Baroreflex Sensitivity Is Impaired in Bilateral Carotid Atherosclerosis

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Background and Purpose—The arterial baroreflex is an important determinant of the short-term regulation of blood pressure and cardiovascular variability. The purpose of our study was to determine whether baroreflex sensitivity (BRS) and heart rate (HR) variability are altered in patients with carotid atherosclerosis (CA) and to assess the impact of characteristics of CA on BRS.

Methods—BRS and HR variability were prospectively evaluated in 75 consecutive patients undergoing carotid duplex examination in a neurosonology unit. Resting BRS was measured with the sequence method. HR variability was evaluated using spectral analysis.

Results—BRS was significantly reduced in patients with bilateral CA compared with patients without CA \( (P=0.015) \) and patients with unilateral CA \( (P=0.045) \). BRS was unaltered in patients with unilateral CA compared with patients with no CA. BRS was already reduced in mild (stenosis <50%), bilateral CA and was not further impaired in more severe CA. The association of BRS impairment with bilateral CA remained significant after adjustment for age, hypertension, and a history of stroke or transient ischemic attack. The study of HR variability demonstrated a reduction in the power of high-frequency band in patients with bilateral CA compared with patients with unilateral CA or without CA \( (P=0.015) \).

Conclusion—Bilateral CA is associated with an impairment of BRS and a shift of the sympathovagal balance toward a relative decrease of the parasympathetic component of HR variability. These changes are already present in mild, bilateral CA. (Stroke. 2005;36:1891-1895.)

Key Words: atherosclerosis ■ baroreflex ■ carotid stenosis ■ carotid ultrasound ■ dysautonomia ■ stroke ■ sympathetic nervous system

The arterial baroreflex is an important determinant of the short-term regulation of blood pressure and cardiovascular variability. Variations in the extent of stretch applied to carotid sinus and aortic arch receptors modulate the afferent discharge transmitted to the central nervous system and trigger reflex adjustments that dampen the changes in blood pressure.\(^1\) The baroreflex sensitivity (BRS) measures the gain of baroreflex. Reduced BRS is a common finding in aging,\(^2,3\) hypertension,\(^4,5\) diabetes,\(^6\) and after myocardial infarction.\(^7\) BRS impairment has been associated with the severity of coronary narrowing in patients with stable coronary disease.\(^8\) It has also been reported in patients with acute stroke.\(^9\)

BRS modifications after carotid endarterectomy have largely been addressed in previous work.\(^10,11\) In contrast, very few studies have investigated the impact of carotid atherosclerosis (CA) on BRS reduction in patients who have not undergone carotid surgery. These studies did not consider the role of CA characteristics such as bilaterality and different degrees of CA severity. The purpose of our study was to explore the impact of nonoperated CA on BRS and heart rate (HR) variability and to assess the role of CA bilaterality and severity in modifying these parameters.

Methods

Patients

Consecutive patients aged \( \geq 18 \) years, who underwent a carotid Doppler-sonography in our Neurosonology Unit were considered for inclusion. Exclusion criteria were diabetes, cardiac rhythm disorders, heart failure, symptomatic coronary disease, neurological disorders known to be associated with autonomic failure, previous carotid endarterectomy or angioplasty, carotid dissection, carotid occlusion, hemorrhagic stroke, brain stem stroke location, and medications known to interfere with autonomic cardiovascular regulation: neuroleptics, \( \beta \)-blockers, and calcium inhibitors that may increase the QT (diltiazem and verapamil).

CA Grading

CA was graded using bilateral carotid duplex (ATL Ultramark 9 HDI). CA was graded on each side from 0 to 3: absence of CA (0); CA with a narrowing effect below 50% (1); CA causing a 50% to 70% stenosis of the carotid lumen (2); severe atheroma with a carotid stenosis higher than 70% (3). Patients with a score of 0 on one side and >0 on the contralateral side were classified as having unilateral CA. Patients with a score >0 on both sides were classified as having bilateral CA. The right and left scores were added to form a total score ranging from 0 to 6 and measuring the severity of CA in both carotid arteries.
Aortic Arch Atheroma Grading
Aortic arch atheroma was graded using transesophageal echography in stroke patients who underwent this exploration. Aortic arch atheroma was graded from 0 to 2: absence of aortic arch atheroma (0); aortic arch atheroma measuring <4 mm at the maximal thickness zone (1); aortic arch atheroma measuring ≥4 mm at the maximal thickness zone (2).

BRS Measurement
Resting BRS was measured using the sequence method. During the test, patients were lying supine in a quiet room at controlled temperature. Cardiac interbeat intervals (IBI) were derived from the time in milliseconds between sequential R spikes on a 3-lead ECG monitor. A peak detection circuit was used to measure each R-R interval to 1-ms accuracy. After each QRS, the subsequent highest and diastolic pressures, respectively. Blood pressure was measured with the noninvasive Finapress device (Ohmeda). The run-time of systolic blood pressure (SBP) and IBI monitoring was of 10 minutes. Baroreflex sequences were defined by at least 3 consecutive beats in which the SBP and R-R interval of the following beat either increased or decreased. A linear regression was applied to each selected sequence and the mean slope was determined as the average of all slopes within a given time period. The mean slope of IBI–SBP variation sequences is considered to be an index of BRS.

Spectral Analysis
The HR variability was analyzed using spectral analysis after fast Fourier transform. Harmonic HR oscillations are concentrated into at least 2 distinct spectrum regions. One is referred to as high-frequency band (HF: 0.15 to 0.5 Hz), with respiration being its primary rhythmic stimulus. Spectral power in the HF band is mediated mainly by the parasympathetic nervous system activity. The other component is the lower-frequency band (LF: 0.04 to 0.15 Hz) and is mediated by both the sympathetic and parasympathetic nervous system activity. The spectrum of harmonic components was analyzed to determine the power in the LF and HF bands. HF power was used as an indicator of parasympathetic activity. The ratios HF/total power and LF/HF were used as normalized indicators of parasympathetic and sympathetic activities respectively. The software used to perform spectral analysis has been designed by Notocord Systems.

Statistical Analysis
Results are presented as means (SEM) unless otherwise specified. We used nonparametric tests (Kruskal–Wallis test, Mann–Whitney U test, Spearman rank correlation coefficient) to study the relationships between the mean baroreflex slope and the following variables: age, gender, hypertension, CA, aortic arch atheroma, history of stroke or transient ischemic attack (TIA), lesion of the insular cortex. Variables associated with BRS in univariate analysis with a P value of ≤0.1 were then tested in a logistic regression model. In addition, taking into account reports on BRS increase in patients under antihypertensive medications or statins, the variable “antihypertensive or statin therapy” was forced into the model. We used the median BRS as a cut-off point. The relationship of LF, HF, HF/T, and LF/HF with BRS, and CA were tested using nonparametric tests. A P value of <0.05 was considered to be significant.

Results
Patient Characteristics
We recruited 75 patients. There were 44 men and 31 women. Their median age was 63.9 years (range, 30 to 84 years). Thirty-four patients were hypertensive. Forty-one patients had a history of ischemic stroke and 17 of TIA. The median delay from the onset of symptoms to BRS and HR variability assessments was of 4 days (range, 1 to 800 days). All patients with stroke or TIA had a brain CT or MRI. Clinical symptoms indicated an involvement of the left cerebral hemisphere in 29 patients, and of the right cerebral hemisphere in 29 patients. The infarcted area included the insular cortex in 18 patients. The diagnoses or the referral reasons in the 17 patients who did not present with stroke or TIA were as follows: transient global amnesia (5 patients), migraine with aura (3 patients), anorganic deficit (2 patients), facial nerve palsy (2 patients), ocular motor nerve palsy (1 patient), amaurosis fugax (1 patient), vasovagal syncope (1 patient), optic neuritis (1 patient), and screening for asymptomatic CA (1 patient).

CA was bilateral in 27 patients, unilateral in 16 patients, and absent in 32 patients. The distribution of patients according to total CA score is shown in the Figure. All patients with a total score >1, except 1 patient had bilateral CA. Among patients presenting with stroke or TIA, 30 patients underwent a transesophageal cardiac echography. Twenty patients had no aortic arch atheroma, 8 patients had grade 1 aortic arch plaques, and 2 patients had grade 2 aortic arch plaques.

Twelve-eight patients were under antihypertensive treatment other than β-blockers or calcium inhibitors that may increase the QT interval, which were exclusion criteria. Eleven patients were taking a statin. Patients under antihypertensive treatment or statin therapy had bilateral CA (17 patients), unilateral CA (6 patients), and no CA (10 patients).

Resting BRS
The median value was 5.15 ms/mm Hg (range: 1.2 to 30.9). BRS was significantly reduced in patients with bilateral CA compared with patients without CA (P=0.015) and with patients with unilateral CA (P=0.045). In contrast, there was no significant difference in BRS between patients with unilateral CA and without CA (Table 1).

| TABLE 1. BRS in Patients With No CA, Unilateral CA, or Bilateral CA |
|-----------------|-----------------|-----------------|-----------------|
|                 | No CA           | Unilateral CA   | Bilateral CA    |
| No.             | 32              | 16              | 27              |
| BRS (ms/mm Hg), mean (SEM) | 8.30 (1.21) | 7.66 (1.12) | 4.48 (0.49) |

Values are means (SEM). BRS was significantly reduced in bilateral CA compared with no CA (P=0.015) and unilateral CA (P=0.045). The difference between unilateral CA and no CA was not significant. P values were calculated using the Mann–Whitney U test and the Bonferroni’s correction.
We used the total CA score to explore the relationship between BRS and CA severity. BRS was significantly reduced in patients with a total CA score >1 compared with patients with a CA score of 0 to 1: 4.37 ms/mm Hg (0.49) versus 8.24 ms/mm Hg (0.89) (P=0.0005). However, there was no further impairment of BRS with higher degrees of CA (Table 2). In the subgroup of patients who underwent a transesophageal cardiac echography, no correlation was found between aortic arch atheroma and BRS measurements.

Age was significantly associated with BRS attenuation (P<0.0001). There was no difference in BRS according to gender. There were nonsignificant trends toward reduced BRS in patients with hypertension (P=0.1) and in patients with a history of stroke or TIA (P=0.1). No significant impairment of BRS was found in the subgroup of patients with a lesion in the insular cortex (P=0.5).

Data were analyzed in a multivariate logistic model including age, bilateral CA, hypertension, a history of stroke or TIA, and antihypertensive or statin therapy as independent variables. BRS was considered to be reduced below 5.15 ms/mm Hg. Age (P=0.008) and bilateral CA (P=0.019) were significantly associated with BRS reduction, whereas hypertension, a history of stroke or TIA, and antihypertensive or statin therapy were not.

Heart Rate Variability
HF and HF/T were positively correlated to BRS (P=0.0002 and P=0.0015, respectively). LF was also found to be positively correlated to BRS (P=0.004). In contrast, no significant correlation was found between LF/HF and BRS (P=0.15).

HF was significantly reduced in patients with bilateral CA compared with patients with unilateral CA or without CA (P=0.015). In contrast, HF/T, LF, and LF/HF were not significantly correlated to bilateral CA.

Discussion
In the present study, bilateral CA was associated with a lowering of resting BRS. This association remained significant after adjustment on other factors associated with BRS reduction. In contrast, BRS was not altered in patients with unilateral CA. To our knowledge, this is the first report to demonstrate that BRS is impaired in bilateral but not unilateral CA. Akinola et al18 studied 46 patients with carotid stenosis (23 unilateral, 23 bilateral) and compared them with 21 hypertensive patients and 27 normal subjects. More than 1-third of patients with significant carotid stenosis had postural hypotension and attenuated HR response, suggesting an impairment of baroreflex. No difference was found between patients with unilateral significant carotid stenosis and those with bilateral carotid stenosis. However, significant carotid stenosis was defined as >80% stenosis, and most patients with such a unilateral stenosis had a contralateral 40% to 50% stenosis, thus corresponding with bilateral CA according to the criteria used in our study. Chao et al19 compared 99 patients with symptomatic >50% carotid stenosis with 43 healthy subjects. They found a significant reduction of BRS in patients with carotid stenosis. No attempt was made to differentiate the effects of unilateral and bilateral stenosis in their study.

Our results indicate no correlation between BRS reduction and the severity of CA. BRS was significantly reduced in patients with mild (<50% stenosis), bilateral CA and was not further impaired in more severe degrees of CA. This finding is consistent with the previous study by Gianaros et al20 who reported that BRS was already impaired in patients with increased intima media thickness in the carotid bulb. Also, Chao et al19 found no differences in BRS values between patients with moderate (50% to 75%) stenosis and patients with severe (>75%) stenosis. The lack of correlation between BRS reduction and the severity of CA may reflect a threshold effect of mild, bilateral CA. Low BRS may be caused by the impact on baroreceptors of decreased arterial distensibility on both sides. Paracrine factors associated with atherosclerosis may potentiate the effect of the structural modulation and, consequently, contribute to diminished BRS in early stages of CA.21

We could not find any correlation between aortic atheroma and BRS. This finding should be interpreted with caution because aortic atheroma was assessed in only 30 patients. Physiological studies on the relative importance of carotid versus aortic baroreceptors in humans have yielded contrasting results.22 Our finding may suggest a predominance of the carotid component of baroreflex on its aortic component in the clinical setting of atherosclerotic disease. Further studies are needed to confirm this.

BRS was not significantly reduced in patients with a history of stroke or TIA. This finding does not correspond well with that of Robinson et al, who reported a reduction of BRS in patients with acute stroke.9 The small number of patients with an insular lesion in our study may be a reason for our findings because previous experimental and clinical studies have suggested that the insular cortex modulates the sympathovagal balance.23,24 On the other hand, in their study of patients with acute stroke, Robinson et al did not consider CA, which may have been a potent determinant of BRS reduction. The discrepancy of our results with those of Robinson et al highlights the debate on vasculocentricity versus cerebrocentricity in the modification of the autonomous cardiovascular system in stroke patients.25 Although a number of experimental studies have shown that occlusion of the middle cerebral artery can significantly modify the cardiovascular regulation, clinical characteristics of stroke

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### TABLE 2. BRS According to the Severity of Atherosclerosis in Both Carotid Arteries

<table>
<thead>
<tr>
<th>CA score</th>
<th>BRS (ms/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n=32)</td>
<td>8.30 (1.21)</td>
</tr>
<tr>
<td>1 (n=15)</td>
<td>8.09 (1.11)</td>
</tr>
<tr>
<td>2 (n=15)</td>
<td>4.67 (0.76)</td>
</tr>
<tr>
<td>3 (n=1)</td>
<td>3.46</td>
</tr>
<tr>
<td>4 (n=5)</td>
<td>3.78 (1.05)</td>
</tr>
<tr>
<td>5 (n=6)</td>
<td>4.30 (1.05)</td>
</tr>
<tr>
<td>6 (n=1)</td>
<td>4.04</td>
</tr>
</tbody>
</table>

Values of BRS are means (SEM). BRS was significantly attenuated in patients with a CA score >1 compared with patients with a CA score of 0–1 (P=0.0005).

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patients are different because they often present with atherosclerosis on carotid and aortic segments where baroreceptors are located. In a recent report on the differential contribution of stroke and vascular modifications to BRS reduction in stroke patients, acute stroke was not related to cardiac BRS level when aortic stiffness was considered. Consistent with these findings, in our stroke patients, the bilateral character of CA outweighed stroke in BRS impairment.

HF and HF/T were found to be related to BRS in our study. These correlations are already known and reflect the vagal mediation of baroreflex activity. The positive correlation we found between LF and BRS is possibly attributable to the parasympathetic component of the LF band. More interesting is the negative correlation between bilateral CA and HF. HF is an indicator of the parasympathetic component of cardiovascular regulation by the autonomic nervous system. This result suggests that the sympathovagal balance is altered in bilateral CA with a relative decrease of the vagal component.

Although our results were statistically significant concerning the association between bilateral CA, BRS impairment and a shift of the sympathovagal balance, our study population may have been too small to detect other relevant clinical correlations such as BRS impairment in stroke patients that we discussed above and BRS impairment in hypertension. The association between hypertension and BRS reduction was not found to be statistically significant in our study. In addition to the relatively small number of hypertensive patients, this absence of correlation may be attributable to the fact that most of our hypertensive patients were under antihypertensive therapy. Although β-blockers and calcium inhibitors that may prolong the QT were exclusion criteria, other antihypertensive therapy such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may have increased the BRS in these patients, confounding the effect of hypertension on BRS. In contrast, BRS impairment in bilateral CA cannot be explained by the effect of these medications because more patients were under antihypertensive treatment. Although antihypertensive and statin therapy in bilateral CA group compared with unilateral CA and no CA groups. Despite the potential BRS increase resulting from these medications in the bilateral CA group, these patients still showed a reduction of BRS compared with patients with unilateral or no CA. Also, antihypertensive and statin therapy was forced into the multivariate analysis and did not affect the significance of bilateral CA in BRS impairment. Another limitation of our study is that the number of patients with severe atherosclerosis was relatively small compared with patients with mild atherosclerosis. Therefore, the absence of correlation between CA severity and BRS impairment should be interpreted with caution, even though, as discussed above, this absence of correlation is coherent with previous reports.

In conclusion, the present study demonstrates a reduction in BRS and a shift of the sympathovagal balance toward a relative decrease of the parasympathetic component of HR variability in patients with bilateral CA. These changes are already present when bilateral CA is only mild. Although our study was not designed to assess the clinical significance of the BRS impairment associated with bilateral CA, these findings have potential clinical implications. BRS impairment has been associated with increased SBP variability, which is an independent risk factor for stroke in untreated hypertensive patients. In addition, patients with low parasympathetic activity as defined by low short-term R-R interval variability have an increased risk for sudden death. Further investigations are therefore needed to assess the impact of BRS impairment on the risk of stroke and sudden death in patients with CA.

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References

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