57.49 ± 7.59		83.67 ± 12.67		0.002 * † §
RR-SAP LF K²	-	0.75±0.04		0.54±0.04		0.54 ± 0.07		0.58 ± 0.06		0.004 * † ‡
RR-SAP LF Ph	rad	-0.95±0.13		-1.14±0.30		-2.09 ± 0.14		-1.10 ± 0.40		
RR-SAP HF	mHz	231.37±15.72		270.69±12.35		259.16 ± 14.95		285.21 ± 16.79		
RR-SAP HF K²	-	0.85±0.03		0.73±0.05		0.79 ± 0.07		0.93 ± 0.02		0.018 * ‡‡
RR-SAP HF Ph	rad	-0.31±0.11		0.61±0.21		-0.17 ± 0.42		0.16 ± 0.14		0.009 * ††
RR-SAP Gain (LF)	msec/mmHg	12.809±1.422		5.221±1.026		6.07 ± 1.24		5.22 ± 1.43		0.001 * † ‡
RR-SAP Gain (HF)	msec/mmHg	20.064±2.512		8.384±1.739		9.66 ± 3.16		5.70 ± 1.42		0.001 * † ‡

Abbreviations: SEM=Standard Error, Alpha=frequency domain index of baroreflex sensitivity, BRS=Baroreceptor Reflex Sensitivity, XAR=Causal Baroreflex Index, SAP=Systolic Arterial Pressure, LF=Low Frequency, HF=High Frequency, K²=Squared Coherence, Ph=Phase.

Significant differences: YOUNG controls vs OLD controls * , YOUNG controls vs e-CEA † , YOUNG controls vs s-CEA ‡ , OLD controls vs e-CEA †† , OLD controls vs s-CEA ‡‡ , e-CEA vs s-CEA §.

Table 3A - Summary statistics of RR and SAP variability at STAND

	Measure units	YOUNG controls		OLD controls		e-CEA		s-CEA		ANOVA
		Average	SEM	Average	SEM	Average	SEM	Average	SEM	
RR	msec	793.66±34.12		922.86 ± 36.48		900.38 ± 41.27		801.21 ± 44.15		0.037 * ‡‡
RR σ^2	msec ²	3148.41±524.86		717.78 ± 107.59		770.59 ± 142.76		438.87 ± 101.24		0.001 * † ‡
RR LFa	msec ²	1533.34±380.23		300.92 ± 84.98		151.60 ± 60.82		102.38 ± 50.81		0.001 * † ‡
RR HFa	msec ²	131.85±31.30		59.36 ± 15.31		84.10 ± 20.60		56.17 ± 21.92		
RR LFnu	nu	85.46±3.74		67.50 ± 4.91		46.69 ± 6.97		48.15 ± 9.46		0.001 * † ‡ †† ‡‡
RR HFnu	nu	11.09±2.47		21.92 ± 4.27		43.80 ± 5.90		40.51 ± 9.45		0.001 † ‡ †† ‡‡
RR LF/HF	-	18.00±4.80		8.17 ± 2.45		1.50 ± 0.48		7.30 ± 5.21		0.047 * †
SAP	mmHg	113.28±5.45		138.87 ± 7.00		148.84 ± 4.38		150.65 ± 4.77		0.001 * † ‡
SAP σ^2	msec ²	153.82±81.27		44.46 ± 5.00		57.00 ± 23.75		51.25 ± 11.92		
SAP LFa	mmHg ²	28.43±4.17		18.03 ± 4.00		3.10 ± 1.08		5.41 ± 1.90		0.001 * † ‡ †† ‡‡
SAP HFa	mmHg ²	4.62±0.85		4.11 ± 0.62		7.43 ± 5.19		6.15 ± 1.22		
RESP HF	mHz	0.27±0.01		0.28 ± 0.01		0.26 ± 0.01		0.31 ± 0.02		

Abbreviations: SEM=Standard Error, σ^2 =variance, LF=Low Frequency, HF=High Frequency, a=Absolute Units, nu=Normalized Unit, SAP=Systolic Arterial Pressure, RESP=Respiration.

Significant differences: YOUNG controls vs OLD controls * , YOUNG controls vs e-CEA † , YOUNG controls vs s-CEA ‡ , OLD controls vs e-CEA †† , OLD controls vs s-CEA ‡‡ , e-CEA vs s-CEA §.

Table 3B - Summary statistics of bivariate analysis of RR and SAP variability at STAND

	Measure units	Normali Young		Normali OLD		e-CEA		s-CEA		ANOVA
		Average	SEM	Average	SEM	Average	SEM	Average	SEM	
Alpha	msec/mmHg	6.44±0.78		4.83±1.00		6.47 ± 1.36		3.91 ± 0.83		
BRS	msec/mmHg	7.83±0.66		3.71±0.35		7.04 ± 1.99		3.57 ± 1.20		0.001 * ‡ †† §
XAR	msec/mmHg	3.77±0.59		2.14±0.99		2.01 ± 1.52		0.61 ± 0.22		
RR-SAP LF	mHz	0.10±0.01		0.08±0.01		0.08 ± 0.02		0.06 ± 0.01		0.032 ‡
RR-SAP LF K²	-	0.80±0.04		0.67±0.04		0.50 ± 0.07		0.50 ± 0.04		0.001 * † ‡ †† ††
RR-SAP LF Ph	rad	-1.13±0.08		-1.05±0.31		-0.30 ± 0.68		-1.78 ± 0.28		
RR-SAP HF	mHz	0.22±0.02		0.27±0.02		0.24 ± 0.02		0.27 ± 0.02		
RR-SAP HF K²	-	0.63±0.07		0.60±0.05		0.75 ± 0.08		0.84 ± 0.05		0.041 ‡ ††
RR-SAP HF Ph	rad	-0.30±0.15		-0.03±0.29		-0.10 ± 0.23		-0.14 ± 0.23		
RR-SAP Gain (LF)	msec/mmHg	6.53±0.53		4.04±0.75		5.85 ± 1.79		2.39 ± 0.48		0.01 * ‡ §
RR-SAP Gain (HF)	msec/mmHg	5.47±0.82		3.49±0.79		5.40 ± 1.38		3.20 ± 1.11		

Abbreviations: SEM=Standard Error, Alpha=frequency domain index of baroreflex sensitivity, BRS=Baroreceptor Reflex Sensitivity, XAR=Causal Baroreflex Index, SAP=Systolic Arterial Pressure, LF=Low Frequency, HF=High Frequency, K²=Squared Coherence, Ph=Phase.

Significant differences: YOUNG controls vs OLD controls * , YOUNG controls vs e-CEA † , YOUNG controls vs s-CEA ‡ , OLD controls vs e-CEA †† , OLD controls vs s-CEA ††† , e-CEA vs s-CEA §.

FIG. R1 - Comparison of simple hemodynamics (HR, left; SAP, right) and power of selected spectral components ($LF_{RR[nu]}$, left; LF_{SAP} , right) in young (Y) and old (O) controls, as well as in e-CEA (E) and S-CEA (P). Notice the lack of orthostatic hypotension in controls and in both groups of patients.

Empty bars = Rest; stippled bars = Stand.

Figure R1

