Prognostic Implications of Right-Sided Insular Damage, Cardiac Autonomic Derangement, and Arrhythmias After Acute Ischemic Stroke

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

Background and Purpose—Acute stroke is associated with impairment of cardiac autonomic balance and increased incidence of arrhythmias. These abnormalities appear more relevant in the case of involvement of the right insula in the infarct area. The aim of this study was to assess the impact of right-sided insular damage, cardiac autonomic derangement, and arrhythmias on clinical outcome after acute ischemic stroke.

Methods—Holter monitoring for 24 hours was performed in 208 consecutive patients with first-ever acute ischemic stroke. Time- and frequency-domain measures of heart rate variability and arrhythmias were considered in all cases. All patients were followed for a 12-month period after the initial event.

Results—During the 12-month follow-up period, 48 patients died (1-year probability of death, 0.23; 95% CI, 0.17 to 0.30). Multivariate analysis demonstrated that age (hazard ratio [HR], 1.06; 95% CI, 1.01 to 1.10; \( P=0.0087 \)), stroke severity on admission (HR, 1.25; 95% CI, 1.13 to 1.39; \( P=0.0001 \)), presence of right-sided insular damage (HR, 2.01; 95% CI, 1.13 to 1.39; \( P=0.0187 \)), as well as lower values of the SD of all normal-to-normal RR intervals (HR, 3.32; 95% CI, 1.67 to 6.24; \( P=0.002 \)), and presence of nonsustained ventricular tachycardia during Holter monitoring (HR, 2.99; 95% CI, 1.58 to 5.67; \( P=0.0007 \)) were independent predictors of 1-year mortality.

Conclusions—The integration of traditional risk stratifiers with autonomic and arrhythmic markers, and the careful search for right-sided insular involvement, may represent an effective approach for identification of stroke patients at risk for early mortality. (Stroke. 2005;36:1710-1715.)

Key Words: heart rate ■ outcome ■ stroke

Recent studies have shown that acute stroke is associated with impairment of cardiac autonomic balance and increased incidence of arrhythmias. Abnormalities of cardiovascular autonomic control may also retain prognostic relevance, as reduced heart rate variability (HRV) and impaired cardiac baroreceptor sensitivity have both been associated with adverse clinical outcome after stroke. Furthermore, all stroke-related autonomic abnormalities appear more relevant in patients with right-sided hemispheric infarctions, with concurrent involvement of the right insula implying further derangement of cardiovascular function and even an increase of the odds of death within 3 months of acute stroke. However, to date, the relative prognostic significance in stroke patients of right-sided insular involvement in the infarct area, as well as that of cardiac autonomic impairment and arrhythmias, has not been fully clarified.

Accordingly, this prospective study was undertaken to assess the impact of right-sided insular damage, cardiac autonomic derangement, and arrhythmias on clinical outcome after acute ischemic stroke.

Subjects and Methods
Consecutive patients reporting to the emergency department of our institution for acute stroke in a 48-month period were screened for inclusion. Our institution is a 750-bed hospital, providing care to an area with \( \sim 250000 \) inhabitants. During the selection period, 1746 consecutive patients with acute stroke reported to the emergency department. Patients were included in the study only if they fulfilled 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 (CT or MRI).
3. Absence of diabetes mellitus or 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.
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, alterations in consciousness, or any relevant hemodynamic compromise on admission.

After prospective selection, 208 consecutive patients (116 men and 92 women; mean age, 69.5±7.8 years) fulfilled the inclusion criteria, provided informed consent, and were included in the study. Stroke severity on admission was assessed by the National Institutes of Health Stroke Scale.14 No patient received thrombolytic therapy. Neuroimaging studies (CT or MRI) were performed on admission and repeated by the end of the first week to confirm brain infarct size and localization. In 32 patients (15.3%), neuroimaging studies also revealed the presence of some minor lacunar lesion. As previously described,12 the presence of right-sided insular involvement was assessed on the basis of brain imaging by an experienced neuroradiologist blinded to clinical details. No stroke was found to be restricted exclusively to the insular cortex. The volume of each stroke was calculated from the CT or MRI films according to the modified ellipsoid method.16

The presumed etiology of strokes and the consequent final discharge diagnosis of stroke subtype were defined by the attending physician on the basis of personal clinical judgment and laboratory features and classified according to TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment).17

Particular care was taken to exclude any major concurrent cardiac disease. Congestive heart failure, moderate-to-severe valvular dysfunction, any cardiomyopathy, previous acute myocardial infarction, and left ventricular hypertrophy were ruled out by a comprehensive clinical evaluation, which included history, physical examination, 12-lead electrocardiography, and echocardiography. Transthoracic echocardiography was performed in 204 patients (98.0%), whereas transesophageal echocardiography was performed in 87 cases (41.8%). In 29 cases (13.9%), echocardiography revealed the presence of asymmetric cardiac abnormalities, including atrial septal aneurism (16 patients), patent foramen ovale (4 patients), and spontaneous echo-contrast within the left atrium that was associated with reduced left-atrial appendage velocities (9 patients).

All patients underwent 24-hour Holter monitoring (HM) within 72 hours from admission. HM was performed using a 3-channel bipolar recorder and was evaluated after digitization. As previously reported,13 the following data were considered for each recording:
1. Maximal and minimal heart rate.
2. Total number of premature ventricular contractions (PVCs).
3. Presence of ventricular couplets.
4. Presence of episodes of nonsustained ventricular tachycardia (NSVT; ≥3 consecutive PVCs).
5. Total number of premature supraventricular contractions.
6. Presence of episodes of supraventricular tachyarrhythmia (SVT), including atrial tachycardia and atrial fibrillation.

The mean sinus heart rate was derived from the mean RR intervals (after exclusion of abnormal beats).

HRV was analyzed from the HM 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 SD of all normal-to-normal RR intervals (SDNN) and root-mean-square of differences of adjacent normal-to-normal RR intervals (rMSSD), were obtained using the continuous data for 24 hours. The 24-hour frequency-domain analysis of HRV was performed by a fast Fourier transform (FFT) of the RR intervals, which produced a power spectrum from the 0.01 to 1.0 Hz unit. The Synescope system automatically edits all artifacts and obtains a regular signal by linear interpolation of the HR tachogram. The interpolated signal is sampled at a frequency of 4 Hz. The FFT is calculated in periods of 256 seconds. The periodogram technique is used to obtain spectra over periods >256 seconds. This consists of calculating the sliding mean of several FFT with an overlay of 150 seconds between 2 spectra. Before calculation of the FFT, each 256 window of the tachogram is interpolated and multiplied point by point by a window (Hanning window) commonly used to limit border effects related to truncation of the signal.

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.

Follow-Up and Primary End Point
All patients were followed for a 12-month period after the initial event. Follow-up data after discharge were obtained from family physicians or through telephone follow-up and outpatient visitation. No patient was lost during the follow-up.

The primary end point of the study was death from any cause within 12 months of the index event. This end point has already been used in similar previous studies6,14 and was preferred to cardiovascular mortality, as the latter has several possible limitations, including incorrect documentation and inaccurate assessment in an environment with low autopsy rates.18 Most data on clinical outcome during the follow-up period were collected through telephone interviews of the patients and family members or by contact with family physicians (87.0% of cases). In the case of death, every effort was made to obtain hospital records or death certificates.

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. Group differences for continuous data were examined by unpaired Student t test or by Mann–Whitney 2-sample test, as appropriate. In the case of categorical variables, group differences were examined by χ² or Fisher exact test, as appropriate.

The cumulative risk of experiencing the primary end point was estimated by means of the Kaplan–Meier method. Survival curves of subgroups were formally compared using the log-rank test.

Univariate and multivariate Cox proportional hazard regression analyses were used to identify risk factors for time-related occurrence of the primary end point during the 12-month follow-up. All variables, determined from the baseline evaluation, with a probability value lower than 0.10 in the initial univariate analysis, were considered potential predictors of the primary end point. All variables were analyzed in a stepwise fashion to develop Cox models of the study end point (12-month all-cause mortality). The assumption of proportionality for Cox models was tested and met for all covariates. The results of the Cox proportional hazards model are presented as the hazard ratio (HR) and the 95% CI.

As in another study,19 for the purpose of survival and multivariate analyses, patients were categorized in 2 groups with lower (SDNN<100 ms), or higher SDNN values (SDNN>100 ms). The cut-off value of 100 ms for SDNN was chosen as it allowed the best discrimination for subsequent mortality, as assessed by the receiver operating characteristic curve.20

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

Results
During the 12-month follow-up period, the primary end point (death from any cause) occurred in 48 patients. Eleven patients died during hospitalization, thereby giving an in-hospital mortality of 5.2%. The remaining 37 patients died after discharge. Consequently, the overall 1-year probability of death was 0.23 (95% CI, 0.17 to 0.30). This finding is in accordance with available data concerning mortality after a first-ever ischemic stroke in Italy.21 According to hospital records and death certificates, death was considered cardiovascular in 31 cases (64.5%); 12 recurrent ischemic strokes,
12 acute coronary syndromes, 6 sudden deaths, and 1 aortic dissection), noncardiovascular in 8 (16.6%; 6 pneumonias; 2 malignancies). Owing to a lack of consistent data, the cause of death remained of unknown origin in the rest of the patients (18.7%).

Baseline clinical characteristics of the study population, as well as unadjusted comparisons between survivors and patients who died within 12 months from stroke, are shown in Table 1. In particular, patients were more likely to die during follow-up if they were older, with more severe presenting clinical deficit, and had right-sided insular involvement (Table 1).

Baseline laboratory findings in the study population are summarized in Table 2. Patients who died during follow-up showed significantly lower values for SDNN and rMSSD and more frequent and complex cardiac arrhythmias in the HM performed during the index admission (Table 2).

No significant differences were noted between survivors and nonsurvivors as to the prescribed pharmacological therapy (Table 3).

The Kaplan–Meier survival curves of patients according to the presence of right-sided insular damage, NSVT, and SDNN/11021 100 ms are shown in Figures 1, 2, and 3, respectively.

**TABLE 1. General Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (N=208)</th>
<th>Survivors (N=160)</th>
<th>Nonsurvivors (N=48)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.5±7.8</td>
<td>68.4±8.0</td>
<td>73.3±5.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Females, no. (%)</td>
<td>92 (44.2)</td>
<td>71 (42.2)</td>
<td>21 (43.7)</td>
<td>0.854</td>
</tr>
<tr>
<td>Right-sided stroke, patients (%)</td>
<td>101 (48.5)</td>
<td>73 (43.4)</td>
<td>28 (58.3)</td>
<td>0.068</td>
</tr>
<tr>
<td>Right-sided insular damage, patients (%)</td>
<td>60 (28.8)</td>
<td>39 (23.2)</td>
<td>21 (43.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>NIH stroke scale score</td>
<td>9.0±2.6</td>
<td>8.6±2.5</td>
<td>10.6±2.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Infarct volume, m³</td>
<td>31±28</td>
<td>30±32</td>
<td>33±31</td>
<td>0.566</td>
</tr>
<tr>
<td>Hypertension, patients (%)</td>
<td>126 (60.5)</td>
<td>98 (61.2)</td>
<td>28 (58.3)</td>
<td>0.716</td>
</tr>
<tr>
<td>Localization of ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortico-subcortical, patients (%)</td>
<td>112 (53.8)</td>
<td>86 (72.5)</td>
<td>26 (57.5)</td>
<td>0.959</td>
</tr>
<tr>
<td>Cortical, patients (%)</td>
<td>45 (21.6)</td>
<td>34 (21.2)</td>
<td>11 (22.9)</td>
<td>0.805</td>
</tr>
<tr>
<td>Subcortical, patients (%)</td>
<td>51 (24.5)</td>
<td>40 (25.0)</td>
<td>11 (22.9)</td>
<td>0.768</td>
</tr>
<tr>
<td>Stroke subtypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel disease, patients (%)</td>
<td>73 (35.0)</td>
<td>55 (34.3)</td>
<td>18 (37.5)</td>
<td>0.690</td>
</tr>
<tr>
<td>Small vessel disease, patients (%)</td>
<td>21 (10.0)</td>
<td>15 (9.3)</td>
<td>6 (12.5)</td>
<td>0.528</td>
</tr>
<tr>
<td>Cardioembolic, patients (%)</td>
<td>26 (12.5)</td>
<td>19 (11.8)</td>
<td>7 (14.5)</td>
<td>0.618</td>
</tr>
<tr>
<td>Undetermined etiology, patients (%)</td>
<td>88 (42.3)</td>
<td>71 (44.3)</td>
<td>17 (35.4)</td>
<td>0.270</td>
</tr>
</tbody>
</table>

*Comparison between survivors and nonsurvivors.

**TABLE 2. Laboratory Features in the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (N=208)</th>
<th>Survivors (N=160)</th>
<th>Nonsurvivors (N=48)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass, g/m²</td>
<td>109±21</td>
<td>108±23</td>
<td>111±19</td>
<td>0.411</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>3.7±0.7</td>
<td>3.6±0.8</td>
<td>3.9±0.9</td>
<td>0.141</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.64±0.18</td>
<td>0.66±0.17</td>
<td>0.63±0.19</td>
<td>0.298</td>
</tr>
<tr>
<td>Heart rate variability measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79.2±8.2</td>
<td>78.1±10.2</td>
<td>80.8±11.2</td>
<td>0.117</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>107.1±11.5</td>
<td>109.5±10.5</td>
<td>99.1±10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>26.5±4.3</td>
<td>27.1±5.2</td>
<td>25.2±3.3</td>
<td>0.018</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>837±451</td>
<td>848±378</td>
<td>811±249</td>
<td>0.428</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>341±213</td>
<td>352±311</td>
<td>298±244</td>
<td>0.270</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>2.6±1.1</td>
<td>2.5±1.3</td>
<td>2.8±1.0</td>
<td>0.142</td>
</tr>
<tr>
<td>Arrhythmias in 24-hour Holter monitoring</td>
<td>329±232</td>
<td>238±207</td>
<td>348±296</td>
<td>0.019</td>
</tr>
<tr>
<td>PVC, no.</td>
<td>61 (29.3)</td>
<td>40 (25.0)</td>
<td>21 (43.7)</td>
<td>0.012</td>
</tr>
<tr>
<td>Ventricular couplets, patients (%)</td>
<td>25 (12.0)</td>
<td>9 (5.6)</td>
<td>16 (33.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PSVC, no.</td>
<td>186±121</td>
<td>174±102</td>
<td>217±134</td>
<td>0.044</td>
</tr>
<tr>
<td>SVT, patients (%)</td>
<td>41 (19.7)</td>
<td>26 (16.2)</td>
<td>15 (31.2)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Comparison between survivors and nonsurvivors.
Multivariate analysis demonstrated that age (HR, 1.06; 95% CI, 1.01 to 1.10; \(P=0.0087\)), stroke severity on admission (HR, 1.25; 95% CI, 1.13 to 1.39; \(P=0.0001\)), presence of right-sided insular damage (HR, 2.01; 95% CI, 1.13 to 1.39; \(P=0.0187\)), as well as lower values of the SD of all normal-to-normal RR intervals (HR, 3.32; 95% CI, 1.67 to 6.24; \(P=0.002\)), and presence of nonsustained ventricular tachycardia during HM (HR, 2.99; 95% CI, 1.58 to 5.67; \(P=0.0007\)) were independent predictors of the primary end point.

**Discussion**

In this study, we prospectively evaluated the predictors of 1-year mortality in a relatively large homogeneous cohort of patients with acute first-ever ischemic stroke. In accordance with previous studies, we found that age and severity of presenting clinical deficit have a major impact on outcome after ischemic stroke.\(^{22,23}\) Furthermore, we also observed that 1-year mortality is significantly affected by evidence of right-sided insular involvement in the infarct area, decreased HRV, and complex nonsustained ventricular arrhythmia on HM.

Right insular cortex is believed to play a major role in the autonomic modulation of cardiac activity\(^{4,11–13}\) and in affective and attentional aspects of human behavior.\(^{24}\) In fact, inclusion of right insular cortex in cerebral infarct may result in a pathological sympathetic activation of the cardiovascular system, as well as in disorders of neglect.\(^{11–14,24}\) Furthermore, right-sided insular infarction has also been associated with an unfavorable clinical outcome.\(^{10,11,14}\) Indeed, our study further confirms that ischemic damage of right insular cortex is of particular clinical relevance and has a negative impact on prognosis. Moreover, in our series, the predictive value of insular damage appear as independent from all other major clinical and laboratory features, including age, stroke severity, HRV measures, and arrhythmias. This finding suggests that right-sided insular involvement affects outcome through different and complex mechanisms, possibly including the post–ictal development of abnormalities in arousal, attention, and activation, which have already been noted in patients with right insular damage.\(^{25,26}\)

Recent studies have shown that in poststroke patients, there is an association between direct and derived measures of increased sympathetic activation and/or reduced vagal activity and a greater propensity for adverse cardiovascular events.\(^{5,6,26}\) These observations are confirmed in this study, as we found that lower SDNN values predicted an increased 1-year mortality after acute stroke. This finding may have potential implications for clinical practice, as SDNN is an
estimate of overall 24-hour HRV behavior, while also representing the best-known, best-validated, and easiest HRV index to use.12,19

In this study, we also found that NSVT during HM represents an independent predictor of increased risk after stroke. Actually, NSVT among the most common problems encountered in modern cardiovascular medicine.27 The term, defined as ≥3 consecutive premature ventricular beats, with a rate >120 bpm, and lasting <30 seconds, denotes an electrocardiographic finding that can be associated with a wide range of clinical conditions. In several diseases, including coronary artery disease and dilated cardiomyopathy, NSVT is a marker of increased risk for subsequent cardiac death.27 Our findings open a new clinical scenario, as this arrhythmia seems to be clinically relevant also after ischemic stroke, even in patients without significant cardiac dysfunction.

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.

The presumed etiology and final discharge diagnosis of stroke subtype were defined by the attending physician during the index admission. However, we know that guidelines for etiologic diagnoses of brain infarctions are not always correctly implemented in clinical practice.28 Inconsistency in some of the final diagnoses cannot be excluded also in this study, and we acknowledge this point as a limitation.

However, the distribution of stroke subtypes was similar in...
study subgroups and seem to be devoid of prognostic relevance.

The frequency-domain analysis of HRV was performed over the course of 24 hours. Consequently, diurnal variability may have possibly obscured interesting trends, thereby limiting information deriving from such analysis.

Conclusions

The high incidence of ischemic stroke, as well as the great variability in clinical outcome of such condition, has led to a particular interest in the identification of accurate prognostic predictors. To date, several clinical variables have been identified as potential predictors of clinical outcome. In particular, age, stroke severity, and the presence of significant cardiac comorbidity have all been found to be predictive of both short- and long-term outcome. The present study adds new information to this debated issue. In fact, among patients with ischemic stroke, the recognition of right insular involvement and the analysis of autonomic and arrhythmic markers may constitute an improved strategy that more accurately identifies patients at high risk for total mortality. Consequently, the integration of traditional risk stratifiers, such as age and stroke severity, with autonomic and arrhythmic markers, as well as the careful search for right-sided insular involvement, may represent a more powerful approach for effective identifications of stroke patients at risk for early mortality.

References

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