Baroreflex and Cerebral Autoregulation Are Inversely Correlated
Nathalie Nasr, MD, PhD; Marek Czosnyka, PhD; Anne Pavy-Le Traon, MD, PhD; Marc-Antoine Custaud, MD, PhD; Xiuyun Liu, BSc; Georgios V. Varsos, BSc; Vincent Larrue, MD

Background: The relative stability of cerebral blood flow is maintained by the baroreflex and cerebral autoregulation (CA). We assessed the relationship between baroreflex sensitivity (BRS) and CA in patients with atherosclerotic carotid stenosis or occlusion.

Methods and Results: Patients referred for assessment of atherosclerotic unilateral >50% carotid stenosis or occlusion were included. Ten healthy volunteers served as a reference group. BRS was measured using the sequence method. CA was quantified by the correlation coefficient (Mx) between slow oscillations in mean arterial blood pressure and mean cerebral blood flow velocities from transcranial Doppler. Forty-five patients (M/F: 36/9), with a median age of 68 years (IQR:17) were included. Thirty-four patients had carotid stenosis, and 11 patients had carotid occlusion (asymptomatic: 31 patients; symptomatic: 14 patients). The median degree of carotid steno-occlusive disease was 90% (IQR:18). Both CA (P=0.02) and BRS (P<0.001) were impaired in patients as compared with healthy volunteers. CA and BRS were inversely and strongly correlated with each other in patients (rho=0.58, P<0.001) and in healthy volunteers (rho=0.939; P<0.001). Increasing BRS remained strongly associated with impaired CA on multivariate analysis (P=0.004).

Conclusions: There was an inverse correlation between CA and BRS in healthy volunteers and in patients with carotid stenosis or occlusion. This might be due to a relative increase in sympathetic drive associated with weak baroreflex enhancing cerebral vasomotor tone and CA. (Circ J 2014; 78: 2460–2467)

Key Words: Atherosclerosis; Autonomic nervous system; Baroreceptor; Carotid artery; Cerebrovascular circulation

The relative stability of cerebral blood flow (CBF) despite fluctuations in blood pressure is maintained by two regulatory mechanisms: the baroreflex and cerebral autoregulation (CA). The baroreflex controls blood pressure in the short term by modulating heart rate, cardiac contractility and vascular tone. CA refers to the capacity of cerebral vessels to react through vasodilatation or vasoconstriction to changes in cerebral perfusion pressure that would threaten either to reduce CBF or cause cerebral hyperemia. Both the baroreflex and CA can be impaired in carotid atherosclerosis.\(^5\)\(^-\)\(^4\) Attenuation of baroreflex sensitivity (BRS) in carotid atherosclerosis is likely to result from the reduced distensibility of carotid bulbs infiltrated by atherosclerosis.\(^5\)\(^6\) Also, it is possible that impaired BRS can accelerate atherosclerosis through inflammation and endothelial cell changes.\(^7\)\(^8\) The mechanism of CA impairment is less clear. CA impairment is usually viewed as a consequence of cerebral vessel dilation secondary to reduced perfusion pressure downstream of the carotid stenosis.\(^9\)

Whether baroreflex and CA are two independent or interdependent mechanisms is not known. Recent data in healthy volunteers showed an inverse correlation between CA and BRS,\(^9\) while other data did not confirm this inverse correlation.\(^11\)\(^12\) No data are available for a pathological setting such as carotid atherosclerosis.

The purpose of the present study was to test for the correlation between BRS and CA assessed in time domain, using the sequence method for baroreflex,\(^13\) and the Mx correlation method for CA,\(^14\) in patients with carotid atherosclerotic stenosis or occlusion and in a group of healthy volunteers.
Methods

Subjects

Carotid Stenosis or Occlusion Patients We retrospectively analyzed data for consecutive patients referred to the Neuroradiology Unit of Toulouse University Hospital between January 2007 and July 2012 for assessment of cerebral hemodynamics distal to a carotid stenosis or occlusion.

Patients with unilateral atherosclerotic ≥50% stenosis or occlusion of the internal carotid artery were considered for inclusion.

Exclusion criteria were: ≥50% stenosis or occlusion of contralateral internal carotid artery; ≥50% stenosis or occlusion of the ipsilateral intracranial carotid artery or middle cerebral artery (MCA); insufficient temporal bone acoustic window for transcranial Doppler (TCD) measurements; respiratory failure; history of sleep apnea syndrome; history of brainstem stroke; treatment with β-blockers, or calcium inhibitors that may increase the QT (diltiazem and verapamil); neurologic disease associated with impairment of the autonomic nervous system.

Carotid stenosis or occlusion was considered symptomatic if the patient had ischemic stroke, transient ischemic attack, or retinal ischemic event ipsilateral to the stenotic/occluded vessel during the previous 2 years.

The study was approved by the institutional review board. Patient consent to participate was not required because the study was retrospective and data had been acquired as part of routine clinical care.

Healthy Volunteers The control group consisted of 10 volunteers taking part in a prospective study that evaluated the cardiovascular and cerebrovascular consequences of microgravity simulation using anti-orthostatic positioning at −6° in healthy men. The data we used for this study were collected at baseline, before the volunteers underwent the anti-orthostatic experiment. Before CA was assessed, the ipsilateral cervical carotid artery was screened to rule out atherosclerosis.

The study in healthy volunteers was approved by the institutional review board. Volunteers gave written consent for their participation in the study.

CA and BRS were assessed using the same methods in healthy volunteers and in patients with carotid stenosis or occlusion.

Assessment of Carotid Stenosis

Carotid stenosis quantification was made using duplex sonography (Philips, IU22) based on the consensus of the Society of Radiologists in Ultrasound.15 The degree of carotid stenosis was confirmed using computed tomography (CT) or magnetic resonance (MR) angiography in all cases. Ruling out intracranial stenosis was based on CT or MR angiography.

Assessment of carotid stenosis using ultrasound was followed by assessment of the circulation in the ophthalmic artery distal to carotid stenosis or occlusion using transcranial color-coded sonography. Reversed circulation in the ipsilateral ophthalmic artery is a marker of severe hemodynamic impact of carotid stenosis or occlusion.16

Assessment of CA

CA was assessed using the Mx method14 using TCD in supine patients and healthy volunteers, at rest, during the same period as BRS assessment. The MCA distal to carotid stenosis or occlusion was insonated unilaterally through the temporal bone at a depth of 50–55 mm with a 2-MHz probe using a DWL Multidop X2 (DWL, Germany). The probe was then fixed using a rigid headframe (Lamrack; DWL). Continuous monitoring of ABP was achieved using a servo-controlled finger plethysmograph (Finapres, Ohmeda, CO, USA for patients with carotid stenosis; and Nexfin, BMI for volunteers). Mean ABP and mean CBFV velocities (CBFV) in the MCA were recorded over 10–20 min. Analog outputs from the pressure monitor and TCD unit (maximal frequency outline) were connected to an analog-to-digital converter and were synchronized. ABP and CBFV signals were collected into a computer and were analyzed using the Mx autoregulatory index.

Mx is a correlation coefficient derived from the spontaneous slow variations of mean ABP and mean CBFV.14,17 As compared to static and dynamic CA, the Mx method is best described as assessment of semi-static CA because it accounts for slow dynamic components of CA, correlating short- and mid-term variations of ABP and CBFV.18

Altered CA manifests as an increase in Mx. Mx close to +1 indicates that slow fluctuations in ABP produce synchronized slow changes in CBFV and indicate defective CA. Mx around 0 indicates that variations in ABP are not associated with variations in CBFV, indicating that CA is preserved. The magnitude of the increase in Mx reflects the severity of CA impairment.14,17 Determination of an absolute cut-off for CA impairment is difficult. The threshold of Mx >0.45 is believed to reasonably characterize CA impairment19 and is more specific as compared to the threshold of 0.3, which has also been used in previous studies.17

CA has been validated against the Aaslid et al reference method assessing dynamic CA.20,21 It also correlated well with the measurement of CA using steady-state methods.17

Assessment of BRS

Resting BRS was measured at rest using the sequence method23 with patients lying supine in a quiet room at controlled temperature. Cardiac inter-beat intervals were derived from 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 lowest arterial blood pressures were taken of ABP was achieved using a servo-controlled finger plethysmograph (Finapres, Ohmeda, CO, USA for patients with carotid stenosis; and Nexfin, BMI for volunteers). Mean ABP and mean CBFV velocities (CBFV) in the MCA were recorded over 10–20 min. Analog outputs from the pressure monitor and TCD unit (maximal frequency outline) were connected to an analog-to-digital converter and were synchronized. ABP and CBFV signals were collected into a computer and were analyzed using the Mx autoregulatory index.

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The run-time of systolic blood pressure and inter-beat interval monitoring was 10 min. Baroreflex sequences were defined by at least 3 consecutive beats in which the systolic blood pressure and R-R interval of the following beat either increased or decreased by at least 1 mmHg and 5 ms, respectively. 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 [inter-beat intervals]–[systolic blood pressure] variation sequences is considered to be an index of BRS.

Measurement of Cerebrovascular Reactivity

Assessment of cerebrovascular reactivity was based on the acetazolamide challenge. ABP and CBFV of MCA ipsilateral to carotid stenosis/occlusion were continuously monitored over 10 min before, and 30 min after i.v. acetazolamide 13 mg/kg.22

ABP and CBFV signals were synchronized, collected into a computer and analyzed using pdl (Notocord Systems, France).

Cerebrovascular reactivity to acetazolamide (CVR-ACZ) was defined as the maximal increase of mean CBFV averaged over 1-min periods up to 30 min after acetazolamide and was expressed as increase in percentage of baseline mean CBFV.23

CVR-ACZ <25% was considered as impaired.16,22
age of 68 years (IQR, 17 years) were included. Thirty-four patients had carotid stenosis, and 11 patients had carotid occlusion. The carotid lesion was asymptomatic in 31 patients, and symptomatic in 14 patients. The median degree of carotid sten-occlusive disease was 90% (IQR, 18%).

Thirty patients (68.9%) had hypertension, 9 patients (20%) had diabetes, 29 patients (64.4%) had hypercholesterolemia and 14 patients (31.1%) were smokers.

Median Mx, CVR-ACZ, and BRS in this group were, respectively, 0.461 (IQR, 0.312), 30.7% (IQR, 22.5%) and 4.75 ms/mmHg (IQR, 4.265 ms/mmHg).

Patients with carotid stenosis or occlusion had higher Mx (P=0.02) and lower BRS (P<0.001) than the healthy volunteers.

Similarly to healthy volunteers, Mx strongly correlated with BRS (rho=0.588, P<0.001; Figure 1) in patients with carotid atherosclerosis (respectively, rho=0.939, P<0.001; rho=0.588, P<0.001; Spearman’s rank correlation), indicating that worse autoregulation correlated with better BRS.

Patient characteristics according to CA impairment are summarized in Tables 1, 2. The degree of carotid steno-occlusive disease was not correlated with CA impairment (Table 1).

There was a non-significant trend toward an association between altered CA and reversed ophthalmic artery flow, ipsilateral to carotid stenosis or occlusion (P=0.09; Table 1). CA impairment was strongly associated with higher BRS (P<0.001; Table 2).

In patients with carotid stenosis or occlusion, the association of altered CA (ie, Mx>0.45) with BRS was further assessed on binary logistic regression. Variables associated on univariate analysis with altered CA with P<0.1 were included. Systematic adjustment was made for age, sex and degree of carotid steno-occlusive disease. Statistical tests were 2-tailed. The level of significance was set at P<0.05.

Results

Healthy Volunteers

The control group of healthy volunteers was composed of 10 men aged 20–44 years (median age, 38 years). Median Mx and BRS in this group were, respectively, 0.31 (IQR, 0.204) and 22.69 ms/mmHg (IQR, 9.869).

Mx strongly correlated with BRS (rho=0.939; P<0.001; Figure 1), indicating that enhanced BRS was associated with weaker CA.

Patients With Carotid Stenosis or Occlusion

A total of 45 patients, 36 men and 9 women, with a median age of 68 years (IQR, 17 years) were included. Thirty-four patients had carotid stenosis, and 11 patients had carotid occlusion. The carotid lesion was asymptomatic in 31 patients, and symptomatic in 14 patients. The median degree of carotid steno-occlusive disease was 90% (IQR, 18%).

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On logistic regression analysis adjusting for age, sex, carotid occlusion vs. stenosis and reversed ophthalmic artery flow, increasing BRS remained strongly associated with altered CA (P=0.004; Table 3).

CVR-ACZ measured in 40 patients was not correlated with BRS (rho=–0.182; P=0.262; Figure 2). There was no correlation between Mx and CVR-ACZ (rho=0.004, P=0.98; Figure 3). CVR-ACZ impairment was strongly associated with the degree of carotid steno-occlusive disease (P=0.001) and with

Statistical Analysis

Continuous data are given as median (IQR). Comparison of Mx and BRS in patients with carotid stenosis or occlusion vs. healthy volunteers was done using the Mann-Whitney U-test. Correlation between CA (Mx) and BRS as well as correlation between CVR-ACZ and BRS, and correlation between CA and CVR-ACZ were tested using Spearman rank correlation coefficient.

Comparisons between patients with normal CA and those with altered CA, and comparisons between patients with normal CVR-ACZ and those with altered CVR-ACZ were done using Fisher’s exact test for discrete variables and the Mann-Whitney U-test for continuous variables.

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Baroreflex and Cerebral Autoregulation

There was a major difference in the experimental protocol between the 2 studies: in the Tzeng et al study, as in the present study, baroreflex was not manipulated and the results were based on correlation between BRS and CA, which do not have absolute indexes and present with individual variations. In contrast, in the Ogoh et al study, acute suppression of BRS was performed in each subject.

The divergent results between the present study and the Tzeng et al study, and the Ogoh et al study could be explained by these large differences in the experimental protocols: acute suppression of baroreflex in the Ogoh et al study compared reversed circulation in the ophthalmic artery ipsilateral to carotid stenosis or occlusion (P=0.002).

### Discussion

BRS and CA were inversely correlated in healthy volunteers and in patients with carotid atherosclerotic stenosis or occlusion: weaker BRS correlated with better CA. This correlation was strongly significant and independent of potential confounders including age.

#### Inverse Correlation Between BRS and CA

This finding of inverse correlation between BRS and CA in patients with atherosclerosis is novel because there are no previous reports on such a correlation in a pathological setting.

The inverse correlation found between BRS and CA in healthy volunteers in the present study was found in 1 previous study, by Tzeng et al. In 19 volunteers, the authors assessed CA using the leg cuff test, and BRS using 3 methods: derived from nitroprusside, derived from phenylephrine and from low-frequency alpha index, and found that dynamic CA was inversely correlated with BRS.

This inverse relation between BRS and CA was not found in 2 other studies in healthy volunteers. In the Ogoh et al study, dynamic CA was assessed in 9 healthy volunteers using the leg cuff test before and after baroreflex suppression achieved using metoprolol and glycopyrrolate. They found that CA was attenuated after baroreceptor suppression, implying a direct (rather than inverse) relationship between BRS and dynamic CA.

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### Table 1. Subject Characteristics in Relationship With CA Impairment

|                  | Normal CA (n=22) | Impaired CA† (n=23) | P-value‡    |
|------------------|-----------------|---------------------|            |
| Age (years)      | 61 [18]         | 68 [17]             | 0.2        |
| Male             | 17 (77.2)       | 19 (82.6)           | 0.7        |
| Body mass index  | 25 [4]          | 25.7 [5.6]          | 0.751      |
| Hypertension     | 14 (63.6)       | 17 (73.9)           | 0.6        |
| Diabetes         | 6 (27.3)        | 3 (13.0)            | 0.2        |
| Hypercholesterolemia | 15 (68.2)     | 14 (60.9)           | 0.8        |
| Smoking          | 6 (27.3)        | 8 (34.8)            | 0.7        |
| ACEI or ARB      | 14 (63.6)       | 13 (56.5)           | 0.8        |
| Statins          | 18 (81.8)       | 16 (69.6)           | 0.5        |
| Symptomatic stenosis/occlusion | 6 (27.3) | 8 (34.8) | 0.7 |
| Degree of carotid disease (%) | 87.5±26        | 90±15               | 0.3        |
| Carotid occlusion | 6 (27.3)       | 5 (21.7)            | 0.7        |
| Reversed ophthalmic artery flow | 3 (15)       | 9 (40.9)            | 0.09       |

Data given as median [IQR] or n (%). †Mx >0.45. ‡Fisher’s exact test for discrete variables, Mann-Whitney U-test for continuous variables.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CA, cerebral autoregulation.

### Table 2. Heart and Brain Parameters in Relationship With CA Impairment

|                        | Normal CA (n=22) | Impaired CA† (n=23) | P-value‡    |
|------------------------|-----------------|---------------------|            |
| Heart rate (beats/min) | 72.5 [15]       | 68.5 [16.8]         | 0.152      |
| Mean ABP (mmHg)        | 101 [24]        | 100 [26.8]          | 0.555      |
| Mean CBFV (cm/s)       | 50.2 [26.4]     | 52.8 [20.1]         | 0.633      |
| BRS (ms/mmHg)          | 3.73 [3.54]     | 8.25 [6.85]         | <0.001     |

Data given as median [IQR]. †Mx >0.45. ‡Mann-Whitney U-test. ABP, arterial blood pressure (measured with Dinamap); BRS, baroreflex sensitivity; CBFV, cerebral blood flow velocities (measured in the middle cerebral artery with transcranial Doppler).

### Table 3. Multivariate Predictors of Impaired CA

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1–1.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex</td>
<td>1.7</td>
<td>0.2–16.1</td>
<td>0.665</td>
</tr>
<tr>
<td>Carotid occlusion vs. stenosis</td>
<td>1.1</td>
<td>0.1–10.9</td>
<td>0.906</td>
</tr>
<tr>
<td>Reversed ophthalmic artery flow</td>
<td>4.3</td>
<td>0.6–32.3</td>
<td>0.158</td>
</tr>
<tr>
<td>BRS</td>
<td>1.6</td>
<td>1.2–2.1</td>
<td>0.004</td>
</tr>
</tbody>
</table>

†After adjustment for age, sex, carotid occlusion vs. stenosis and reversed flow in the ipsilateral ophthalmic artery. ‡Mx >0.45. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.
with the intact baroreflex in the Tzeng et al study and in the present study.

In an earlier study, Ogoh et al demonstrated important changes in terms of participation of the vasomotor and cardio-regulatory efference of baroreflex to ABP regulation when baroreflex is acutely altered, as compared to baroreflex at baseline: participation of the vasomotor efference of baroreflex dropped from 77% at baseline to 0% during the first seconds that followed baroreflex impairment. Therefore, a potential impact of the vasomotor efference of baroreflex on CA could not be demonstrated in the study using acute autonomic blockade.

Aengevaeren et al compared 2 groups: 11 master athletes and 12 healthy sedentary elderly, for BRS and dynamic CA both assessed at rest using the transfer function. Additionally, CA was also assessed using the sit-stand test. A relationship between BRS and CA was not found. The Aengevaeren et al study differed from the present one methodologically in that the transfer function used by Aengevaeren et al assessed the rapid properties of CA rather than its slower dynamic components, which we assessed using Mx.

The present findings of inverse correlation between BRS and CA in carotid atherosclerosis are novel. Other disease, however, is likely to enhance this correlation. Hypertension is probably the most characteristic example suggesting an in-
verse correlation between BRS and CA. In hypertension, which is known to be associated with impaired BRS, most studies have found CA to be preserved. These 2 sets of results in hypertension—low BRS; preserved CA—have prevented the development of atherosclerosis in rats and is more associated with BRS than sympathetic activity. Decrease in vagal activity associated with low BRS in carotid atherosclerosis could thus result in the development of atherosclerosis in rats and rabbits. This effect was independent of ABP lowering. Also, in experimental studies on hypertensive rats, the restoration of BRS yielded protection against end-organ damage and against cognitive impairment. Thus, improvement of baroreflex function could be viewed as a potential therapeutic target not only in stroke but also in situations involving risk for cerebrovascular disease.

In humans, pharmacological and non-pharmacological interventions have been shown to improve baroreflex function. Pharmacological interventions include β-blockers, clonidine, moxonidine and mecobalamin. Non-pharmacological interventions include physical training and direct electric stimulation of carotid baroreceptors with an implantable device.

**Study Limitations**

The control group was composed of a small number of healthy volunteers (n=10) who were not matched for age or sex with patients with carotid atherosclerotic stenosis or occlusion. The control group was younger than the patient group. Expectedly, in the control group, BRS was higher and CA was lower as expected.
compared to the patients with carotid stenosis or occlusion. The aim of the study, however, did not pertain to this comparison. The aim was to assess the relationship between baroreflex and CA within the patient group and within the healthy volunteer group as a reference, using the same methods for baroreflex and CA assessment in both groups.

The use of TCD for CBF monitoring requires the diameter of the MCA to remain constant during the tests so variations of CBVf can be interpreted as variations of CBF. This potential limitation is inherent to all CA studies using TCD. A previous study using ABP variations during neurosurgical procedures showed that the diameter of the trunk of the MCA does not significantly change during ABP variations.50 The MCA diameter has also been found to be stable during ABP variation in an MRI study.51

CO₂ was not monitored during the tests. CO₂ is a potent cerebral vasodilator and its variations might have influenced the results of CA assessment. The Mx method, however, is based on averaging variations of ABP and CBVf over serial periods of time,14 which probably reduces the impact of episodic CO₂ variations due to sighs for instance on CBVf. Also, we excluded patients with clinical conditions associated with hypercapnia.

Conclusions
We found an inverse correlation between BRS and CA in healthy controls and in patients with carotid stenosis or occlusion. This inverse correlation might be due to baroreflex modulation of the autonomic drive to the cerebral vasculature.

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Disclosures
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