Baroreflex Control of Muscle Sympathetic Nerve Activity After Carotid Body Tumor Resection


Abstract—Bilateral carotid body tumor resection causes a permanent attenuation of vagal baroreflex sensitivity. We retrospectively examined the effects of bilateral carotid body tumor resection on the baroreflex control of sympathetic nerve traffic. Muscle sympathetic nerve activity was recorded in 5 patients after bilateral carotid body tumor resection (1 man and 4 women, 51 ± 11 years) and 6 healthy control subjects (2 men and 4 women, 50 ± 7 years). Baroreflex sensitivity was calculated from changes in R–R interval and muscle sympathetic nerve activity in response to bolus injections of phenylephrine and nitroprusside. In addition, sympathetic responses to the Valsalva maneuver and cold pressor test were measured. The integrated neurogram of patients and control subjects contained a similar pattern of pulse synchronous burst of nerve activity. Baroreflex control of both heart rate and sympathetic nerve activity were attenuated in patients as compared with control subjects (heart rate baroreflex sensitivity: 3.68 ± 0.93 versus 11.61 ± 4.72 ms/mm Hg (phenylephrine, P = 0.011) and 2.53 ± 1.36 versus 5.82 ± 1.94 ms/mm Hg (nitroprusside, P = 0.05); sympathetic baroreflex sensitivity: 3.70 ± 2.90 versus 7.53 ± 4.12 activity/100 beats/mm Hg (phenylephrine, P = 0.10) and 3.93 ± 4.43 versus 15.27 ± 10.03 activity/100 beats/mm Hg (nitroprusside, P = 0.028)). The Valsalva maneuver elicited normal reflex changes in muscle sympathetic nerve activity, whereas heart rate responses were blunted in the patients with bilateral carotid body tumor resection. Maximal sympathetic responses to the cold pressor test did not differ between the two groups. Denervation of carotid sinus baroreceptors as the result of bilateral carotid body tumor resection produces chronic impairment of baroreflex control of both heart rate and sympathetic nerve activity. During the Valsalva maneuver, loss of carotid baroreflex control of heart rate is less well compensated for by the extra carotid baroreceptors than the control of muscle sympathetic nerve activity. (Hypertension. 2003;42:143-149.)

Key Words: baroreflex • baroreceptors • carotid arteries • sympathetic nervous system • blood pressure

Effective sympathetic nerve traffic is strongly governed by the restraining effects of arterial and cardiopulmonary baroreceptors.1 Direct stimulation of carotid sinus baroreceptors in humans causes a reduction of muscle sympathetic nerve activity (MSNA).2 In contrast, anesthetic deafferentation of arterial and cardiopulmonary baroreceptors results in a strong increase in MSNA accompanied by hypertension and tachycardia.3 In addition, normal cardiac rhythmicity of MSNA is lost after baroreceptor denervation. Apart from experimental denervation, iatrogenic denervation of baroreceptors may occur as complication of bilateral carotid body tumor resection (BCBR).4,5 neck or mediastinal irradiation,4,6,7 and carotid endarterectomy.5 The resulting clinical syndrome of baroreflex failure is characterized by recurrent bouts of unrestrained sympathetic excitation, manifesting as severe hypertension, headache, and diaphoresis. The findings of excessive rises in plasma catecholamines during these attacks and of exaggerated pressor responses to cold and mental stress in these patients suggest the loss of baroreflex-mediated inhibition of efferent sympathetic nerve activity.5,6 In a previous study, we have demonstrated that although BCBR elicits the full-blown syndrome of baroreflex failure only in a minority of patients,9 baroreflex control of heart rate is impaired and blood pressure variability is increased in the long term after BCBR.9,10 Whether BCBR also affects baroreflex control of sympathetic outflow has not yet been established in humans.

The aim of this study was to examine the chronic effects of BCBR on the baroreflex control of sympathetic nerve activity. In this cross-sectional, retrospective study of patients with BCBR and age-matched healthy control subjects, sympathetic baroreflex sensitivity was calculated from MSNA responses to (de-)activation of baroreceptors by phenylephrine and nitroprusside bolus injections. In addition, MSNA responses to the Valsalva maneuver and cold pressor test were assessed.

Methods

Patients and Control Subjects
Five patients (1 man and 4 women) who had undergone 2-stage BCBR at the Department of Otolaryngology of the University...
Medical Center Nijmegen, the Netherlands, were included in this study. Individual information on tumor size, additional tumor localizations, and surgical details of these 5 patients are shown in the Table. The median interval between the second operation and the study was 6.7 years (range, 4.4 to 20.3 years). Patients were free of diabetes and neurological, cardiovascular, and pulmonary disease. Six healthy subjects (2 men and 4 women) served as control subjects. Full medical history and physical examination including blood pressure measurements revealed no abnormalities. Groups were matched for age (BCBR: 51.2 ± 8.5 versus control subjects: 8.5 versus 9.0 years, 7.4 U/week). The $e$-tort of individual bursts of sympathetic nerve activity by an online computer system was applied for automatic detection and quantification of individual bursts of sympathetic nerve activity by an online computer system.

### Blood Pressure, Heart Rate, Breathing Frequency

Investigations were carried out during the morning after an overnight fast in a room with an ambient temperature of 22–24°C. Subjects had abstained from caffeine, tea, alcohol, chocolate, and smoking for at least 24 hours. Office systolic and diastolic blood pressure (SBP/DBP) was determined from the mean of 3 supine sphygmomanometric readings. A 20-minute baseline period, graded bolus injections of PHE (25 to 50 to 100 to 150 μg) followed by injections of SNP (12.5 to 25 to 50 to 100 μg) were given intravenously at intervals of 10 minutes. The dosage producing an increase (PHE) or decrease (SNP) in arterial blood pressure of 15 mm Hg was repeated 3 times. After 15 minutes of supine rest, baroreflex control of heart rate and sympathetic nerve traffic was assessed from R-R interval and MSNA responses to increments and decrements in blood pressure induced by phenylephrine (PHE) and sodium nitroprusside (SNP), respectively.13 After a 20-minute baseline period, graded bolus injections of PHE (25 to 50 to 100 to 150 μg) followed by injections of SNP (12.5 to 25 to 50 to 100 μg) were given intravenously at intervals of 10 minutes. The dosage producing an increase (PHE) or decrease (SNP) in arterial pressure of 15 mm Hg was repeated 3 times. After 15 minutes of supine rest, baroreflex control of HR and MSNA during the Valsalva maneuver was examined.14,15 Subjects were asked to maintain an expiratory pressure of 40 mm Hg during 15 seconds, by means of forced expiration into a mouthpiece connected to a pressure transducer. Closure of the glottis was prevented by a small leak to maintain a flow of air.

### Study Protocol

After 20 minutes of supine rest, 10 minutes of baseline MSNA was recorded. Baroreflex control of heart rate and sympathetic nerve traffic was assessed from R-R interval and MSNA responses to increments and decrements in blood pressure induced by phenylephrine (PHE) and sodium nitroprusside (SNP), respectively.13 After a 20-minute baseline period, graded bolus injections of PHE (25 to 50 to 100 to 150 μg) followed by injections of SNP (12.5 to 25 to 50 to 100 μg) were given intravenously at intervals of 10 minutes. The dosage producing an increase (PHE) or decrease (SNP) in arterial pressure of 15 mm Hg was repeated 3 times. After 15 minutes of supine rest, baroreflex control of HR and MSNA during the Valsalva maneuver was examined.14,15 Subjects were asked to maintain an expiratory pressure of 40 mm Hg during 15 seconds, by means of forced expiration into a mouthpiece connected to a pressure transducer. Closure of the glottis was prevented by a small leak to maintain a flow of air.

### Data Analysis

A computer-assisted method was applied for automatic detection and quantification of individual bursts of sympathetic nerve activity by...
means of a curve-fitting method. During a prescan of the tracing, the neurogram was correlated with a triangular signal by applying a least-squares algorithm. To define “reference bursts,” the 100 largest triangular waves detected during the prescan were taken. After discarding the 20 largest waves for possible artifacts, the remaining 80 were taken as a reference. Their mean amplitude and delay from the corresponding R wave on the ECG were determined. During a subsequent scan, the individual amplitudes and time delays of all triangular waves were compared with the mean amplitude and delay of the reference waves. Waves were accepted and marked as sympathetic bursts on two conditions: an amplitude of >20% of the mean reference amplitude and a time delay of <200 ms beneath or above the mean reference delay. Automatically calculated burst amplitude correlated well (r >0.9) with manual burst detection (unpublished data). MSNA was expressed as number of bursts per minute and per 100 beats, total integrated activity (summed amplitude of bursts) per minute (TIA/min), and total integrated activity per 100 beats (TIA/100 beats).

Baroreflex control of HR (hBRS) was assessed by means of linear regression analysis between changes in SBP and R-R interval during PHE- and SNP-induced BP ramps. The mean slope of at least 3 statistically significant regression lines of PHE and SNP trials were taken as hBRS_{PHE} and hBRS_{SNP}, respectively. Sympathetic baroreflex sensitivity (sBRS) was calculated from changes in MSNA evoked by absolute changes in DBP induced by PHE and SNP, since DBP correlates more closely to MSNA than SBP.14 After combining MSNA and pressure data of the 3 SNP trials, relative changes in total integrated MSNA activity (% TIA/min, % TIA/100 beats) were pooled over 3–mm Hg pressure ranges.13,19 Any heart beat not followed by a burst was assigned an MSNA activity of zero. Linear regression analysis between relative changes in MSNA and DBP was performed. The slope of a statistically significant regression line was taken as sBRS_{SNP}. Values for sBRS_{PHE} were calculated in a different way, since the relation between changes in MSNA and DBP is not necessarily linear. In our experience, PHE-induced rises in BP often elicit abrupt silencing of MSNA. Therefore, we compared mean MSNA during the BP ramp after PHE injection with the mean MSNA during 20 seconds at baseline. sBRS_{PHE} was calculated as the mean decrease in MSNA (% TIA/min, % TIA/100 beats) of 3 PHE trials divided by the mean increase in DBP during the ramp.

The HR response to the Valsalva maneuver was expressed as the maximal increase in HR during phase 2 and the ratio between the highest and lowest heart rate during phase 2 and phase 4, respectively (Valsalva ratio).13 The maximal phase 2 decrease in BP was calculated as the difference between the maximal and minimal BP during phase 2. Phase 4 BP overshoot was calculated as the maximal increase in SBP and DBP as compared with baseline. The MSNA response to the Valsalva maneuver was expressed as the mean increase in MSNA during late phase 2 and the mean decrease in MSNA during the first 15 seconds of phase 4 overshoot, relative to baseline.14 Relative changes in BP, HR, and MSNA in response to the cold pressor test were expressed as 1-minute averages during the stimulus and during 2 minutes of recovery as compared with 1 minute at baseline.

**Statistics**

Results are given as mean±SD, unless indicated otherwise. Differences between patients and control subjects with respect to nominal variables were compared by use of the χ² test. Other variables were compared by use of the Student’s t test or Mann-Whitney rank-sum test when appropriate. A 2-sided P<0.05 was taken as the level of significance. Statistical analysis was performed with the use of SPSS (Statistical Package for the Social Sciences) for Windows 6.1.3.

**Results**

**MSNA at Baseline**

At baseline, sphygmonomaneometric SBP/DBP, and HR did not differ between patients and control subjects: 120.8±11.1/

79.0±5.9 mm Hg, 66.8±8.5 bpm versus 123.3±11.9/81.5±7.6 mm Hg, 66.2±6.5 bpm. On visual inspection, the neurograms of both patients and control subjects were characterized by a regular burst pattern and cardiac rhythmicity. The neurograms contained no skin sympathetic nerve (like) activity.1 The mean time delay between reference bursts and corresponding R waves was not different between patients (1.342±88 ms) and control subjects (1.337±82 ms). In patient neurograms, 34.1±24.9% of the triangular waves were discarded as possible bursts, since they did not meet the time delay (and amplitude) criterion, which was similar to a proportion of 31.0±18.7% in control subjects. Sympathetic burst frequency at baseline did not differ between patients and control subjects: 39.6±20.0 versus 38.8±11.5 bursts/min and 49.3±21.5 versus 59.0±19.8 bursts/100 beats.

**Baroreflex Sensitivity**

Tracings of an individual BP, HR, and MSNA response to PHE and SNP in control subject 1 are shown in Figure 1. Baroreflex control of heart rate was lower in patients than in control subjects [hBRS_{SNP}: 2.53±1.36 versus 5.82±1.94 ms/mm Hg (P=0.05); hBRS_{PHE}: 3.78±0.93 versus 11.61±4.72 ms/mm Hg (P=0.011)] (Figure 2). Sympathetic BRS calculated from SNP responses was also lower in patients than in control subjects [hBRS_{SNP}: 3.93±4.43 versus 15.27±10.03% TIA/min/mm Hg, P=0.028 and 4.41±3.60 versus 14.25±7.77% TIA/100 beats/mm Hg, P=0.028]. PHE resulted in a similar mean increase in DBP (patients: 9.52±2.93 mm Hg versus control subjects: 9.75±2.71 mm Hg, NS). sBRS_{PHE} tended to be lower in patients than in control subjects [3.74±2.92 versus 7.87±3.96% TIA/min/mm Hg (P=0.097) and 3.70±2.90 versus 7.53±4.12% TIA/100 beats/mm Hg (P=0.10)].

**Valsalva Maneuver**

In response to the Valsalva maneuver, the maximal increase in HR during phase 2 was lower in patients than in control subjects (11.0±8.3 versus 38.7±18.1 bpm, P=0.004), as was the Valsalva ratio (1.28±0.15 versus 2.04±0.31, P=0.004).
The maximal phase 2 decrease in SBP and DBP was similar in patients and control subjects (SBP: 48.5 ± 25.0 mm Hg vs. 18.3 ± 11.5 mm Hg; DBP: 25.0 ± 19.0 mm Hg vs. 11.5 ± 9.6 mm Hg) (Figure 3). Phase 4 SBP and DBP overshoot was lower in patients than in control subjects (SBP: 36.2 ± 19.0 mm Hg vs. 21.2 ± 9.6 mm Hg; DBP: 19.0 ± 11.5 mm Hg vs. 9.6 ± 6.1 mm Hg). Patients and control subjects showed an increase in MSNA during phase 2 of 76.3 ± 75.3% TIA/min and 75.3 ± 71.7% TIA/100 beats, which was not significantly different. Phase 4 decrease in MSNA was also similar in patients and control subjects (SBP: 44.9 ± 68.6% TIA/100 beats; DBP: 64.1 ± 12.7% TIA/100 beats).

Cold Pressor Test
In both patients and control subjects, the cold pressor test elicited increases in BP, HR, and MSNA that were not significantly different between groups (Figure 4).

Discussion

Summary
Patients who had BCBR showed no permanent effects on burst incidence or pulse synchronicity of supine resting MSNA at baseline. However, there is a chronic decrease in the baroreflex adjustments of both heart rate and MSNA, as indicated by attenuated responses to both PHE-induced hypotension and SNP-induced hypotension. In contrast to an abnormal HR response to the Valsalva maneuver, normal compensatory changes in MSNA were observed in patients with BCBR.

Effect of BCBR on Baseline MSNA
Fagius et al. have shown that chemical deafferentation of arterial and cardiopulmonary baroreceptors in humans has a profound effect on the characteristics of MSNA. After a local anesthetic block of vagus and glossopharyngeal nerves, pulse synchronicity of MSNA disappeared and the resulting neurogram was characterized by bursts of impulses of variable duration occurring in a slow, irregular rhythm. Disruption of the phase lock between sympathetic discharges and the cardiac rhythm has also been demonstrated after sinoaortic denervation of arterial baroreceptors in cats. In the present study, neurograms of patients with BCBR exhibited a normal burst pattern, including a normal cardiac rhythmicity and an unaltered mean reflex latency of sympathetic bursts of 1.3 seconds. The heterogeneous expression of clinical and physiological baroreflex dysfunction suggests that the extent to which the carotid sinus baroreceptors become denervated...
by BCBR differs considerably among patients.\textsuperscript{9,10} Therefore, the presence of cardiac rhythmicity of MSNA after BCBR may originate from residual carotid baroreceptors and/or unaffected aortic and cardiopulmonary baroreceptors. Absence of pulse synchronicity of MSNA in a patient after selective sinoaortic denervation as the result of bilateral carotid bypass surgery and mediastinal irradiation\textsuperscript{6} suggests that MSNA rhythmicity is not generated by cardiopulmonary mechanoreceptors.

BCBR does not result in a permanent elevation of resting MSNA (this study), nor does it result in chronic hypertension.\textsuperscript{10} The acute phase of iatrogenic carotid sinus denervation is characterized by sympathoexcitation, which may persist for hours to days.\textsuperscript{4,4,5,7,8} Unselective anesthetic deafneriration is characterized by sympathoexcitation, which may originate from residual carotid and aortic baroreceptors causes complete abolishment of MSNA responses to PHE and SNP.\textsuperscript{6} This suggests that both carotid and aortic receptors are important modulators of sympathetic nerve traffic in humans.

MSNA responses to PHE were analyzed in a different manner than SNP ramps, since pressure elevations usually provoked sudden silencing of MSNA in control subjects. In line with previous reports,\textsuperscript{24,25} linear regression analysis between pressure and MSNA during PHE ramps yielded no significant correlation coefficients. However, this does not imply a larger gain of sympathetic BRS during pressure increases than during decreases. Brusque MSNA silencing by PHE is explained by the fact that resting blood pressure level is near the threshold for sympathetic activation on the sigmoid relation between MSNA and blood pressure.\textsuperscript{26} Therefore, SNP administration is a more sensitive tool for the evaluation of baroreflex control of sympathetic outflow than PHE. In addition, we prefer bolus injections over stepwise infusion of SNP, since MSNA is determined by changes rather than absolute levels of baroreceptor activity.\textsuperscript{18}

Figure 4. Cold pressor test. Relative changes from baseline in mean arterial pressure (MAP, top left), R-R interval (bottom left), and MSNA expressed as TIA per 100 beats (top right) and per minute (bottom right). Data are presented as minute averages during 2 minutes of cold stimulation (dotted square) and 2 minutes of recovery.

Effect of BCBR on Baroreflex Sensitivity

Our previous report on an attenuated baroreflex control of HR in patients with BCBR\textsuperscript{9} was confirmed by the present study. In addition, we demonstrated that BCBR causes a chronic decrease in sympathetic BRS as well. However, reflex changes in heart rate and MSNA still did occur in response to both PHE and SNP injections in all patients, except in patient 2, in whom repeated blood pressure decreases of 15 mm Hg in did not elicit any change in MSNA (Figure 2). In contrast, in our findings in patients with presumed carotid-selective denervation, deafferentiation of both carotid and aortic baroreceptors causes complete abolishment of MSNA responses to PHE and SNP.\textsuperscript{6} This suggests that both carotid and aortic receptors are important modulators of sympathetic nerve traffic in humans.

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Effect of BCBR on Functional Baroreflex Performance During Valsalva Maneuver

Phase 2 and 4 changes in blood pressure during the Valsalva maneuver elicited normal reciprocal adjustments of MSNA in patients with BCBR and control subjects,\textsuperscript{14} whereas HR responses were blunted in patients. This discrepancy suggests a differential effect of BCBR on the functional baroreflex modulation of HR and sympathetic nerve activity. The relative roles of carotid sinus and aortic baroreceptors in the reflex control of HR and vascular resistance during changes in arterial blood pressure have been investigated by denervation experiments in rabbits.\textsuperscript{27} It was shown that reflex heart rate responses to PHE were impaired significantly by denervation of either carotid or aortic baroreceptors. In contrast, reflex vascular responses in the hindlimb (perfused at constant blood flow) were preserved except for a slight impairment of reflex vasoconstriction after aortic baroreceptor denervation. In line with these observations, (partial) denervation of carotid baroreceptors as the result of BCBR is not
compensated by aortic receptors with respect to HR control. In contrast, residual aortic baroreceptors after BCBR are capable of reflex modulation of MSNA to a certain extent. Previous studies on the relative importance of carotid and aortic baroreceptors in the reflex modulation of heart rate have yielded contrasting results. Experiments on selective (un)loading of aortic baroreceptors by simultaneous infusion of vasoactive substances and application of neck suction/pressure to maintain a stable carotid sinus transmural pressure indicated that aortic baroreceptors are dominant in the baroreflex control of heart rate, with the carotid baroreceptors contributing only \( \approx 30\% \).28,29 In line with these observations, baroreflex control of heart rate in mainly determined by the distensibility of the aortic arch than of the carotid sinus.30 In contrast, combined neck suction/pressure with nonpharmacological (de)loading of aortic baroreceptors indicate that carotid baroreceptors are the principal contributors to baroreflex control of heart rate.31 Our findings are in favor of the latter study.

Despite their potent baroreceptor properties, the contribution of cardiopulmonary baroreceptors to reflex adjustments during the Valsalva maneuver are probably limited, since reflex heart rate responses to changes in airway pressure are abolished in conscious dogs with denervated arterial baroreceptors and intact cardiopulmonary reflexes.32 Acute MSNA silencing during the short pressure rise in phase 1 of the Valsalva maneuver has been attributed to increased carotid baroreceptor firing, since simultaneous reduction of aortic cross-sectional area (and therefor decreased wall tension) during this phase14,33 suggests an opposing input to aortic baroreceptors and intact cardiopulmonary reflexes.32 Acute MSNA silencing during early phase 2 was clearly present in BCBR patients 1, 3, and 4 (data not shown), indicating again that some residual carotid sinus baroreceptor function is present in these patients.

During phase 4 of the Valsalva maneuver, blood pressure overshoot was lower in patients than in control subjects. This cannot be explained by an attenuated reflex increase in MSNA during phase 2, since MSNA responses were shown to be normal. Attenuation of phase 4 blood pressure overshoot might be explained by a lower reflex increase in cardiac sympathetic nerve activity (and thereby stroke volume), which is not measured by peripheral microneurography. Baroreceptor denervation may have a differential effect on the reflex control of muscle versus cardiac sympathetic nerve activity.

In conclusion, in the long term after BCBR, patients have a normal pulse synchronous burst pattern of MSNA. Denervation of carotid sinus baroreceptors as the result of BCBR produces a chronic decrease in baroreflex-mediated adjustments of both HR and sympathetic nerve activity. However, this impairment of carotid baroreceptor function in humans has differential effects with regard to HR and MSNA. During the Valsalva maneuver, sympathetic nerve activity appears to be controlled by both carotid and extracarotid baroreceptors, whereas baroreflex modulation of HR outflow appears to depend largely on the integrity of carotid baroreceptors.

**Perspectives**

Our knowledge of the relative contribution of carotid receptors to baroreflex function is mainly derived from experimental denervation studies in animals. For obvious reasons, no human counterparts for these well-controlled prospective studies are available. Inadvertent damage to the carotid sinus as a complication of surgical treatment of rare bilateral carotid body tumors may serve as a human model of carotid sinus denervation. Despite evidence for permanent abnormalities in the reflex regulation of sympathetic nerve activity and HR in these patients, full-blown baroreflex failure with unrestrained sympathetic activation, hypertension, and tachycardia is mainly limited to the acute phase after denervation. Prospective studies before and after the surgical denervation might improve our understanding of the importance of carotid baroreflex function in humans.

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