Cardiac Autonomic Derangement and Arrhythmias in Right-Sided Stroke With Insular Involvement

Furio Colivicchi, MD, FESC; Andrea Bassi, MD; Massimo Santini, MD, FESC, FACC; Carlo Caltagirone, MD

Background and Purpose—The insula of the right cerebral hemisphere may have a major role in cardiac autonomic control. This study was aimed at assessing the effects of acute right insular ischemic damage on heart rate variability (HRV) and arrhythmias.

Methods—Holter monitoring for 24 hours was performed in 103 consecutive patients with first-ever acute ischemic stroke. Time and frequency domain measures of HRV and arrhythmias were considered in all cases.

Results—Forty-nine patients (47.5%) had a right-sided infarction, whereas 54 (52.5%) had a left-sided infarction. Insular involvement was present in 33 patients with right-sided stroke (67.3%) and in 36 patients with left-sided stroke (66.6%). When compared with all other stroke patients, subjects with right-sided insular damage showed significantly lower values of the standard deviation of all normal-to-normal (SDNN) R wave to R wave (RR) intervals and of the root mean square of differences (rMSSD) of adjacent normal-to-normal RR intervals, and higher low-frequency/high-frequency ratio values ($P<0.05$). Right insular stroke was also associated with more complex arrhythmias than any other localization ($P<0.05$). Moreover, in the whole population of stroke patients, lower values of SDNN were associated with the presence of more frequent and complex arrhythmias.

Conclusions—These findings further support the notion that the right insula is implicated in the autonomic control of cardiac activity and that acute right insular damage may lead to a derangement of cardiac function with potential prognostic implications. (Stroke. 2004;35:2094-2098.)

Key Words: arrhythmia ■ heart rate ■ stroke, acute

Considerable evidence has been collected over the past 20 years suggesting that acute stroke may determine a major derangement of cardiovascular function. In particular, an impairment of the autonomic balance and an increased incidence of cardiac dysrhythmias have both been noted. Cardiac abnormalities seem to be more frequent in patients with right-sided strokes, whereas concurrent insular damage may further impair autonomic function and constitute, at least in the acute phase, increased risk of adverse cardiovascular events.

The analysis of heart rate variability (HRV) is known to provide useful information about disturbances in autonomic regulation in several cardiac affections. Moreover, this methodology has already been used with promising results in the assessment of the autonomic imbalance associated with acute stroke. However, the specific impact of acute right insular ischemic damage on both HRV and cardiac arrhythmias has not yet been fully elucidated.

This study was designed and undertaken to test the hypothesis that the involvement of the right insula in acute ischemic stroke is associated with a more relevant cardiac autonomic derangement and with a higher incidence of arrhythmias than any other stroke localization.

Patients and Methods

Consecutive patients reporting to the emergency department of our institution for acute stroke in a 24-month period were prospectively screened for inclusion. Our institution is a 750-bed hospital providing primary and tertiary care to an area with ~250,000 inhabitants. On average, ~60,000 patients are visited in the emergency department every year. In the prespecified selection period, 942 consecutive patients with acute stroke reported to the emergency department. Patients were included in the study only if they fulfilled all of the following criteria:

1. admission for first-ever acute ischemic stroke;
2. evidence of a single acute hemispheric ischemic lesion consistent with clinical manifestations and exceeding 30 mm in diameter, as determined by neuroimaging study (computed tomography or magnetic resonance imaging);
3. absence of diabetes mellitus or any other concomitant nervous system, cardiac, or pulmonary disease possibly affecting the autonomic nervous system and HRV;
4. absence of any clinically relevant arrhythmia on admission, including atrial fibrillation;

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5. absence of any pharmacological treatment, including beta-blockers, possibly affecting the autonomic nervous system and HRV;
6. absence of any major concurrent illness, including renal failure and malignancies;
7. absence of fever, hypoxia, severe hypertension, or any relevant hemodynamic compromise on admission.

After prospective selection, 103 consecutive patients (57 men and 46 women; mean age 69.2 ± 8.0 years) fulfilled the aforementioned reported criteria, provided informed consent, and were included in the study. Stroke severity on admission was assessed by the National Institutes of Health Stroke Scale.13

Neuroimaging studies (computed tomography or magnetic resonance imaging) were performed on admission and repeated by the end of the first week to confirm brain infarct size and localization. Insular involvement was assessed on the basis of brain imaging by an experienced neuroradiologist blinded to clinical details. The volume of each stroke was calculated from the computed tomography or magnetic resonance imaging films according to the modified ellipsoid method.14

In all cases, particular care was taken to exclude any relevant form of concomitant cardiac dysfunction. In particular, congestive heart failure, valvular dysfunction, any form of cardiomyopathy, previous acute myocardial infarction, and left ventricular hypertrophy were all preliminarily excluded on clinical and laboratory grounds.

The control group consisted of 103 healthy subjects (57 men and 46 women; mean age 67.3 ± 8.5 years) who had no clinical manifestations of any nervous system, cardiac, pulmonary, or metabolic disease, and who were using no medications known to affect the autonomic nervous system and HRV.

All patients underwent 24-hour Holter monitoring (HM) within 72 hours from admission, whereas control subjects underwent HM during their ordinary daily activities.

HM was performed using a 3-channel bipolar recorder and was evaluated after digitization. For each recording, the following data were considered:

1. maximal and minimal heart rate (HR);
2. total number of premature ventricular contractions (PVC);
3. presence of ventricular couplets (VC);
4. presence of episodes of nonsustained ventricular tachycardia (NSVT, 3 or more consecutive PVC);
5. total number of premature supraventricular contractions (PSVC);
6. presence of episodes of supraventricular tachyarrhythmias (SVT), including atrial tachycardia and atrial fibrillation.

The mean sinus HR was derived from the mean R wave to R wave (RR) intervals (after exclusion of abnormal beats).

HRV was analyzed from the Holter recordings using commercially available software (ELA Medical Synescope version 1.0 analysis system). The beat classification was verified and corrected appropriately by an experienced cardiologist blinded to clinical details. Time domain measures of HRV, including standard deviation of all normal-to-normal (SDNN) RR intervals and root mean square of differences of adjacent normal-to-normal (rMSSD) RR intervals, were obtained by using the continuous data for 24 hours. The frequency domain analysis of HRV was performed by a fast Fourier transform of the RR intervals, which produced a power spectrum from the 0.01–Hz to 1.0–Hz unit. Three frequency domain measures of HRV, including low-frequency (LF) (range, 0.04 to 0.15 Hz), high-frequency (HF) (range, 0.15 to 0.40 Hz), and LF/HF ratio, were calculated.

SDNN, rMSSD, and the HF component of HRV correlate with respiratory rhythm and have generally been considered as measures of parasympathetic tone, whereas the LF component correlates with peripheral vasomotor activity and thermoregulation, representing both parasympathetic and sympathetic influences.15 The LF/HF ratio appears to be an accurate marker of the shifts in sympathovagal balance.15

Statistical Analysis
Means (±SD) were calculated for continuous variables, whereas frequencies were measured for categorical variables. Distributions of continuous variables were determined by the Kolmogorov-Smirnov test, and all were found to be nonparametric. Group differences for continuous data were then examined by Kruskal-Wallis 1-way ANOVA, followed by the Mann-Whitney 2-sample test if significant differences between groups were detected. In case of categorical variables, group differences were examined by χ² or Fisher exact test as appropriate.

As the primary hypothesis of this study was that right insular damage is associated with more relevant cardiac abnormalities, planned comparisons were performed versus patients with right insular involvement and no corrections for multiple comparisons were applied. This allowed us to avoid the increase of type II error, usually associated with a conservative post-hoc approach.

Spearman correlation coefficients were used to analyze correlations between all different individual measures of HRV and number of PVC and PSVC in acute stroke patients. Multiple stepwise logistic regression analysis was used to define any possible relation between the presence of each more complex arrhythmia (VC, NSVT, and SVT), as dependent variables, in acute stroke patients, and all individual measures of HRV as predictors. All individual HRV measures were forced in the final multivariate regression model.

Data analysis was performed by using the SPSS statistical software package (SPSS 11.5). P < 0.05 was considered statistically significant.

Results
Stroke patients were divided into 4 subgroups according to the side of brain infarction and the presence of insular involvement. In particular, 49 of the 103 patients (47.5%) had a right infarction, whereas 54 (52.5%) had a left ischemic lesion. The right insula was included in the area of the infarction in 33 of the 49 patients with right hemispheric damage (67.3%), whereas 36 of the 54 left-sided lesions (66.6%) involved the left insular region. According to the primary hypothesis of the study, clinical and laboratory data of patients with right insular involvement were compared with those of all other stroke subgroups.

Patients with right insular damage did not differ from other stroke patients or from controls for age, gender prevalence, echocardiographic characteristics, and serum electrolytes (Table 1).

Stoke severity as assessed by the National Institutes of Health Stroke Scale on admission was similar in all subgroups of patients (9.2 ± 2.9 for right-sided infarctions with insular involvement, 8.8 ± 2.9 for right-sided infarction without insular involvement, 9.1 ± 2.8 for left-sided infarctions with insular involvement, and 9.0 ± 2.7 for left-sided infarction without insular involvement; P = 0.420).

The mean volume of strokes was similar in all subgroups of patients (28 ± 30 cm³ for right-sided infarctions with insular involvement, 29 ± 27 for right-sided infarction without insular involvement, 31 ± 29 for left-sided infarctions with insular involvement, and 32 ± 31 for left-sided infarction without insular involvement; P = 0.370).

The mechanism of stroke was unknown in most cases (71/103 patients, 68.0%), whereas in the rest of the population (32/103 patients, 32%) stroke was caused by large-artery atherosclerosis. The mechanisms of stroke were found to be similar in all subgroups of patients (P = 0.890).
Mean values of HR and of all measures of HRV in the study population are shown in Table 2. All subgroups of stroke patients showed a significant decrease of all HRV components and higher LF/HF ratio values with respect to controls. When stroke subgroups were compared, patients with right-sided infarcts including the insula showed significantly lower SDNN and rMSSD values and higher LF/HF ratio values than all other stroke patients.

Table 3 presents the mean values of PVC and PSVC and the prevalence of VC, NSVT, and SVT in the study population. Both ventricular and supraventricular arrhythmias were found to be more frequent and complex in all subgroups of stroke patients than in controls. Also, patients with right-sided insular damage showed significantly more PVC and PSVC than patients with left-sided infarctions and a significantly higher prevalence of both NSVT and SVT than all other stroke subgroups.

In the whole population of stroke patients, a significant negative linear correlation between SDNN and the number of PVC ($r = -0.597$, $P < 0.01$) and PSVC were noted ($r = -0.417$, $P < 0.01$). A similar negative correlation between rMSSD and the number of PVC ($r = -0.249$, $P < 0.05$) and PSVC were also noted ($r = -0.218$, $P < 0.05$). Moreover, multiple stepwise logistic regression indicated that the only significant predictor of the presence of complex arrhythmias was SDNN. In particular, in stroke patients, lower values of the time domain parameter SDNN were significantly associated with the presence of VC (odds ratio [OR] = 0.90; 95% CI, 0.86 to 0.96; $P < 0.01$), of NSVT (OR = 0.88; 95% CI, 0.82 to 0.95; $P < 0.01$), and of SVT (OR = 0.90; 95% CI, 0.84 to 0.96; $P < 0.01$).

Total in-hospital mortality of stroke patients was 7.7% (8/103 patients). Three deaths were sudden and unexpected (2.9% of all stroke patients), without any preceding clinical deterioration in neurological status. In 1 case, sudden death occurred during electrocardiographic monitoring, which showed a ventricular tachycardia degenerating into ventricular fibrillation; in the remaining 2 cases, the arrhythmia

### TABLE 1. Demographic Characteristics, Serum Electrolytes, and Echocardiographic Features in Control Subjects and in Patients With Different Localizations of Ischemic Stroke

<table>
<thead>
<tr>
<th>Patients (n=103)</th>
<th>Right-Sided Stroke</th>
<th>Left-Sided Stroke</th>
<th>P</th>
<th>Kruskal–Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Subjects (n=103)</td>
<td>With Insular Involvement (n=33)</td>
<td>Without Insular Involvement (n=16)</td>
<td>With Insular Involvement (n=36)</td>
<td>Without Insular Involvement (n=18)</td>
</tr>
<tr>
<td>Age, y</td>
<td>67.3±8.5</td>
<td>69.8±7.8</td>
<td>68.1±8.2</td>
<td>69.3±7.7</td>
</tr>
<tr>
<td>Females</td>
<td>46/103</td>
<td>15/33</td>
<td>7/16</td>
<td>17/36</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.1±0.7</td>
<td>4.1±0.6</td>
<td>4.2±0.8</td>
<td>4.2±0.4</td>
</tr>
<tr>
<td>Magnesium, mmol/L</td>
<td>0.94±0.11</td>
<td>0.92±0.22</td>
<td>0.95±0.26</td>
<td>0.94±0.18</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.36±0.19</td>
<td>2.38±0.22</td>
<td>2.39±0.21</td>
<td>2.37±0.21</td>
</tr>
<tr>
<td>LV mass, g/m²</td>
<td>106±11</td>
<td>110±14</td>
<td>110±15</td>
<td>109±16</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>3.6±0.5</td>
<td>3.7±0.6</td>
<td>3.6±0.7</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.68±0.13</td>
<td>0.64±0.16</td>
<td>0.65±0.14</td>
<td>0.66±0.17</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; LA, left atrial; EF, ejection fraction.

### TABLE 2. Heart Rate and Measures of Heart Rate Variability in Control Subjects and in Patients With Different Localizations of Ischemic Stroke

<table>
<thead>
<tr>
<th>Patients (n=103)</th>
<th>Right-Sided Stroke</th>
<th>Left-Sided Stroke</th>
<th>P</th>
<th>Kruskal–Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Subjects (n=103)</td>
<td>With Insular Involvement (n=33)</td>
<td>Without Insular Involvement (n=16)</td>
<td>With Insular Involvement (n=36)</td>
<td>Without Insular Involvement (n=18)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>78.8±10.1</td>
<td>79.6±9.8</td>
<td>81±4.9</td>
<td>79.0±8.1</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>138.2±23.2</td>
<td>96.9±10.5†</td>
<td>103.3±7.1†</td>
<td>108.2±11.7†</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>33.9±17.2</td>
<td>21.7±7.3† *</td>
<td>26.0±4.6†</td>
<td>27.1±3.9†</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>1105±630</td>
<td>821±592†</td>
<td>824±680†</td>
<td>860±596†</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>597±439</td>
<td>292±207†</td>
<td>358±257†</td>
<td>352±236†</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.9±0.5</td>
<td>2.8±0.4†</td>
<td>2.5±0.4†</td>
<td>2.5±0.5†</td>
</tr>
</tbody>
</table>

SDNN indicates standard deviation of all normal-to-normal RR intervals; rMSSD, root mean square of differences of adjacent normal-to-normal RR intervals; LF, low frequency; HF, high frequency.

* $P<0.050$ vs all other stroke subgroups (Mann–Whitney 2-sample test).
† $P<0.001$ vs control subjects.
Table 3. Arrhythmias in Control Subjects and in Patients With Different Localizations of Ischemic Stroke

<table>
<thead>
<tr>
<th>Control Subjects (n=103)</th>
<th>With Insular Involvement (n=33)</th>
<th>Without Insular Involvement (n=16)</th>
<th>Total with Insular Involvement (n=38)</th>
<th>Without Insular Involvement (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVC, N</td>
<td>12±21</td>
<td>539±335*§</td>
<td>371±246†</td>
<td>280±289†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VC, patients (%)</td>
<td>1 (0.9)</td>
<td>17 (51.5)†</td>
<td>6 (37.5)†</td>
<td>12 (33.3)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSVT, patients (%)</td>
<td>0 (0)</td>
<td>11 (33.3)†</td>
<td>1 (6.2)‡</td>
<td>4 (11.1)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSVC, N</td>
<td>15±19</td>
<td>244±206§</td>
<td>255±207‡</td>
<td>108±133†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVT, patients (%)</td>
<td>0 (0)</td>
<td>12 (36.3)†</td>
<td>1 (6.2)‡</td>
<td>5 (13.8)‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P<0.050 vs all other stroke subgroups.
†P<0.001 vs controls.
‡P<0.05 vs controls.
§P<0.010 vs left-sided stroke subgroups.
Kruskal–Wallis for continuous variables and χ² for categorical variables.
P<0.05 vs left-sided stroke subgroups (Mann–Whitney test for continuous variables, χ², or Fisher test for categorical variables).

Discussion

In accordance with previous reports,\cite{4,6,7,10,11} the present investigation confirms that acute stroke results in a decrease in all time and frequency domain HRV parameters and in higher LF/HF ratio values. These abnormalities indicate the presence of a complex derangement of autonomic balance, possibly involving both sympathetic and parasympathetic systems.\cite{9} Moreover, in our series, the decrease of all HRV measures was more pronounced in patients with right-sided insular involvement, thus confirming the prominent role of the right insula in reflex cardiovascular regulation.\cite{8}

This study also allowed the description of the arrhythmic profile of the acute phase of ischemic stroke in a relatively large cohort of patients without clinical and laboratory evidence of heart disease. In particular, as previously noted in smaller series,\cite{5,7} right-sided brain infarctions were found to be associated with more frequent arrhythmias than left-sided lesions. Furthermore, right insular damage was associated with more complex dysrhythmias, namely VC, NSVT, and SVT, than any other localization. These findings once more suggest a major role of the right insula in the pathogenesis of cerebrogenic cardiac disturbances.\cite{8}

Another interesting aspect of this study is the analysis of the possible interplay between HRV abnormalities and arrhythmias in patients with acute brain infarction. To the best of our knowledge, this is the first study reporting the existence of a significant negative correlation between a specific HRV parameter, namely SDNN, and all kinds of arrhythmias in the acute phase of ischemic stroke. In fact, in our series, lower values of 24-hour SDNN were associated with a higher number of PVC and PSVC and also predicted the presence of more complex arrhythmias, such as VC, NSVT, and SVT. Actually, SDNN, which is an estimate of the overall 24-hour HRV behavior,\cite{5} is the best known, best validated, and easiest HRV index to use.\cite{16} A decrease of SDNN has been considered to reflect a diminished vagal activity directed to the heart, which may lead to a relative prevalence of sympathetic modulation and to a cardiac electrical instability.\cite{9,17,18} This interpretation is in agreement with the clinical evidence that SDNN reduction is an independent predictor of an increased arrhythmic mortality in several conditions characterized by autonomic imbalance, such as heart failure, diabetes, and coronary artery disease.\cite{9,17,18} Actually, HRV abnormalities associated with cardiac damage may be determined by a derangement of neural activity of cardiac origin. In particular, changes in the geometry of the beating heart, caused by the presence of diseased noncontracting ventricular segments, may abnormally increase the firing of sympathetic afferent fibers.\cite{9,19} This overflow of sympathetic nerve traffic may in turn attenuate vagal activity. However, in the acute stroke setting, cardiac autonomic abnormalities should have a central origin, despite being similar in terms of HRV behavior. Accordingly, acute brain and acute heart damage show the same final expression, with HRV abnormalities and arrhythmias representing a final common effect, possibly determined by a relative sympathetic prevalence on the sinus node and on the myocardium.

In this study, \(\sim 3\%\) of all stroke patients died suddenly and unexpectedly. This finding is in accordance with previous studies reporting an incidence of sudden death in the course of acute stroke ranging from 2% to 6%\cite{20}. Even if the small number of cases precludes a sound analysis of clinical features possibly predicting the occurrence of such an ominous event, in this study a significant association was found between the presence of NSVT and the subsequent sudden death. Actually, NSVT has already proven effective for the
risk stratification of sudden death in various cardiac conditions. In our series, the presence of NSVT was predicted by lower SDNN values, whereas the arrhythmia was more prevalent in patients with right-sided insular lesions. Both of these findings add evidence to the belief that the autonomic imbalance determined by cerebral ischemic damage could have a role in the pathophysiology of sudden death in the course of acute brain infarction.

The results of this investigation are challenged by evidence emerging from a recently published post-hoc analysis of the NASCET database. In fact, the investigators of the emerging from a recently published post-hoc analysis of the course of acute brain infarction. imbalance determined by cerebral ischemic damage could lower SDNN values, whereas the arrhythmia was more related to coronary artery disease and its clinical expressions. has a prominent role, whereas sudden unexpected deaths probably a catastrophe in which the autonomic derangement sudden arrhythmic death associated with acute stroke is hemispheric ischemic damage in the pathogenesis of cardiac disease, while considering only the acute phase of the cerebrovascular event. Actually, sudden death is a complex event requiring the presence of several concurrent factors, such as an arrhythmic trigger, an anatomic substrate, and a significant autonomic imbalance. Thus, in our opinion, the sudden arrhythmic death associated with acute stroke is probably a catastrophe in which the autonomic derangement has a prominent role, whereas sudden unexpected deaths occurring in the long-term poststroke course are more likely related to coronary artery disease and its clinical expressions.

Limitations of the Study
The size of the study population was based on the availability of consecutive patients with specific clinical and laboratory features in a reasonably long time frame rather than on statistical considerations. We recognize this point as a limitation of our study.

Conclusions
Overall, our findings provide further evidence in support of the notion that the right insula is implicated in the autonomic modulation of cardiac activity and that insular ischemic damage may lead to a significant derangement of cardiac function with potential prognostic implications. However, further studies are needed to precisely define the clinical relevance of HRV abnormalities and of cardiac arrhythmias in the acute phase of ischemic stroke.

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References
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