Autonomic Function Is Impaired in Elderly Stroke Survivors

Andrew McLaren, MRCP; Simon Kerr, MRCP; Louise Allan, MRCP; I. Nicholas Steen, PhD; Clive Ballard, MD, MRCPsych; John Allen, PhD; Alan Murray, PhD; Rose Anne Kenny, MD, FRCP

Background and Purpose—Impaired autonomic function is common in the acute poststroke phase but little is known about the longer term effects, particularly in older people. We sought to determine if autonomic function is impaired after stroke recovery in older patients.

Methods—A cross-sectional case-control study comparing autonomic function in 76 nondemented stroke patients with 70 community-living controls aged older than 75 years.

Results—Cases were assessed on average 9 months after stroke. From power spectral analysis of heart rate variability, stroke patients had lower total (P=0.032) and low-frequency (P=0.014) spectral densities and impaired baroreflex sensitivity (α low-frequency baroreflex sensitivity, P=0.006). From a series of cardiovascular autonomic reflex tests, heart rate variation during forced respiration, Valsalva ratio, and blood pressure overshoot during Valsalva maneuver were significantly lower in stroke patients (P=0.003, <0.001, and 0.027, respectively). Blood pressure response to isometric exercise was significantly exaggerated in stroke patients (P=0.007).

Conclusions—Cardiovascular autonomic function is impaired long after the index event in stroke survivors. Impaired autonomic function may increase the risk of all-cause mortality and cardiovascular mortality in older stroke survivors. (Stroke. 2005;36:1026-1030.)

Key Words: autonomic nervous system ■ stroke

Fatality rates 1 month after stroke are high, ≈23% for all-cause stroke.1 Long-term mortality is also higher than the general population with >2-fold relative risk of death for those surviving beyond 30 days.2 The majority of deaths beyond 30 days are caused by nonstroke-related events, in particular cardiac death.3 One-year fatality rate is ≈31% for cerebral infarction and ≈37% for all-stroke causes.4 From the Dutch TIA Trial Study, sudden death accounted for 43% of serious cardiac events (death or nonfatal myocardial infarction) during long-term follow-up of patients after transient ischemic attack or minor stroke.5

It is clearly established that abnormal autonomic control, measured by heart rate variability, is an independent predictor of death after myocardial infarction.5,6 Reduced heart rate variability has been consistently associated with increased risk of cardiac and overall mortality, and it is hypothesized that this is because of sudden arrhythmic death caused by autonomic imbalance.7

Previous studies of younger stroke patients (mean ages 52 to 69 years) indicate that autonomic function is deranged immediately after stroke,8–10 but little is known about changes in autonomic function over the longer-term. In one study of 31 stroke survivors (mean age 52), autonomic function was impaired up to 6 months after stroke.9 However, there are no long-term studies of autonomic function in older stroke survivors. We hypothesized that impaired autonomic function is persistently impaired after the index event in older stroke patients.

Patients and Methods

Stroke patients 75 years of age or older were recruited from consecutive patients on representative hospital-based stroke registers in Tyneside, UK. Patients had been discharged from hospital and were free of dementia11 or any disabilities that would preclude compliance with autonomic function tests and in sinus rhythm. Stroke was defined using the World Health Organization definition.12 The patient cohort was assessed at a minimum of 3 months after stroke. Evaluation included a cardiovascular and neurological assessment (Oxfordshire Community Stroke Project classification,13 current Scandinavian Stroke Study long-term score14) and head computed tomography (CT) scan results from the index stroke. Case controls were volunteers, matched for age of older community-dwelling people. They had no previous history of transient ischemic attack or stroke, were not institutionalized, and had no evidence of dementia.
The investigation sequence was the same for stroke patients and controls. All subjects were asked to refrain from smoking and caffeine ingestion on the day of the investigations and to eat only a light breakfast. All investigations were performed between 9:00 AM to 1:00 PM in a warm, quiet room. There was a 10-minute supine rest phase before investigations commenced and a 2-minute rest phase after individual tests. The study was approved by the local research ethics committee. All participants gave informed written and signed consent to the study.

Heart Rate Variability and Baroreflex Sensitivity

Single-lead electrocardiogram (ECG) and blood pressure pulses (Portapres TNO) were captured to computer for 5 minutes while subjects lay supine and breathing naturally (sampling rate 1 kHz). Beat-to-beat R wave interval and systolic blood pressure data were extracted using in-house software, with artifact and nonsinus beats removed using a semi-automated interpolation technique. The power spectral density was calculated using fast Fourier transformation-based techniques to obtain the power in 3 separate frequency bands according to international guidelines: low-frequency, 0.04 to 0.15 Hz; high-frequency, 0.15 to 0.40 Hz; and total power <0.40 Hz. The baroreflex sensitivity was determined by a validated technique of synchronization of systolic blood pressure and RR interval data. The α index of baroreflex sensitivity was calculated in the same low-frequency and high-frequency bands using the cross-spectral densities between RR and systolic pressure variability when mutual coherence exceeded 0.5.15

Cardiovascular Reflex Autonomic Tests

ECG and blood pressure data were also recorded to computer during active stand, isometric exercise, Valsalva maneuver, and cold pressor and forced respiration tests. Any recording with excessive movement artifact or nonsinus activity was excluded from the analysis. The 30:15 ratio was obtained from the maximum and minimum RR intervals after standing.18 Orthostatic blood pressure change was the change from mean systolic blood pressure for the 20 beats immediately before standing to nadir during active standing for 3 minutes. Isometric exercise was performed by rising from the supine to sitting position while legs remained flat on the couch, and remaining in that position for 3 minutes. The response was the difference between the mean diastolic blood pressure values for the 20 beats before sitting and 20 beats immediately before the end of isometric exercise. Valsalva maneuver was performed by blowing into a tube at 40 mm Hg for 15 seconds on 3 occasions. The Valsalva ratio was the ratio of maximum/minimum RR interval, and systolic blood pressure response was recorded from baseline to overshoot. Largest ratio and systolic blood pressure response were used for analysis.21 For the cold pressor test, participants immersed the hand in ice-cold water for 1 minute.22 Diastolic blood pressure response was calculated from the 20 beats before immersion to the 20 beats during the final phase of immersion. The mean E/I difference (change in heart rate from inspiration to expiration) was calculated from 6 deep timed breaths over 1 minute.23 The 24-hour ambulatory blood pressure measurement was performed using Spacelabs 90207 monitors (Spacelabs Medical).

Statistical Analysis

Differences in frequency of categorical data were analyzed using Pearson χ² test. RR interval and heart rate variability data were transformed using the natural logarithm, and then group means were compared using the t test to provide a confidence interval for the observed differences. Blood pressure may influence heart rate variability and baroreflex sensitivity.24,25 Analysis of covariance was used to determine whether observed differences in autonomic function could be explained by the difference in systolic ambulatory blood pressure. Stepwise multiple linear regression was used to determine if observed differences in autonomic function could be explained by other potential confounding factors. History of hypertension, chronic obstructive pulmonary disease and/or asthma, myocardial infarction, peripheral vascular disease, diabetes or cardiac failure, alcohol use, and prescription of thiazide, calcium channel-blocker or β-blocker, age, and ambulatory systolic blood pressure were treated as explanatory variables for each autonomic outcome variable. Least significant variables were removed until only significant terms remained, then stroke or control status was entered to obtain the significance of group status as an explanatory variable after adjustment for confounding factors. A significance level of 5% was adopted and, when appropriate, results are given in the form of 95% CI.

Results

Sample Characteristics

Seventy-six stroke patients and 70 controls were enrolled. There was no significant difference in age, gender, body mass index, or comorbidity between the controls and stroke patients with the exception of hypertension (P<0.001) and respiratory disease (asthma or chronic obstructive pulmonary disease, P=0.018) (Table 1). The mean interval from stroke to autonomic assessment was 9±4 months (range, 4 to 28 months). The median long-term Scandinavian Stroke Study score was 47 (interquartile range, 44 to 48). Thirty-two cases had a partial anterior stroke, 26 lacunar, 13 posterior, 2 anterior circulation stroke, and 3 were not classifiable. Fifty-three cases had a visible cerebrovascular lesion (relevant or old) on CT scan at the time of incident stroke: 30 cases had a relevant lesion alone, of which 28 were ischemic infarctions and 2 were infarction with hemorrhagic transformation. Thirteen cases had a combination of relevant plus old lesions, which were all ischemic infarcts, and 10 had only old lesions, which were all ischemic infarcts. Twenty-three cases had no visible lesion on CT.

Prescription of thiazide diuretics (P<0.001) and calcium channel blocker (CCB) (P=0.029) were more frequent in stroke patients. There was no significant difference in other cardiovascular drugs (Table 2). Mean systolic ambulatory blood pressure was higher in stroke patients (130±13 versus 138±15 mm Hg; P=0.001) but there was no difference between diastolic ambulatory blood pressure (70±8 versus

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics</th>
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<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td>Mean age, y</td>
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<tr>
<td>Body mass index, kg/m</td>
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<tr>
<td>Male</td>
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<tr>
<td>Cardiac failure</td>
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<td>Myocardial infarction</td>
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<td>Angina</td>
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<td>Hypertension</td>
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<td>Peripheral vascular disease</td>
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<td>Asthma or COPD</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Current smoker</td>
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<td>Current alcohol</td>
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</table>

*P Pearson χ² exact significance (2-sided) except for * where Student’s t test. COPD indicates chronic obstructive pulmonary disease.
The increase in systolic blood pressure from baseline to peak phase IV of Valsalva maneuver was less in stroke patients (control, 24.3±23.2 mm Hg; stroke, 16.4±17.1; $P=0.027$). Diastolic blood pressure change was exaggerated in stroke patients during isometric exercise (control, 12.0±11.4 mm Hg; stroke, 18.4±15.1 mm Hg; $P=0.007$). The increase in diastolic blood pressure during the cold pressor test (control, 8.6±10.0 mm Hg; stroke, 10.7±13.3 mm Hg) and decrease in systolic blood pressure during orthostasis (control, 24.5 mm Hg; stroke, 31.6 mm Hg) were not significantly different.

After analysis of covariance with systolic ambulatory blood pressure as covariate, the differences in autonomic function remained significant apart from total and low-frequency powers of heart rate variability. After multiple linear regression with all potential confounding factors, the differences in autonomic function remained at the significant level apart from the systolic blood pressure overshoot during Valsalva maneuver ($P=0.052$).

### Discussion

This study demonstrates for the first time that cardiovascular autonomic function is persistently deranged after stroke in older people. Total and low-frequency heart rate variability and baroreflex sensitivity in the low-frequency range were impaired in stroke patients. For the reflex tests, RR interval variation and blood pressure overshoot during Valsalva maneuver, as well as variation in heart rate during forced respiration were impaired in stroke patients, along with an abnormal exaggeration in blood pressure response to isometric exercise.

The lower E-I difference and Valsalva ratio in stroke cases is consistent with impaired cardiovagal function. This conclusion is reinforced by the trend toward reduced high-

### Autonomic Function

Autonomic function data are shown in Table 3. Heart rate variability was decreased in the stroke patients. There were reductions in total power ($P=0.032$) and low-frequency power spectral densities ($P=0.014$), and a trend for impaired high-frequency power ($P=0.111$) in stroke patients.

Baroreflex sensitivity as measured by the $\alpha$ coefficient was reduced in the low-frequency range in stroke patients ($P=0.006$). Stroke patients had impaired cardiovagal function based on Valsalva ratio (medians: control, 1.36; stroke, 1.23) and the E-I difference (medians: control, −6.87 bpm; stroke, −4.85 bpm). The 30:15 ratio was not different between groups (medians: control, 1.11; stroke, 1.10).

### TABLE 3. Autonomic Function in Controls and Stroke Patients

<table>
<thead>
<tr>
<th>Variable (Control No., Stroke No.)</th>
<th>Mean±Standard Deviation</th>
<th>Difference in Means Student $t$ Test</th>
<th>Difference in Means Adjusted for Ambulatory SBP</th>
<th>Difference in Means Adjusted for All Confounding Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Stroke</td>
<td>95% CI $P$</td>
<td>95% CI $P$</td>
<td>95% CI $P$</td>
</tr>
<tr>
<td>Log 30:15 ratio (65, 71)</td>
<td>0.12±0.10 0.12±0.12</td>
<td>−0.04, 0.04 0.956</td>
<td>−0.05, 0.03 0.710</td>
<td>−0.04, 0.03 0.732</td>
</tr>
<tr>
<td>Log Valsalva ratio (66, 69)</td>
<td>0.32±0.15 0.22±0.13</td>
<td>0.06, 0.15 &lt;0.001</td>
<td>0.06, 0.16 &lt;0.001</td>
<td>0.06, 0.15 &lt;0.001</td>
</tr>
<tr>
<td>Log E-I difference (66, 73)</td>
<td>1.95±0.57 1.65±0.61</td>
<td>0.11, 0.50 0.003</td>
<td>0.09, 0.51 0.005</td>
<td>0.00, 0.42 0.049</td>
</tr>
<tr>
<td>Log SD RR interval (64, 68)</td>
<td>3.38±0.54 3.21±0.44</td>
<td>0.00, 0.34 0.044</td>
<td>−0.02, 0.33 0.085</td>
<td>0.03, 0.36 0.025</td>
</tr>
<tr>
<td>Log total power (64, 68)</td>
<td>6.31±1.17 5.90±0.96</td>
<td>0.04, 0.77 0.032</td>
<td>−0.05, 0.72 0.084</td>
<td>0.04, 0.77 0.032</td>
</tr>
<tr>
<td>Log low-frequency power (64, 68)</td>
<td>5.16±1.28 4.65±1.05</td>
<td>0.10, 0.91 0.014</td>
<td>−0.00, 0.84 0.052</td>
<td>0.10, 0.91 0.014</td>
</tr>
<tr>
<td>Log high-frequency power (64, 68)</td>
<td>4.70±1.44 4.33±1.23</td>
<td>−0.09, 0.83 0.111</td>
<td>−0.09, 0.88 0.113</td>
<td>−0.14, 0.77 0.174</td>
</tr>
<tr>
<td>Log alpha BRS low-frequency (41, 39)</td>
<td>1.80±0.67 1.40±0.57</td>
<td>0.12, 0.68 0.006</td>
<td>0.09, 0.68 0.012</td>
<td>0.23, 0.39 &lt;0.001</td>
</tr>
<tr>
<td>Log alpha BRS high-frequency (50, 59)</td>
<td>1.89±0.85 1.68±0.10</td>
<td>−0.10, 0.51 0.189</td>
<td>−0.14, 0.50 0.270</td>
<td>−0.06, 0.51 0.124</td>
</tr>
<tr>
<td>$\Delta$SBP standing/mm Hg (65, 72)</td>
<td>24.5±14.7 23.6±13.3</td>
<td>−15.5, 1.2 0.096</td>
<td>−15.5, 2.1 0.133</td>
<td>−14.5, 2.3 0.153</td>
</tr>
<tr>
<td>$\Delta$DBP isometric exercise/mm Hg (64, 74)</td>
<td>12.0±11.4 18.4±15.1</td>
<td>−10.9, −1.8 0.007</td>
<td>−9.7, −0.4 0.033</td>
<td>−17.0, −1.1 0.027</td>
</tr>
<tr>
<td>$\Delta$DBP cold pressor/mm Hg (64, 72)</td>
<td>8.6±10.0 10.7±13.3</td>
<td>−6.2, 1.9 0.289</td>
<td>−5.86, 2.7 0.471</td>
<td>−5.6, 2.2 0.398</td>
</tr>
<tr>
<td>$\Delta$SBP Valsalva/mm Hg (66, 68)</td>
<td>24.3±23.2 16.4±17.1</td>
<td>0.9, 14.8 0.027</td>
<td>2.3, 16.9 0.011</td>
<td>−0.1, 13.3 0.052</td>
</tr>
</tbody>
</table>

30:15 ratio, Valsalva ratio, E-I difference: peak/trough RR interval ratio, during Valsalva maneuver, and during deep breathing. Log: natural logarithm of RR interval ratio, heart rate variability, or baroreflex sensitivity. $\Delta$DBP indicates change in diastolic blood pressure during reflex test; $\Delta$SSBP, change in systolic blood pressure during reflex test.
frequency heart rate variability, which represents parasympathetic cardiac modulation.26 The lower peak systolic blood pressure at phase IV of the Valsalva maneuver indicates impaired immediate sympathetic response.21 The exaggerated diastolic blood pressure responses to the isometric exercise and cold pressor stimuli are consistent with impaired baroreflex function, as demonstrated in power spectral analysis. Low-frequency heart rate variability is influenced by both sympathetic and parasympathetic activity;16 respiration-induced blood pressure fluctuation leads to fast cardiovagal and slower peripheral sympathetic activity, and their combined action generates the low-frequency oscillations $\approx 0.1$ Hz.27 Therefore, low-frequency represents autonomic activity in response to variation in peripheral vascular tone. Baroreflex sensitivity was significantly reduced in stroke patients for the low-frequency range. This does not appear to be a blood pressure effect, because this difference remained after analysis of covariance with systolic ambulatory blood pressure as a covariate. High-frequency range baroreflex sensitivity did not differ, but in fact the $\alpha$ coefficient of baroreflex sensitivity in the low-frequency range is more closely associated with the gold standard phenylephrine technique than the high-frequency range of $\alpha$.17 Our results infer that the ability to adapt cardiac autonomic function, both parasympathetic and sympathetic, is impaired long after the index stroke.

These findings may be relevant to the risk of all-cause and cardiovascular mortality in stroke survivors. Abnormal autonomic tone is an independent predictor of increased cardiovascular mortality after myocardial infarction.5,6 The postulated mechanism is a reduction in vagal activity, which increases vulnerability to malignant cardiac arrhythmias.28 Stroke victims have high rates of cardiac arrhythmia in the acute poststroke phase.29 Sudden cardiac death accounted for 43% of cardiac deaths in 3021 patients with minor stroke or transient ischemic attack followed-up for >2 years after stroke, and older age was an independent predictor of sudden death.4 The high prevalence of deranged autonomic function in older stroke patients may explain this observation.

This is supported by Robinson’s study that reported that reduced baroreflex sensitivity in the acute stroke phase was an independent predictor for all-cause mortality during a median 4-year follow-up.30 A recent study of 84 stroke patients found abnormal heart rate dynamics, again measured immediately after stroke, was the only independent predictor of all-cause mortality over 7-year follow-up.31 In another study of 62 patients with acute ischemic stroke, mean age 62 years, 7 patients who experienced sudden death had a significantly reduced time domain measure of heart rate variability and a trend toward reduced low-frequency spectral power compared with survivors.32

Previous literature on autonomic dysfunction after stroke has reported on younger patients and concentrates on outcomes in the acute phase. In these studies, Ewing reflex tests10 but another (31 patients, mean age 52 years) reported persistent defects in frequency domain heart rate variability.9

It is likely that deranged autonomic function is caused by ischemic or hemorrhagic damage to autonomic control centers.32,34 CT head scans in this investigation did not provide sufficient detail to accurately localize the lesion site, and one-way ANOVA tests for autonomic function according to OCSP classification did not reveal any significant differences.

We made an a priori decision to include stroke survivors on cardiovascular medication in the analysis because of the current high rate of prescription of such drugs after stroke and the ethical issues associated with discontinuation of medication to facilitate testing of autonomic function. The only prescription rates that differed between stroke patients and controls were for thiazide diuretics and calcium channel-blocking drugs. After multiple linear regression for all potential confounding factors including thiazide, calcium channel-blocker, or $\beta$-blocker drug use, the differences in autonomic function between stroke patients and control groups persisted. $\beta$-blockers do not influence the parasympathetic-controlled RR-interval ratio reflex tests. After multiple linear regression, $\beta$-blockade was a significant explanatory variable for high-frequency heart rate variability only; furthermore, the effect was to increase high-frequency variation (in agreement with literature reports35). Therefore, the nonsignificant reduction in high-frequency heart rate variability in the stroke patients may have been more marked without the benefit of $\beta$-blockers. Multiple linear regression indicated calcium channel-blocker use significantly reduced blood pressure change during Valsalva maneuver, and history of stroke was no longer a significant explanatory variable ($P=0.052$) for this outcome. Calcium channel-blocker usage was a significant and positive predictor of low-frequency baroreflex sensitivity but history of stroke remained a significant and negative explanatory variable for this outcome. The frequency of numerous potential confounding factors and relatively small sample size should introduce caution in our analysis, but it is notable that most of the differences between stroke patients and controls persist after adjustment for potential confounding variables.

In conclusion, we have assessed cardiovascular autonomic function using reflex tests, frequency domain analysis of heart rate variability, and baroreflex sensitivity in older stroke survivors after the acute stroke phase. Results indicate significant impairment of autonomic control in patients who have otherwise made a good cognitive and physical recovery from stroke. This may have important implications for the risk of adverse cardiovascular events and mortality rates in stroke survivors.

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