

Cardiac Baroreceptor Sensitivity Predicts Long-Term Outcome After Acute Ischemic Stroke

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Background and Purpose—The baroreceptor reflex arc is important in the short-term regulation of the cardiovascular system, and small studies have reported impaired cardiac baroreceptor sensitivity (BRS) after acute stroke. However, the prognostic significance of impaired BRS is uncertain.

Methods—One hundred twenty-four patients underwent simultaneous ECG and noninvasive beat-to-beat blood pressure (BP) monitoring within 72 hours of neuroradiologically confirmed acute ischemic stroke. Cardiac BRS was assessed from the combined α -index by means of power spectral analysis techniques. Baseline data for acute stroke patients were compared with those of a control group matched for age, sex, and casual BP. Patients were followed up for a median of 1508 days (range, 9 to 2656 days), and outcome was compared between patients with and without impaired BRS.

Results—Median BRS values were significantly lower in stroke patients than in controls (5 [interquartile range, 3.5 to 7.4] versus 6.2 [interquartile range, 4.5 to 8.3] ms/mm Hg; $P=0.04$). Sixty-one (33 male) patients (mean age, 70.2 [SD 10.5] years) had impaired BRS (≤ 5.0 ms/mm Hg) compared with 63 (35 male) patients (mean age, 70.6 [SD 11.7] years) without impaired BRS (>5.0 ms/mm Hg). Stroke patients with impaired BRS values had a significantly poorer prognosis (28% versus 8% mortality rate during the follow-up period) although there were no differences in age, stroke severity, stroke type, or casual or 24-hour BP parameters between the 2 groups.

Conclusions—Impaired cardiac BRS is associated with increased long-term mortality after acute ischemic stroke, irrespective of age, sex, stroke type, and BP. This may reflect cardiac arrhythmias, but the mechanisms underlying this association are unknown, although therapies that improve cardiac BRS after stroke warrant further investigation. (*Stroke*. 2003;34:705-712.)

Key Words: autonomic nervous system ■ cerebrovascular disorders ■ pressoreceptors ■ prognosis

The baroreceptor reflex arc, which includes peripheral afferent (aortic and carotid baroreceptors) and efferent (vagal and sympathetic tone) as well as central mechanisms (brain stem and higher cerebral centers), is important in the short-term regulation of the cardiovascular system. It is therefore not surprising that the reflex arc may be damaged after stroke given that central control mechanisms are vital for its integrity. Indeed, there is established evidence of abnormal baroreceptor sensitivity (BRS) in both animal models of stroke^{1,2} and patients with chronic cerebrovascular disease.^{3,4} Furthermore, we have previously reported a significant reduction in BRS in ischemic and hemorrhagic stroke patients studied within 72 hours of acute stroke onset compared with control subjects matched with respect to age, sex, and blood pressure (BP).⁵ Other groups have similarly reported abnormalities of cardiovascular autonomic control, including BRS and heart rate variability, after acute stroke.⁶⁻⁹

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Abnormalities of cardiovascular autonomic control have been reported to have prognostic significance after acute myocardial infarction and may be of importance in risk stratification after myocardial infarction.¹⁰ In particular, impaired cardiac BRS is associated with increased cardiac death and life-threatening ventricular arrhythmias.¹¹ The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study assessed cardiac BRS within a mean of 16 days in 1284 post-acute myocardial infarction patients and reported that significantly reduced BRS (<3.0 ms/mm Hg) was significantly associated with increased mortality over a mean follow-up period of 21 months. This effect was independent of other poor prognostic indicators, including impaired left ventricular function and frequent ventricular premature complexes.¹²

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Cardiac complications of acute stroke are common, may be associated with adverse prognosis, and include arrhythmias and symptoms related to concomitant ischemic heart disease.^{13,14} As in acute myocardial infarction patients, impaired BRS may be important in the development of such complications. We have previously shown that increased beat-to-beat BP variability, perhaps reflecting impaired cardiac BRS, is associated with 30-day outcome; the odds ratio for a poor outcome was 1.32 (range, 1.1 to 1.7) for every 1 mm Hg-increase in mean arterial BP variability.¹⁵ However, to our knowledge, the prognostic significance of impaired BRS after acute stroke has not been studied. The aim of this study was therefore to investigate the effects of acute ischemic stroke on BRS and to assess the short- and long-term prognostic significance of any observed changes.

Subjects and Methods

Subjects

One hundred twenty-four consecutive patients (68 male; mean age, 70.4 years; range, 39 to 89 years) with neuroradiologically confirmed first-ever ischemic stroke and admitted to the stroke units of the University Hospitals of Leicester National Health Service (NHS) Trust within 24 hours of acute ictus were studied. Median National Institutes of Health Stroke Scale (NIHSS) score on admission was 6 (interquartile range [IQR], 3 to 10). Stroke type, according to the Oxfordshire Community Stroke Project (OCSP) classification, was also recorded. Those patients requiring the continuation of antihypertensive therapy or any treatment with effects on cardiovascular or autonomic function were excluded. Unconscious patients and those with atrial fibrillation or neurological signs lasting <24 hours were excluded, as were patients with a past medical history or evidence at the time of study of diabetes mellitus, impaired renal function (creatinine >200 $\mu\text{mol/L}$), acute myocardial infarction, unstable angina, or other conditions with autonomic dysfunction.

A control group of 62 healthy subjects chosen to have a similar age, sex, and BP distribution (36 male; mean age, 68.2 years; range, 39 to 82 years) were also studied. These subjects were recruited from among respondents to a local newspaper advertisement. However, to ensure that the study groups would also be matched for casual systolic BP (SBP), a proportion of newly diagnosed or untreated hypertensive control subjects were recruited from among outpatient attendees at the University Hospitals of Leicester NHS Trust Hypertension Clinic and through a liaison with several large local general practices. Control subjects with known diagnoses of atrial fibrillation, ischemic heart disease, diabetes mellitus, or other conditions associated with autonomic dysfunction were excluded.

All subjects gave their informed written consent, and the Leicestershire local research ethics committee approved the study.

Protocol

All patients were assessed by 1 of 3 observers (T.G.R., S.L.D., P.J.E.) within 24 hours of symptom onset. If symptoms were first noticed by the patient on waking, then the time of stroke onset was taken as the time of onset of sleep. BP was recorded by 1 of 3 observers (T.G.R., S.L.D., P.J.E.) using casual and 24-hour techniques. Casual BP was measured in the hemiparetic arm according to recent British Hypertension Society guidelines (ie, 3 consecutive readings in the supine position with the arm at heart level, using a maintained and calibrated standard mercury sphygmomanometer and cuff of appropriate size), to the nearest 2 mm Hg. Control subjects were also assessed with casual BP recorded in the nondominant arm. The mean value was taken in subsequent analysis.

Twenty-four-hour BP monitoring was performed immediately after casual BP measurements with the use of a Spacelabs 90207 recorder (Spacelabs) and started within 24 hours of ictus in all patients. The accuracy of this device has been established according to criteria proposed by the British Hypertension Society.¹⁶ The

recorder was programmed to record BP at 15-minute intervals during the day (7 AM to 10 PM) and at 30-minute intervals at night (10:01 PM to 6:59 AM). BP recorded with the 24-hour BP monitor was calibrated against the casual BP at the beginning of the recording. Any patient in whom there was a discrepancy >5 mm Hg in SBP and diastolic BP (DBP) between the 2 methods was excluded. Data were downloaded onto an IBM-compatible personal computer for further analysis, and patients were excluded if there was <80% data capture. Data were automatically edited to exclude unphysiological readings, ie, those in which DBP was recorded higher than SBP, although no other editing was undertaken. The mean 24-hour BP, day and night SBP and DBP, and the difference between mean day and night SBP and DBP were recorded.

Furthermore, all patients attended the cardiovascular laboratory within 72 hours of acute ictus and at least 2 hours after a light meal, having abstained from smoking, alcohol, and all caffeinated products for at least 12 hours. Control subjects were also assessed on 1 occasion. The investigations took place in a quiet room (ambient temperature 20°C to 24°C), and the patients were asked to micturate before the study. The subject was fitted with chest leads for continuous ECG recording (model CR7, Cardiac Recorders Limited) and the appropriately sized cuff of the 2300 Finapres noninvasive BP monitor (Ohmeda). This is a fully automated instrument that allows continuous noninvasive assessment of finger arterial pressure. It uses the arterial clamp technique of Penaz¹⁷ and is well validated against intra-arterial BP measurements in all age groups.^{18,19} The cuff was fitted to the middle finger or thumb of the hemiparetic arm in stroke patients and nondominant arm in control subjects and was maintained at heart level by resting on an adjustable support throughout.

After a period of at least 15 minutes of rest and after achievement of a satisfactory BP signal from the monitor and the stabilization of BP at the same level (mean 2-minute BP levels not varying by >10 mm Hg over ≥ 10 minutes), recordings were performed for 3 sequential periods of at least 5 minutes each. The Finapres device has a built-in system (Physio-Cal) that briefly interrupts the BP recording automatically to keep the finger arteries fully unloaded and the transmural pressure equal to zero (usually for 2 to 3 beats every 70 beats). This was switched off during the recording period but applied at 10-minute intervals during the monitoring period. Subjects were asked to maintain a respiratory rate >15 breaths per minute, although respiratory rate and tidal volume were not formally measured. The analog outputs from the Finapres and simultaneous surface ECG recordings underwent analog-to-digital conversion at a rate of 200 samples per second and were downloaded to a dedicated personal computer for subsequent analysis and noninvasive estimation of cardiac BRS. Pulse interval (PI) variability was assessed from the SD of the beat-to-beat recordings.

Patients were further reviewed at 1 month after ictus, and the modified Rankin Scale (mRS) score was recorded. Patients were then classified as dependent if exhibiting a moderate to severe handicap (mRS ≥ 3) or independent with no to mild handicap (mRS ≤ 2).²⁰ Finally, mortality was recorded over a median follow-up period of 1508 days (range, 9 to 2656 days) after acute ictus. To ensure data capture as complete as possible, mortality outcome was assessed from a number of sources, including hospital medical records, hospital information systems, general practitioner records, and Health Authority returns from general practitioners and from the registrar for births, marriages, and deaths.

Data Analysis

Software specially written by the Leicester Warwick Medical School Division of Medical Physics (R.B.P.), and which is in routine use in the department at which these studies were undertaken,²¹ was used in the offline analysis of the beat-to-beat BP and PI recordings. The derived PI and SBP series were analyzed by means of power spectral analysis with fast Fourier transform with 512 samples. The data segments used were extracted under visual inspection from the most stable (ie, stationary) segment of each 10-minute recording. The beat-to-beat series of PI and SBP were interpolated with a third-order polynomial and resampled with an interval of 0.5 second to produce signals with a uniform time axis. The power spectra were obtained as

TABLE 1. Demographic and Cardiovascular Variables in Acute Stroke Patients and Control Subjects

Variable	Acute Strokes (n=124)	Control Subjects (n=62)	P Value
Age, y	70.4 (11.1)	68.2 (8.6)	0.14
Sex (M:F)	68:56	36:26	>0.2
Casual BP, mm Hg			
Systolic	163 (27)	161 (20)	0.68
Diastolic	88 (15)	90 (14)	0.42
Mean arterial	113 (17)	113 (14)	0.76
Pulse pressure	75 (21)	71 (15)	0.22
Pulse interval, ms	867 (141)	917 (124)	0.01
24-h BP, mm Hg			
Systolic	155 (21)	143 (17)	<0.001
Diastolic	86 (12)	82 (12)	0.02
Mean arterial	112 (15)	104 (13)	<0.001
Pulse pressure	68 (15)	61 (12)	<0.001
Diurnal BP fall			
Systolic	5 (-2, 13)	15 (12, 21)	<0.001
Diastolic	5 (-1, 10)	13 (8, 16)	<0.001

Values presented as mean (SD) for normally distributed data and median (interquartile range) for non-normally distributed data.

BP indicates blood pressure.

the average of 3 recordings for each patient and were smoothed with a 13-point triangular window. This produced estimates of power spectra of PI and SBP, coherence function, and frequency response between PI and SBP with 58 *df*. Coherence between BP and PI variability reflects the amount of linear coupling between the 2 spectra and is therefore comparable to the correlation coefficient in regression analysis. A coherence value >0.40 was considered significant.²² Recordings with an ectopy rate >2% were rejected. Spikes on the resampled tracings of the PI and SBP recordings were manually removed, and a straight line was interpolated by the computer, although resampled tracings with >4 spikes were excluded from subsequent analysis to avoid bias. Power spectral analysis was undertaken to calculate cardiac BRS as the α -index by means of standard methodology.⁵

Statistical Methods

Normality of the data was determined by construction of a normal probability plot with the use of the Minitab statistical package (Minitab 13 for Windows, Minitab Inc). If a value of $P < 0.05$ was

obtained with the Ryan-Joiner test, then the data were not considered normally distributed. For normally distributed data, the results are presented as mean (SD), and statistical comparisons between acute stroke and control groups were made with the Student's unpaired *t* test. For nonnormally distributed data, results are presented as median (IQR), and statistical comparisons between groups were made with the Mann-Whitney test. With the use of multiple logistic regression analysis, all clinically important variables were included in the model to predict death or dependency. Thereafter, the differences between groups for cardiac BRS measurement were inspected by plots of Kaplan-Meier survival functions. Statistical significance was taken at the 5% level.

Results

Acute stroke patients were studied, and control subjects were chosen to have a similar age and sex distribution (Table 1). Clinical diagnosis by the OSCP classification identified 43 total anterior circulation, 35 partial anterior circulation, 34 lacunar, and 12 posterior circulation strokes. All patients were confirmed to have ischemic stroke by neuroimaging (CT and/or MRI). No significant differences were seen in casual BP between the groups, although PI was significantly reduced in acute stroke patients (Table 1). We found that 24-hour BP monitoring was successful in 101 acute stroke patients and all control subjects; 24-hour BP was significantly higher in the acute stroke group (Table 1). There was also a significant reduction in diurnal BP fall in acute stroke patients compared with control subjects (Table 1). Cardiac BRS, assessed by the combined α -index, was significantly lower in acute stroke patients than in control subjects (5.0 ms/mm Hg [IQR, 3.5 to 7.4] versus 6.2 [IQR, 4.5 to 8.3]; $P = 0.04$; Figure 1).

Sixty-three of the acute ischemic stroke patients were dead or dependent (mRS ≥ 3) at 1 month after ictus. Compared with the 61 independent patients (mRS ≤ 2), these patients were significantly older, more likely to be female, more likely to have had a higher admission NIHSS score, and more likely to have sustained a total anterior circulation stroke (Table 2). Dead or dependent patients had nonsignificantly higher casual BP than independent patients (Table 2). Similarly, no significant differences were observed in BP parameters between the 50 dead or dependent and 51 independent patients with complete 24-hour BP recordings, although a significantly reduced diurnal BP change was recorded in the dead or dependent patients (Table 2). However, no differences were

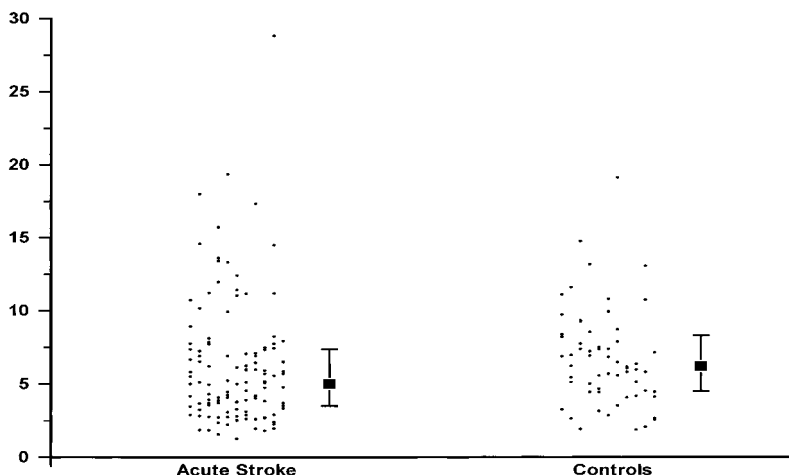


Figure 1. Median, IQR, and all values of cardiac BRS (ms/mm Hg) assessed by the combined α -index in control subjects and acute stroke patients.

TABLE 2. Admission Parameters in Acute Ischemic Stroke Patients Classified as Dead/Dependent or Independent at 1 Month Following Ictus

Variable	Dead/Dependent (n=63)	Independent (n=61)	P Value
Age, y	74.3 (10.0)	66.4 (10.8)	<0.001
Sex (M:F)	27:36	41:20	<0.01
NIHSS score	9 (7, 14)	3 (2, 5)	<0.001
OCSF (TAC:PAC:LAC:POC)	29:12:17:5	14:23:17:7	<0.01
Casual BP, mm Hg			
Systolic	166 (29)	159 (19)	0.17
Diastolic	87 (16)	89 (15)	0.65
Mean arterial	113 (18)	112 (16)	0.68
Pulse pressure	78 (22)	72 (20)	0.09
24-h BP, mm Hg			
Systolic	158 (23)	152 (19)	0.11
Diastolic	87 (13)	86 (11)	0.34
Mean arterial	113 (16)	110 (13)	0.26
Pulse pressure	71 (16)	65 (14)	0.06
Diurnal BP fall, mm Hg			
Systolic	1 (-4, 10)	9 (1, 14)	0.02
Diastolic	1 (-3, 7)	7 (1, 12)	0.004

Values presented as mean (SD) for normally distributed data and median (interquartile range) for non-normally distributed data.

NIHSS indicates National Institutes of Health Stroke Scale; OCSF, Oxfordshire Community Stroke Project classification; TAC, total anterior circulation stroke; PAC, partial anterior circulation stroke; LAC, lacunar stroke; POC, posterior circulation stroke; BP, blood pressure.

found in cardiac BRS measured by the combined α -index within 72 hours of acute ischemic stroke between dead or dependent and independent patients at 30 days after acute ictus (5.5 ms/mm Hg [IQR, 3.7 to 7.1] versus 5.0 [IQR, 3.3 to 7.7]; $P=0.62$). On multiple regression analysis, only age and total anterior circulation stroke were predictive of short-term (30-day) outcome (Table 3).

The overall mortality rate at the end of follow-up was 17.7% (n=22) over a median period of 1508 days (range, 9 to 2656 days). Outcome was compared between the 63 patients with cardiac BRS values greater than the median (5.0 ms/mm Hg) for the whole group and 61 patients with cardiac

TABLE 3. Predictor Variables at Admission of Death/Dependence Versus Independence at Day 30 Following Acute Ischemic Stroke: Results of a Multiple Regression Analysis

Predictor	Coefficient	P Value
NIHSS score >8	0.59	<0.001
Age, y	-0.01	0.004
Total anterior circulation stroke	-0.30	0.05
Cardiac baroreceptor sensitivity (ms/mm Hg)	0.01	0.21
Admission diurnal SBP fall (mm Hg)	0.00	0.24
Admission casual SBP (mm Hg)	0.00	0.68
Admission 24-h SBP (mm Hg)	0.00	0.93

S=0.37, R-Sq=54%, R-Sq (adj)=45.6%.

NIHSS indicates National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

BRS values equal to or below the median for the whole group.^{12,23} There were no significant differences in age, sex, admission NIHSS score, stroke type by the OCSF classification, or BP parameters between the 2 groups (Table 4). However, there were significant differences in PI variability, assessed from SD of beat-to-beat recordings, with reduced variability seen in the impaired cardiac BRS group (26.4 ms [IQR, 18.6 to 49.8] versus 51.0 [IQR, 34.4 to 63.7]; $P<0.001$). Furthermore, those patients with impaired cardiac BRS (\leq median) had a significantly higher mortality rate during the follow-up period (28% versus 8%; $P<0.006$; Figure 2). Those patients with impaired cardiac BRS also had a significantly higher mortality rate even when admission stroke severity (assessed with the NIHSS score) was considered (Figure 3). The causes of death in the impaired cardiac BRS patients included recurrent ischemic stroke (n=6), myocardial infarction (n=5), bronchopneumonia (n=3), cancer (n=2), and unknown (n=1). This compares with recurrent ischemic (n=2) and hemorrhagic stroke (n=1), myocardial infarction (n=1), and ischemic colitis (n=1) in the normal cardiac BRS group.

Discussion

Cardiac BRS, assessed by the combined α -index, was significantly lower in 124 stroke patients studied within 72 hours of neuroradiologically confirmed acute ischemic stroke compared with control subjects matched with respect to age, sex, and casual BP. This confirms our previously reported finding in a smaller study of 37 separate acute ischemic and hemorrhagic stroke patients.⁵ However, to our knowledge, this is the first study to report the long-term prognostic significance of impaired cardiac BRS after acute ischemic stroke. Over a median follow-up period of 1508 days, stroke patients with significantly impaired cardiac BRS (\leq median) had a significantly poorer prognosis with a mortality rate of 28% compared with 8% in patients without significantly impaired cardiac BRS ($>$ median). Importantly, the long-term prognostic significance of cardiac BRS was independent of other well-recognized variables, including age, BP, stroke severity, and stroke subtype.

This finding that impaired BRS may not be a benign phenomenon is in agreement the acute myocardial infarction data. La Rovere and colleagues²⁴ assessed BRS within 30 days of acute myocardial infarction and reported a mortality rate of 50% during a follow-up period of 2 years in patients with a BRS $<$ 3.0 ms/mm Hg compared with 3% in patients with a BRS $>$ 3.0 ms/mm Hg. These findings were subsequently confirmed in the much larger multicenter ATRAMI study and were found to be independent of other significant prognostic indicators, including left ventricular ejection fraction.¹² Interestingly, in both the ATRAMI and our own studies, impaired cardiac BRS appeared to be more of long- than short-term prognostic significance. Possible mechanisms to explain the prognostic significance of impaired BRS have been well studied in post-myocardial infarction patients.

First, impaired vagal reflexes may be associated with the development of life-threatening arrhythmias. Several studies have reported an increased incidence of ventricular tachycardia and/or sudden death²⁴⁻²⁸ in post-myocardial infarction patients with reduced BRS during a follow-up period of up to 2 years.

TABLE 4. Admission Parameters in Acute Ischemic Stroke Patients With Impaired (\leq Median) and Normal ($>$ Median) Cardiac Baroreceptor Sensitivity

Variable	Cardiac BRS (≤ 5.0 msec/mm Hg)	Cardiac BRS (> 5.0 msec/mm Hg)	P Value
Age, y	70.2 (10.5)	70.6 (11.7)	0.83
Sex (M:F)	33:28	35:28	>0.2
NIHSS score	5 (3, 9)	8 (4, 11)	0.13
OCSP classification (TAC:PAC:LAC:POC)	22:15:18:6	21:20:16:6	>0.2
Casual BP, mm Hg			
Systolic	164 (25)	161 (28)	0.59
Diastolic	91 (15)	85 (16)	0.05
Mean arterial	115 (16)	111 (18)	0.15
Pulse pressure	73 (21)	76 (20)	0.48
24-h BP, mm Hg			
Systolic	157 (22)	153 (21)	0.35
Diastolic	89 (11)	84 (13)	0.06
Mean arterial	113 (14)	110 (15)	0.24
Pulse pressure	68 (16)	68 (15)	0.88
Diurnal BP fall			
Systolic	4 (-6, 11)	6 (-1, 15)	0.18
Diastolic	3 (-1, 9)	6 (0, 11)	0.55

Values presented as mean (SD) for normally distributed data and median (interquartile range) for non-normally distributed data. BRS indicates baroreceptor sensitivity; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; TAC, total anterior circulation stroke; PAC, partial anterior circulation stroke; LAC, lacunar stroke; POC, posterior circulation stroke; BP, blood pressure.

Second, reduced BRS is associated with a shift in autonomic balance toward sympathetic dominance, not only as a result of impaired parasympathetic function but also as a result of increased sympathetic activity. In addition to arrhythmogenesis, sympathetic hyperactivity also leads to an increase in coronary vasoconstriction. It is therefore interesting to report that post-myocardial infarction patients with more depressed BRS are at greater risk of having significant 3-vessel coronary artery disease and an occluded infarct-related coronary artery.²⁹ Furthermore, thrombolysis treatment after myocardial infarction, ie, increased coronary artery patency, is associated with increased BRS.³⁰

Finally, sympathetic hyperactivity after myocardial infarction has other important effects, including increased platelet aggregability and impaired ventricular remodelling.^{31,32}

Impaired cardiac BRS after acute stroke may also be associated with central autonomic cardiovascular dysautoregulation, involving both the parasympathetic^{8,33-35} and sympathetic nervous systems.^{13,14,36,37} As with myocardial infarction, the poor prognosis associated with impaired BRS may be manifest through cardiac arrhythmias, which are a common complication of acute stroke.^{13,14,36,38,39} Interestingly, Giubilei and colleagues,⁴⁰ in a small study of 10 patients, reported that the 4

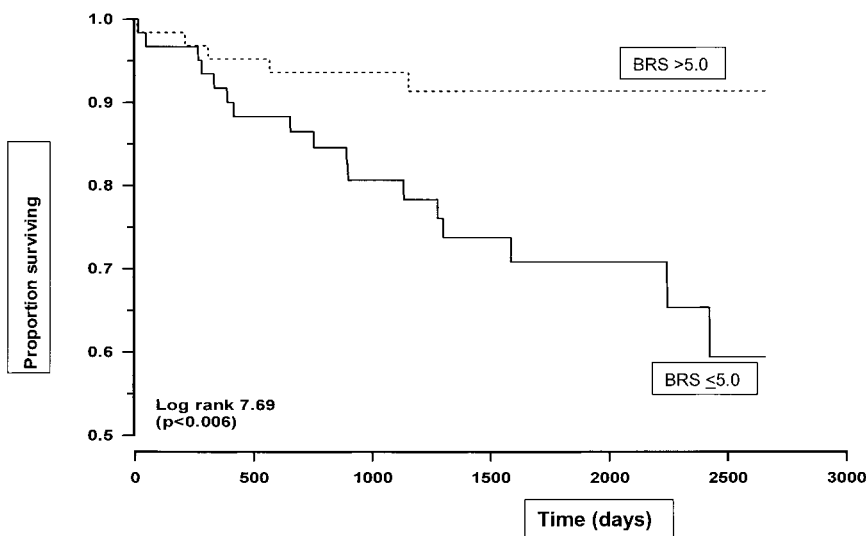


Figure 2. Kaplan-Meier survival curve by subgroups of cardiac BRS in ischemic stroke patients.

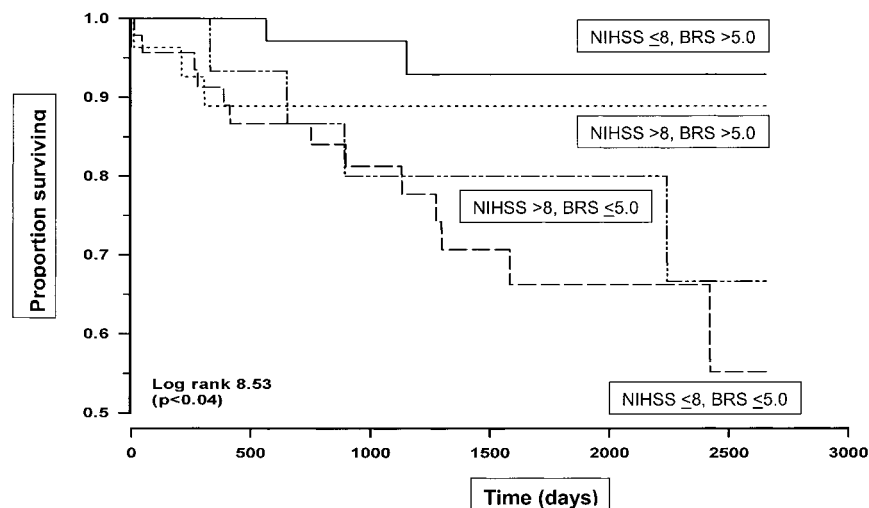


Figure 3. Kaplan-Meier survival curve by subgroups of cardiac BRS and NIHSS score in ischemic stroke patients.

patients with cardiac arrhythmias had significantly lower high-frequency power of heart rate variability than those without arrhythmias. It is a limitation of this study that 24-hour ECG was not undertaken. It is therefore not possible to confirm or refute this possible pathological mechanism to explain the poor prognosis in impaired BRS stroke patients, although the majority of patients died from vascular causes, including cardiovascular and recurrent stroke. However, impaired cardiac BRS and cardiovascular mortality may also be related to concomitant cardiovascular disease, although every effort was made to exclude symptomatic patients with recent myocardial infarction or unstable angina.

A further limitation of the study was that any treatment, including antithrombotic, statin, and angiotensin-converting enzyme inhibitor therapy, instituted during follow-up was not recorded. Such agents may be of prognostic benefit and influence disease mechanisms, although there is no reason to suppose that the impaired BRS group was less or more likely to receive these therapies. Furthermore, this study has reported other evidence of autonomic disturbance, including reduced PI variability in the impaired cardiac BRS group, again reflecting sympathetic predominance and associated with poor prognosis in acute myocardial infarction patients secondary to arrhythmias.¹⁰ Our study also reported reduced diurnal BP fall in acute stroke patients compared with control subjects, in agreement with our previous findings and again likely to reflect central autonomic dysfunction.⁴¹

It is also important to recognize the increasing body of evidence of hemispheric laterality in autonomic cardiovascular and baroreceptor control. Hilz and colleagues⁴² studied BRS in 15 patients with epilepsy refractory to drug therapy during ipsilateral hemispheric inactivation by intra-carotid artery amobarbital sodium injection. They reported that increased sympathetic nervous system activity and impaired BRS was only seen in left hemispheric inactivation, a finding in agreement with other epilepsy studies.^{43,44} A recent study in an animal stroke model has also reported evidence of hemisphere laterality, with the right posterior insular cortex regulating cardiac and vasomotor sympathetic tone and the left insular cortex regulating cardiac parasympathetic and baroreceptor function.⁴⁵ Although evidence of hemispheric laterality has been reported in human acute

stroke patients, the results are contradictory. We have reported a reduction in the high-frequency power and an associated increase in the low- to high-frequency ratio of PI variability after right hemisphere stroke.⁵ Barron and colleagues⁷ found reduced parasympathetic cardiac innervation after right hemisphere stroke, again confirming sympathetic predominance in association with right hemisphere stroke. However, Korpelainen and colleagues⁹ found autonomic cardiovascular disturbances in both right and left hemisphere and medullary, but not pontine, infarcts. It is therefore possible to hypothesize that impaired BRS may be related to stroke site and type, although this information is not provided from the present study.

In summary, this study has demonstrated that impaired cardiac BRS is of long-term prognostic significance after acute stroke, in agreement with findings in the myocardial infarction population. The mechanisms are unclear but may relate to the arrhythmogenic potential of alterations in cardiovascular autonomic balance. However, other manifestations of sympathetic predominance, including increased platelet aggregability, may also be important. Further work is therefore needed to elucidate the pathophysiological mechanisms and in particular the importance of stroke type and site. Therapeutic strategies, including administration of prophylactic arrhythmic agents to high-risk groups or angiotensin-converting enzyme inhibitors to increase BRS activity, could then be tested.

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Editorial Comment

Vasulocentricity Versus Cerebrocentricity: What Stroke-Related Baroreceptor Reflex Sensitivity Changes Might Be Telling Us

It may be suggested that a cerebrocentric approach to stroke is incomplete: the majority are embolic and directly or indirectly related to atherosclerosis. A vasulocentric view might be more viable: atherosclerosis rarely affects a single vascular territory.

Stroke is therefore an indicator of a system-wide phenomenon.¹ Additionally, cerebral infarction can significantly affect cardiovascular regulation. More than 50 years of research has demonstrated the validity of this concept.²

In the accompanying article, Robinson et al report on the result of baroreceptor sensitivity (BRS) assessment in 124 patients after ischemic stroke. Increased mortality after a median of 4 years was predicted by $BRS \leq 5$ ms/mm Hg, with the survival curves diverging markedly after 500 days. Stroke severity did not appear to influence this finding.

This report has important implications and raises intriguing questions. First, could BRS derangement actually have preceded the index stroke? Might it be a marker for widespread atherosclerosis? Atheroma often affects the carotid sinus and aortic arch, specialized vascular segments where baroreceptors are located. In the dog, BRS can be substantially reduced by experimental carotid atheroma involving the carotid sinus.³ In the human, carotid atheroma also decreases BRS, and endarterectomy may improve baroreceptor reflex function: major vascular events were significantly more common in patients in whom carotid endarterectomy failed to increase BRS postoperatively than in those in whom such an increase was observed.⁴

The concomitance of aortic, coronary, and carotid artery atheroma has been noted, the concordance dependent on the aortic segment involved.¹ Coronary artery disease is predicted by ascending aorta atheroma. Arch atheroma (including the baroreceptor regions with consequences affecting BRS), on the other hand, is associated with carotid stenosis $>70\%$. Subsequent vascular event mechanisms therefore include embolization from an aortic plaque or from the heart and progression of latent coronary artery disease during the follow-up period.

On the other hand, are the BRS changes related to a direct effect of the central lesion on cardiovascular regulation? In anesthetized rats, lesions confined to the posterior left insular cortex (a region noted for its involvement in cardiovascular control) increased BRS.⁵ In the present study BRS decreased after stroke. Possibly stroke in locations other than the insula affects BRS differently. However, in our model lesions restricted to the right insula, both anterior insulae, or the surrounding cortex had no effect on BRS. These disparities most likely relate to species and state-dependent differences as well as lesion location.

The authors speculate that BRS reduction may indicate increased sympathetic tone, which certainly has been observed after stroke.⁶ Such changes are associated with QTc prolongation, ventricular tachyarrhythmias, and sudden cardiac death.⁷ How might this predict subsequent stroke or myocardial infarction? One possibility is that deaths were erroneously attributed, being actually sudden in nature and related to cardiac arrhythmia. Alternatively, increased vascular sympathetic tone may cause intraplaque hemorrhage and platelet accretion with a risk of subsequent thromboembolism. This spectrum of changes can be induced in the canine

coronary artery by stimulation of the left stellate ganglion (a source of cardiac and coronary sympathetic neural supply).⁸

Possibly these patients were suffering from latent coronary artery disease. Significant reduction in BRS has been reported with coronary atherosclerosis and heart failure, and this signals an adverse prognosis.⁹ While the authors made an effort to remove patients with a cardiac history, the incidence of significant asymptomatic coronary artery disease in stroke patients is particularly high (40% to 50%) and could have contributed to the findings in this study.¹⁰

Whatever the underlying mechanisms, the implications are clear. Reduced BRS is a prognostic indicator for adverse vascular outcome after ischemic stroke, as it is after myocardial infarction. In practical terms, these measurements can be made easily. They do not require complex machinery, and the software could be provided to stroke units and vascular clinics. Patients demonstrating $BRS \leq 5$ ms/mm Hg may well be candidates for sympatholytic treatment, which has been shown to affect outcome significantly after myocardial infarction. Stroke patients should be considered for assessment of total atheroma burden (coronary, aortic, renal artery, and peripheral). Might it not be best to view stroke as embedded in a system-wide dysfunction and investigate patients in a general vascular context?

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