Impaired Baroreceptor Reflex Sensitivity in Acute Stroke Is Associated With Insular Involvement, But Not With Carotid Atherosclerosis

Marek Sykora, MD; Jennifer Diedler, MD; Andre Rupp, PhD; Peter Turcani, MD; Thorsten Steiner, MD

Background and Purpose—Impaired baroreflex sensitivity (BRS) has been previously shown to be of prognostic value in patients with cardiovascular disease and stroke. Because baroreflex seems to be blunted by both carotid atherosclerosis and by lesions affecting central processing, controversy exists regarding the etiology of stroke-related baroreflex changes. The insula may play a central role in baroreflex modulation. The aim of the study was therefore to examine BRS in patients with acute stroke with regard to carotid atherosclerosis and insular involvement.

Methods—We evaluated spontaneous BRS in 96 patients with acute stroke within 72 hours of ictus and 41 control subjects using a sequential crosscorrelation method.

Results—Fifty-two patients with ischemic stroke and 44 patients with intracerebral hemorrhage, mean age 58.4 years, were included. With comparable carotid atherosclerosis profiles, patients with stroke had significantly lower BRS than control subjects (3.3 versus 5.3, \(P<0.001\)). Carotid atherosclerosis had no influence on variance of the BRS values in the acute stroke group. Patients with insular involvement had significantly lower BRS than patients with no insular involvement (2.55 versus 4.35, \(P<0.001\)) or control subjects (2.55 versus 5.3, \(P<0.001\)). Furthermore, patients with left insular involvement had significantly lower BRS than patients with right insular involvement (2.3 versus 3.5, \(P=0.049\)). There was no significant difference between patients with no insular lesions and control subjects (\(P=0.263\)).

Conclusions—We demonstrated that baroreflex impairment in acute stroke is not associated with carotid atherosclerosis but with insular involvement. Both insulae seem to participate in processing the baroreceptor information with the left insula being more dominant. (Stroke. 2009;40:737-742.)

Key Words: acute stroke ■ atherosclerosis ■ baroreflex sensitivity ■ dysautonomia ■ heart–brain relationships ■ insula

Baroreflex sensitivity and heart rate variability have been previously shown to be of prognostic value in patients with cardiovascular disease and in stroke.1–3 The baroreceptor reflex physiologically compensates spontaneous fluctuations in blood pressure. Baroreceptors are activated by changes in blood pressure; by adjusting the heart rate (vagal) and peripheral vascular tone (sympathetic), the baroreflex prevents wide differences in blood pressure from occurring. Baroreceptors are located in the region of carotid bifurcation and aortic arch, which are the most common sites for atherosclerotic lesions. Atherosclerosis may affect baroreceptor reflex-sensing by reducing wall distensibility.4 Studies in animals showed that atherosclerotic changes at the site of baroreceptors are associated with decreased baroreflex sensitivity.5 Analogously, the effects of carotid atherosclerosis on baroreflex sensitivity have been reported in humans as well.6–8 However, the baroreflex also seems to be influenced by lesions affecting central processing, particularly in hemispheric or brainstem stroke.9,10 Because stroke is directly or indirectly associated with atherosclerosis in the majority of cases, the question of vascular versus cerebral contribution in stroke-related baroreflex changes arises.11

The insular cortex seems to play a central role in modulating baroreflex sensitivity.12–14 Hemispheric lateralization of baroreflex control has also been suggested. Henderson et al studied functional MR changes to baroreceptor activation in cats and found the right insula to be involved in baroreflex-mediated blood pressure regulation.15 Likewise, Zhang et al found that significantly more cells responded to blood pressure changes in the right insula than in the left.16 Conversely, Hilz et al showed that baroreflex sensitivity (BRS) was decreased after inactivating the left hemisphere by administering intracarotid amobarbital in 15 patients with drug-resistant epilepsy.17 Lateralization of autonomic functions has also been reported in patients with acute stroke, but the data remain contradictory.18–20

Received March 12, 2008; accepted April 2, 2008.
From the Department of Neurology (M.S., J.D., A.R., T.S.), University of Heidelberg, Heidelberg, Germany; and the Department of Neurology (M.S., P.T.), Comenius University, Bratislava, Slovakia.
Correspondence to Marek Sykora, MD, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany. E-mail marek.sykora@med.uni-heidelberg.de
© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.519967
The aims of this study were thus (1) to evaluate BRS in patients with acute stroke with regard to carotid atherosclerosis; and (2) to explore the impact of insular involvement and laterality of the lesion on BRS.

Materials and Methods
Ninety-six consecutive patients admitted to our intensive care unit or stroke unit with acute ischemic stroke (IS) or intracerebral hemorrhage (ICH) within 72 hours after onset of symptoms were included in an open, prospective study. Patients with brainstem stroke, subarachnoid hemorrhage, or subarachnoid extension of ICH were excluded. We also excluded patients with a history of stroke, atrial fibrillation, myocardial infarction, diabetes mellitus, chronic renal failure, or other medical conditions known to affect autonomic functions. All patients included in the study were free of antihypertensive therapy or any cardiovascular active treatment at the time of the measurement. Those patients requiring continuation of antihypertensive therapy or any cardiovascular active treatment were excluded. Patients who had been withdrawn from antihypertensive therapy for at least 24 hours due to noncompliance or because no antihypertensive drugs were needed after stroke were included. The type of previous medication was noted. Forty-one control subjects matched for age, sex, history of hypertension, antihypertensive treatment, and atherosclerosis of carotids were enrolled from elective ophthalmologic surgery admissions. Subjects with a history of stroke or any other neurological disease, atrial fibrillation, history of myocardial infarction, diabetes mellitus, chronic renal failure, or other medical conditions known to affect autonomic functions or those presently requiring antihypertensive therapy or any cardiovascular active treatment were excluded. If patients had received antihypertensive drugs previously, they had to have been withdrawn for at least 24 hours before measurement and the type of medication was noted.

The diagnosis of IS or ICH was confirmed by CT or MRI. At admission, patients were scored according to the National Institute of Health Stroke Scale and modified Rankin Scale. The volume of stroke was calculated from the first CT or MRI scan using the "axial/longitudinal diameter of the zone of hypointensity (IS) or hypodensity (ICH) and c=number of sections where the lesion is presented multiplied by the diameter of the sections." This technique has been repeatedly validated and proved to be comparable to computer-assisted volumetric analysis. Insular involvement and the side of the lesion were noted.

Blood pressure for BRS assessment was measured noninvasively using the Finometer device (FMS; Finapres Medical Systems BV, Amsterdam, The Netherlands). This device uses a volume clamp method to capture beat-to-beat (continuous) values of blood pressure and pulse rate in the finger artery. A cuff of appropriate size was attached to the middle finger of the nonhemiparetic hand of patients or of the nondominant hand of control subjects in the supine position and the hand was maintained at the heart level. Continuous blood pressure and pulse rate were recorded by using the Finometer device within 72 hours after onset, once, for a period of 10 minutes. Baroreflex sensitivity was calculated as previously described. This method calculates the crosscorrelation between a 10-second systolic blood pressure series and a 10-second interbeat interval series delayed by 0 to 5 seconds. The delay giving the highest correlation is selected if significant at a preset level (P=0.01). Then the regression slope is recorded as one BRS value. Subsequently, the process is repeated for series of systolic blood pressure and interbeat interval samples 1 second later. BRS gain values were expressed in ms/mm Hg. An ultrasound examination of the carotid arteries was conducted in all subjects. Duplex ultrasonographic examination of the carotid arteries was performed with the Aspen Ultrasound System (Acuson, Mountain View, Calif). An atherosclerotic lesion was defined as localized intima media thickness >1 mm with a >100% increase in thickness compared with adjacent wall segments. Uni- or bilaterality of the lesions in the carotid bulb was recorded. A clinical neurological examination was conducted in all patients in the control group to exclude any possible neurological disorders. The local ethics committee approved the study. All patients or their relatives and all control subjects gave written informed consent.

Statistics
Distribution of the data was tested using histograms and a one-sample Kolmogorov-Smirnov test. For normally distributed data, the results are presented as mean, range, and SD, and for nonnormally distributed data as median, range, and interquartile range. For comparison between the groups, the χ2 test, Fisher exact test, Mann–Whitney test, Kruskal-Wallis test, or Student unpaired t test was used, as appropriate. Univariate analysis of variance was performed to explore the influence of various factors on baroreflex gain values. A stepwise multivariate linear regression model was used to study the associations with regard to independence. For correlation analysis, Spearmann’s correlation coefficient was used. Values of P<0.05 were considered statistically significant in all tests. All statistics were performed using the statistical software SPSS 15.0 for Windows.

Results
From October 2006 to December 2007, approximately 780 patients with acute stroke were screened for the study. Ninety-six patients with acute stroke and 41 control subjects were included. The characteristics and ultrasound findings did not differ significantly between the 2 groups (Tables 1 and 2). Clinical characteristics of the stroke group are shown in Table 3. Mean time from onset of symptoms to measuring BRS was 42.7 hours (range, 3 to 72). The BRS was significantly lower in patients with acute stroke than in the control group (acute stroke, 3.3; range, 0.7 to 21.1; interquartile range [IQR], 3.9; control: 5.3; range, 1.8 to 23.3; IQR, 3.2; P<0.001). In the 2 stroke subgroups (IS, ICH), the median BRS did not differ significantly (IS, 3.4; range, 1.1 to 17.8; IQR, 3.95; ICH, 3.3; range, 0.7 to 21.1; IQR, 4.13; P=0.817). In the correlation analysis and in univariate analysis of variance, BRS gain values in the stroke group were not associated with age, sex, history of hypertension, previous antihypertensive therapy, side of the lesion or type of the stroke, admission status, etiology of stroke, or time to measurement (all P>0.05). Furthermore, in the univariate analysis, atherosclerosis of the carotids or unilateral/bilateral atherosclerosis of the carotids did not influence the BRS values in the acute stroke group (Table 4). There was no difference in BRS between patients with or without carotid atherosclerosis (3.25 versus 3.5, P=0.85) and between patients with unilateral, bilateral, and no carotid atherosclerosis (unilateral, 4.6; bilateral, 3.3; no atherosclerosis, 3.25; P=0.37). In the control group, the subjects with atherosclerosis had lower BRS values than subjects without; however, the difference was not significant (4.9 versus 5.4; P=0.17). In the control group, a nonsignificant correlation trend was found between age and BRS (r=−0.3, P=0.058) and history of hypertension and BRS (r=−0.3, P=0.052).

In the univariate analysis, the BRS values in the acute stroke group were significantly associated with the stroke volume and insular involvement (Table 4). These effects also remained significant after adjusting the analysis for carotid atherosclerosis. When the effects of stroke volume and insular involvement on BRS were examined by using a stepwise linear regression model, insular involvement was...
significantly associated with BRS ($b=-0.38$, $P<0.001$), whereas volume of the stroke was not ($P=0.22$). Patients with insular involvement, regardless of the side, had significantly lower BRS than patients with no insular involvement (2.55 versus 4.35, $P=0.001$). Furthermore, patients with left insular involvement presented significantly lower BRS values than patients with right insular involvement (2.3 versus 3.5, $P=0.049$) and no insular involvement (2.3 versus 4.4, $P<0.001$) or control subjects (2.3 versus 5.3, $P=0.001$). Patients with right insular involvement had significantly lower BRS values than patients with no insular involvement (3.5 versus 4.4, $P=0.028$) or control subjects (3.5 versus 5.3, $P=0.001$). BRS did not differ significantly in patients with no insular involvement or in control subjects (4.4 versus 5.3, $P=0.263$; Figure). This finding could be repeated also when analyzing the ISs and ICHs separately (medians of BRS in IS: no insular involvement 2.3, $P=0.007$; medians of BRS in ICH: no insular involvement 4.3, right insular involvement 3.7, left insular involvement 1.9, $P=0.018$). The distribution of insular lesions did not differ significantly in the 2 subgroups (IS: no insular involvement 20 [38.5%], right insular involvement 16 [30.8%], left insular involvement 16 [30.8%]; ICH: no insular involvement 25 [56.8%], right insular involvement 13 [29.5%], left insular involvement 6 [13.6%]; $\chi^2=4.78$, $P$ not significant). Size of the lesions in IS and ICH was comparable (median, 33.8 mL versus median 40.4 mL, $P=0.238$). In the ICH subgroup, volume of the bleeding and presence of intraventricular blood correlated significantly with decreased BRS ($r=-0.58$, $P<0.001$ and $r=-0.33$, $P=0.026$). However, this effect disappeared when the analysis was adjusted for insular involvement. Lobar or deep localization of the ICH had no influence on BRS ($r=0.1$, $P=0.5$).

**Discussion**

The etiology of impaired cardiac BRS in acute stroke is still unresolved. In our study, we found no association between atherosclerosis of the carotids and decreased BRS in patients with acute stroke. Certainly, atherosclerosis of the carotid bulbus, an area with a high density of baroreceptors, modifies BRS. As previously shown by Gianaros et al, intima media thickness >0.9 mm in the carotid bulb was associated with reduced BRS.6 Uni- or bilaterality of the atherosclerotic lesions may also play a role. Nasr et al found a BRS impairment in bilateral, but not in unilateral, carotid atherosclerosis.7 Therefore, we studied a control group with a comparable carotid atherosclerosis profile, also including the uni- or bilaterality of the lesions. The 2 groups were also similar regarding other possible confounding factors, including age, hypertension, current blood pressure, and previous antihypertensive medication. We showed decreased baroreflex function in the stroke group as compared with control subjects, which we thus attribute to lesions affecting central processing. This is a new finding because previous studies demonstrating BRS impairment in acute stroke have not considered the possible effects of carotid atherosclerosis.10

Interestingly, the study by Eveson et al showed that a reduction in BRS was not related to stroke when adjusted for aortic stiffness.28 The aortic arch represents another area with a high density of baroreceptors, and atherosclerotic lesions at

---

**Table 1. Characteristics of Patients With Stroke and Control Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Stroke</th>
<th>Control</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>96</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Age, mean (range; SD)</td>
<td>58.2 (15–85;14.5)</td>
<td>54.1 (25–81;14.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>56 (58.3%) males</td>
<td>17 (41.4%) males</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61 (63.5%)</td>
<td>21 (51.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean (range; SD)</td>
<td>137.7 (77.5–220.9; 31.2)</td>
<td>134 (96.3–173.6; 19.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg, mean (range; SD)</td>
<td>73.2 (39.4–114.5; 15.4)</td>
<td>73.3 (51.9–93.4; 10.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mean (range; SD)</td>
<td>96.6 (60.5–146.9; 19.9)</td>
<td>96.9 (70.3–121.9; 13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, mean (range; SD)</td>
<td>74.8 (43.7–122.5; 15)</td>
<td>68.9 (48–96; 11.2)</td>
<td>NS</td>
</tr>
<tr>
<td>No previous antihypertensive therapy</td>
<td>68 (70.8%)</td>
<td>27 (65.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>14 (14.6%)</td>
<td>8 (19.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>16 (16.7%)</td>
<td>5 (12.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin receptor antagonists</td>
<td>7 (7.3%)</td>
<td>2 (4.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>9 (9.4%)</td>
<td>3 (7.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6 (6.3%)</td>
<td>3 (4.9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant at $P>0.05$.

---

**Table 2. Carotid Ultrasound Findings for the Stroke Group and Control Subjects**

<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>Acute Stroke</th>
<th>Control Subjects</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>96</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>No atherosclerosis of the carotids</td>
<td>50 (52.1%)</td>
<td>24 (58.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atherosclerosis of the carotids</td>
<td>46 (47.9%)</td>
<td>17 (41.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unilateral atherosclerosis</td>
<td>7 (7.3%)</td>
<td>3 (7.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bilateral atherosclerosis</td>
<td>39 (40.6%)</td>
<td>14 (34.1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant at $P>0.05$. 

---
found no association between BRS and age, hypertension, or previous antihypertensive treatment. Despite the mentioned measures, the effects of previous antihypertensive therapy on BRS may not be ruled out completely. However, we found no statistical significant influence when tested for this. Effects of age and hypertension on BRS, albeit not significant, were statistical significant influence when tested for this. Effects of previous antihypertensive therapy on BRS may not be ruled out completely. However, we found no association between BRS and age, hypertension, or previous antihypertensive treatment. Despite the mentioned measures, the effects of previous antihypertensive therapy on BRS may not be ruled out completely. However, we found no statistical significant influence when tested for this. Effects of age and hypertension on BRS, albeit not significant, were seen in the control group. We hypothesize that these effects were present also in the stroke group but were presumably outweighed by stroke-related changes in BRS.

The mean age in the stroke group was 58.4 years. The mean age in the patients with IS and those with ICH did not differ significantly (57.32 versus 59.33, £ 0.52). The lower mean age may have resulted in overrepresentation of patients with less severe atherosclerosis. Nevertheless, the degree of atherosclerosis has not been shown to influence BRS.

Insular cortex has been implicated in the control of cardiac baroreflex. We found no difference in BRS between patients with stroke with no insular involvement and control subjects matched for age, sex, hypertension, actual blood pressure, previous medications, and carotid atherosclerosis. Moreover, BRS was significantly lower in patients with left or right insular involvement than in patients without insular involvement and in control subjects. These findings suggest that both insulae play a role in supramedullary baroreflex regulation. In previous studies, both the left and right insula have been suggested to participate in the highly complex process of modulating BRS. Furthermore, baroreflex-related neuronal interconnections have been observed between the right and left insula, suggesting that the 2 insulae may interact in integrating circulatory control information.

Moreover, in our series, left insular lesions decreased BRS significantly more than did right insular lesions. This observation is in agreement with the findings of Hilz et al, who showed a decrease in BRS in conjunction with left-sided hemispheric inactivation in patients with epilepsy. Because BRS assessment in our study mainly addressed the parasympathetic component of the baroreflex, our findings may also
be seen as consistent with those of Zamrini et al, who showed right-sided dominance of sympathetic and left-sided dominance of parasympathetic modulation of heart rate and blood pressure during intracarotid amobarbital infusions in patients who had undergone epileptic surgery. Analogously, Oppenheimer et al demonstrated the same effects by direct stimulation of the insulae intraoperatively in patients with complex partial seizures. In line with these observations, acute left insular strokes were shown to augment sympathetic and decrease parasympathetic cardiac tone. Left insular strokes were also associated with adverse cardiac outcome due to the proposed shift with increased sympathetic tone and decreased parasympathetic tone. On the other hand, some studies in patients with IS found a reduction in parasympathetic and an increase in sympathetic heart rate modulation in right-sided strokes, contributing to the right–left controversy in central autonomic control. Interestingly, lesioning of the left insula increased BRS in rats. The discrepancy of our results with the latter may relate to species differences as well as to the effects of general anesthesia used in the rat experiment.

Of clinical importance, impaired BRS has been shown to independently predict mortality after myocardial infarction and was associated with poor prognosis of chronic heart failure. Similarly, decreased BRS has been related to less favorable long-term outcome after acute IS. Autonomic derangement seems to persist after stroke and may increase the risk of all-cause and cardiovascular mortality. However, investigating the effects of impaired BRS on outcome was beyond the scope of this study.

In summary, we observed baroreflex impairment in acute stroke independent of carotid atherosclerosis, adding more evidence to the concept of cerebrocentricty in stroke-related baroreflex changes. Moreover, the central role of the insula in baroreflex regulation could be demonstrated. Both insulae seem to participate in baroreceptor information processing in a complex manner, with the left insula being more dominant in baroreflex control presumably through parasympathetic outflow modulation.

Source of Funding
This study was supported by grant VEGA 1/3423/06 (P.T.).

Disclosures
None.

References


Impaired Baroreceptor Reflex Sensitivity in Acute Stroke Is Associated With Insular Involvement, But Not With Carotid Atherosclerosis
Marek Sykora, Jennifer Diedler, Andre Rupp, Peter Turcani and Thorsten Steiner

*Stroke*. 2009;40:737-742; originally published online December 31, 2008;
doi: 10.1161/STROKEAHA.108.519967
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/3/737

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/