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Effects of Stroke Localization on Cardiac Autonomic Balance and Sudden Death

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Background and Purpose—Stroke has been shown to alter autonomic function. The purpose of this study was to show the differential effects of stroke localization on autonomic function parameters assessed by heart rate variability (HRV).

Methods—To determine the differential effect of ischemic stroke localization on autonomic cardiac innervation, we evaluated 62 patients with ischemic stroke and 62 age- and sex-matched controls. The localization of the infarct was determined by CT and MRI. Power spectrum analysis of HRV was performed. Myocardial necrosis was ruled out by echocardiography and creatine kinase myocardial isoenzymes measurements.

Results—All stroke patients had significantly decreased low frequency, high frequency, and standard deviation of all relative risk intervals values ($P<0.001$). However, patients with right-middle cerebral artery (R-MCA) and insula lesions had significantly lower power spectrum analysis values compared with all other localizations ($P<0.001$). In addition, 5 patients with R-MCA insular lesions died suddenly compared with 2 patients with left-middle cerebral artery insular lesions during hospitalization. Both sympathetic- and parasympathetic-controlled HRV were decreased in patients with ischemic stroke. The most pronounced decrease was found in the territory of R-MCA insular cortex, which suggests that cardiac autonomic tone may be regulated by insula and that these patients are more prone to cardiac complications such as arrhythmias and sudden death due to autonomic imbalance.

Conclusion—We conclude that stroke in the region of insula (especially the right) leads to decreased HRV and to increased incidence of sudden death. **(*Stroke*. 1999;30:1307-1311.)**

Key Words: heart rate ■ neurological deficits ■ stroke assessment ■ autonomic dysfunction

It is well known from animal and clinical studies that cerebrovascular diseases can alter cardiovascular and autonomic function.[1] Stroke has been shown to produce changes in autonomic function, increase the incidence of cardiac arrhythmias, cause myocardial damage, and raise plasma catecholamine levels.[2,3,4] The most important consequence of these changes is an increased susceptibility to sudden death. In patients with acute stroke, the incidence of sudden death as a result of arrhythmic causes has been reported to be ≈6%.[5] In clinical and experimental studies, the most important control sites of the autonomic function are found to be the insular cortex, amygdala, and lateral hypothalamus.[6] In addition, evidence exists for cortical asymmetry in the regulation of cardiovascular functions. Animal studies have revealed that stroke in the right hemisphere produces more significant sympathetic effects than left-sided stroke, and a few recent clinical trials have yielded evidence to support this asymmetry.[7] However, it is still not well established how the localization of stroke affects the autonomic function parameters and prognosis in these patients.

Power spectrum analysis (PSA) of heart rate variability (HRV) has been shown to be useful for assessing sympathetic and parasympathetic autonomic effects on the heart.[8,9] Experimental evidence shows an association between a propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity. HRV has been shown to be a powerful tool to assess prognosis in clinical conditions such as myocardial infarction, in which a decreased HRV is a predictor for arrhythmias, and sudden cardiac death, independent of other recognized risk factors.[10,11] The aim of this study was to demonstrate the differential effects of stroke localization on autonomic function parameters assessed by HRV.

Subjects and Methods

Study Population and Entry Criteria

One hundred fifty-eight patients who were diagnosed with their first acute ischemic stroke and hospitalized between February 1995 and March 1997 in Hacettepe University School of Medicine were evaluated for this study. Patients were admitted to the study if they fulfilled the following criteria: (1) Patients presented with acute stroke in which the onset of stroke was precisely known. (2) Patients underwent cranial MRI and repeated CT that confirmed a single acute infarct >3 cm in diameter consistent with clinical manifestations and located in the territory of the middle cerebral artery

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(MCA). (3) The absence of coexisting situations that may affect HRV indices such as dilated or hypertrophic cardiomyopathy, acute ischemic coronary syndromes including myocardial infarction and angina pectoris, class 3 and 4 congestive heart failure, renal or pulmonary disease, previously diagnosed diabetes mellitus, alcoholism, electrolyte disturbances, and mechanical ventilation. (4) Use of medications, such as β-blockers, that may affect the autonomic nervous system. (5) Absence of arrhythmias such as atrial fibrillation on admission.

Patients with fever, hypoxia, and severe hypertension (>170/100 mm Hg) at the time of HRV measurement were not included in the study. HRV measurement was performed after the above conditions resolved during the first 3 days after stroke. In the patient group, mean respiratory frequency during HRV recording was also noted.

Only the 62 patients who fulfilled the above criteria were included in the study. There were 37 male and 25 female patients with a mean age of 61.5±10.6 years. Patients were evaluated extensively by use of a multidisciplinary approach. To confirm infarct localization and size, cranial CT was repeated for all patients at the beginning of the second week after stroke or cranial MRI was obtained. Eventual MCA stroke was considered as "eligible" if it involved an area >30 mm in diameter in any 1 plane of the neuroimaging study. Initial stroke severity was assessed with the use of the NIH Stroke Scale, and disability was evaluated by the Barthel's index. In addition to the clinical cardiac evaluation and daily ECG recordings, patients had their heart rate variability measured within the first three days of the stroke. HRV measurements were performed between 6:00 and 9:00 PM. Patients were monitored with a bedside monitor for 24 hours on admission. Cardiac necrosis that preceded the stroke was ruled out by creatine kinase myocardial isoenzyme measurements.

Sixty-two age- and sex-matched healthy subjects served as the control group for the HRV analysis. The mean age was 60±9 years. There were 37 male and 25 female patients in the control group. All the exclusion criteria were applied to the control group as well.

During the hospitalization period, any patient who died and was clinically stable previously and had experienced symptoms for <1-hour before death was classified as sudden death.[12] Death during sleep was also classified as sudden death. Of the 62 patients in the stroke group, 7 patients (11%) died suddenly according to this definition.

HRV Analysis

All patients were monitored and followed by bedside continuous cardiac monitoring for the initial 3 days during the hospitalization period. Data were recorded in the recumbent position. Respiration rates of each group were not statistically different ($P>0.05$).

All recordings were made with a PC-based high resolution ECG system (Kardiosis) in the first 3 days after stroke. Bipolar X deviation (0.5 to 340 Hz) was recorded and sampled at a rate of 1000 samples per second and digitized with an 8-bit A/D converter. Each recording lasted 8 minutes, and raw data were stored to disk for postprocessing. A segment of 5 minutes of the recording with no artifacts and premature depolarizations was processed to provide the results of HRV analysis. The relative risk (RR) tachograms were extracted from data. The detection of R waves was done with a thresholding algorithm. The detected R waves were visually confirmed and any undetected regular R wave was marked either manually or by interpolation. Similarly, any point that was not an R wave but was found as one was unmarked manually. By this method, raw RR tachogram was extracted. Raw tachogram was then interpolated at 1-second intervals by linear interpolation. From the interpolated RR tachogram, power spectral densities were calculated by autoregressive modeling. Power spectrums for heart rate variations were calculated with autoregressive modeling. In power spectrums of RR intervals, 3 major peaks were observed: 1 around DC (very low frequency [LF] peak), 1 around 0.1 Hz (LF peak), and the other around 0.2 Hz (high frequency [HF] peak). When RR spectrums were investigated, it was observed that a considerable amount of energy was in the very LF range (<0.03 Hz). Very LF oscillations are much less defined but suggested to be related with thermoregulation.[13,14,15] Therefore, to prevent these oscillations from masking other frequency ranges (<0.03Hz), they were filtered out from the tachograms before modeling. The power spectra of HRV were quantified by measuring the area under the spectral curve in 2 frequency bands. The area from 0.03 to 0.15 Hz was calculated as LF power, and the area from 0.15 to 0.4 Hz was categorized as HF power. In addition, the SD of RR intervals was also calculated from the time series of RR intervals.[16] The absolute values of the results were in ms for the time domain and ms^2 for the PSA.

TABLE 1. SDNN in Patients With Stroke, Subgroup of Stroke, and in Healthy Controls

	SDNN
Control, n=62	48±15
Stroke total, n=62	31±11*
Left-sided stroke, n=32	32±12*‡
Right-sided stroke, n=30	30±10*‡
Left MCA-insula, n=25	36±11*†
Right MCA-insula, n=23	26±9*†

*According to control groups, $P<0.001$; †Left MCA-insula vs right MCA-insula, $P<0.001$); ‡Left-sided vs right-sided, $P=0.38$.

Statistical Analysis

All values are presented as mean±SD. Univariate comparisons were performed by use of the t test or Mann-Whitney U tests for continuous variables, and the χ^2 test was used for categorical variables. $P<0.05$ was considered statistically significant. SPSS release 6.0 for MS Windows was used for statistical analysis.

Results

Of the 62 patients, 32 suffered from left hemisphere and 30 from right hemisphere infarction. Twenty-three of the patients with right hemisphere infarction had the right insula included in the infarct, whereas 25 of the left-sided lesions involved the left insula. The degree of neurological deficit was compared between right- and left-sided strokes. The NIH score was not different in right- and left-sided lesions by 16.8±6.2 and 17.1±5.6, respectively ($P=0.87$). Similarly, the Barthel index of both sides was similar (2.5±3.1 for right and 2.0±1.8 for left, $P=0.38$). Stroke severity as assessed by the NIH stroke scale showed no significant difference in patients with lesions that involved the insular region versus lesions that did not involve the insular region (17.0±6.1 versus 16.7±4.8, $P=0.86$). The heart rate was not different in the control and stroke group (74.8±11.6 versus 76.8±13.0, $P>0.05$), in right- and left-sided lesions (76.3±10.8 versus 77.2±14.9, $P>0.05$), and in the right-insular and left-insular group (76.4±11.5 versus 78.1±14.6, $P>0.05$). The SD of RR intervals (SDNN) was evaluated by time-domain analysis. The SDNN was 31.6±11 in patients with stroke and 48.5±15 in healthy controls, which indicated a significant difference ($P=0.001$; Table 1). Subgroup analysis of SDNN was lower in patients with right hemisphere lesion, although this failed to reach significance (30.3±10 versus 32.8±12, $P=0.38$).

When the lesions including the right and left insula were analyzed separately, patients with right insular lesions had the lowest SDNN ($P<0.001$) of the whole group of patients with stroke (Table 1). Because age may affect SDNN, we com-

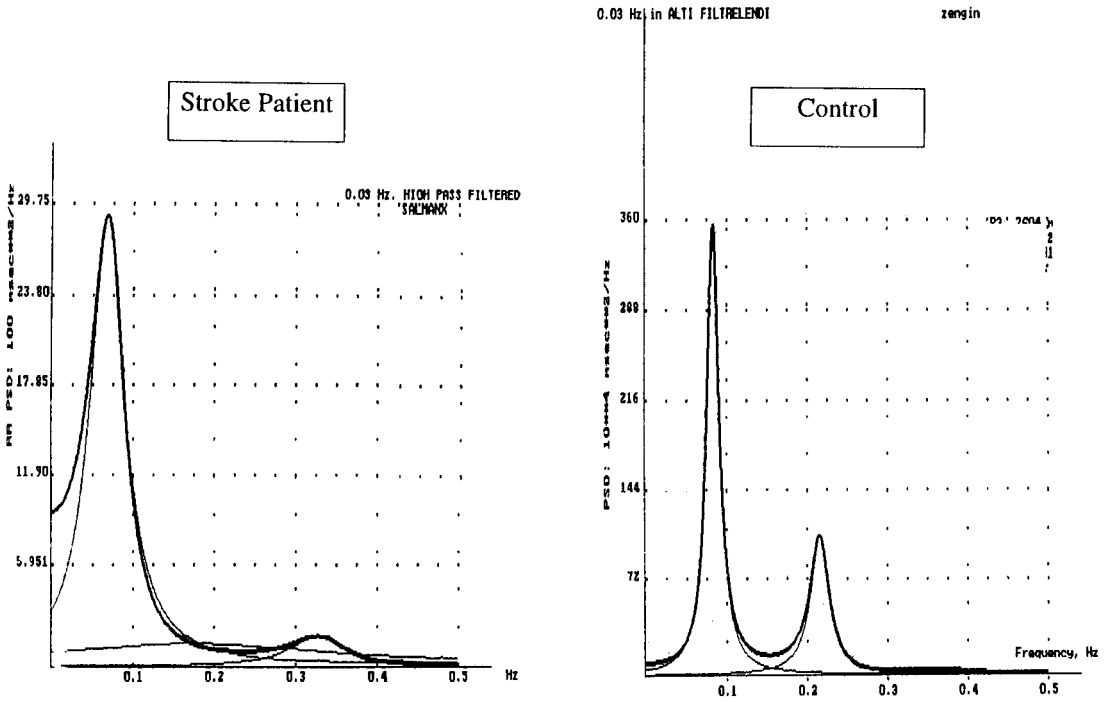

Figure 1. On PSA, the LF and HF amplitudes were lower in patients with stroke. Attention to power values of analysis.

pared the ages of patients with right and left insular lesions. Age was not different in the left- and right-sided lesion group (59.9±10.4 versus 63.2±10.9, $P>0.05$) or in the left and right insular group (59.8±10.5 versus 62.4±10.8, $P>0.05$).

On PSA, the LF and HF amplitudes were lower in patients with stroke (Figure 1). The LF amplitudes were 243.4±174 in patients with stroke and 835.9±486 in healthy controls ($P<0.001$). In addition, the HF amplitudes were 83.4±86 in patients with stroke and 424.8±268 in controls, with statistically significant difference ($P<0.001$). Patients with right hemisphere lesion had lower HF and LF values than those with left hemisphere lesion ($P<0.001$ and $P=0.004$). Furthermore, patients with right insula lesions had the lowest HF and LF values, which can be observed in Table 2 ($P<0.001$).

The ratio of LF to HF was significantly greater in patients with stroke than control subjects (3.93±3.33 versus 2.35±1.39, $P<0.001$), which may reflect a change in sympathovagal balance in favor of increased sympathetic tone. However, the lateralization of stroke and the involvement of insular region had no significant effect on the LF to HF ratios (3.89±3.27 and 3.95±3.45 for left- and right-sided stroke, respectively [$P=0.95$]; and 3.56±2.07 and 4.09±3.87 for left- and right-insular lesion, respectively [$P=0.55$]).

TABLE 2. PSA of Stroke, Subgroup of Stroke Patients, and in Healthy Controls

	LF, ms²/Hz	HF, ms²/Hz
Control, n=62	835±486	424±268
Stroke total, n=62	243±174*	83±86*
Left-sided stroke, n=32	314±188*†	113±109*‡
Right-sided stroke, n=30	166±120*†	51±30*‡
Left MCA-insula, n=25	328±161*§	110±88*‖
Right MCA-insula, n=23	144±129*§	46±34*‖

LF: 0.04–0.015 Hz; HF: 0.15–0.40 Hz.

*According to control group, $P<0.001$; †LF left-sided vs LF right-sided, $P<0.001$; ‡HF left-sided vs HF right-sided, $P=0.004$; §LF left MCA-insula vs LF right MCA-insula, $P<0.001$; ‖HF left MCA-insula vs HF right MCA-insula, $P<0.001$.

Seven sudden deaths occurred during hospitalization. Sudden death occurred during monitoring in 3 of these patients, in which a ventricular tachycardia deteriorating into ventricular fibrillation was observed. In the remaining 4 patients, the preceding arrhythmia was not documented electrocardiographically. All the deaths were sudden without any initial deterioration in the neurostatus or clinical finding, which implied a new stroke or expansion of the previous stroke. Neurological deficit and mean age were not significantly higher in this group (NIH stroke scale; 18.4±4.9 versus 16.7±5.9, $P=0.48$, and mean age 62.4±10.4 versus 60.1±10.7, $P=0.63$, for death and survival groups, respectively). All the patients who died suddenly had lesions that involved the insula. Five of these patients had a right insular lesion (Figure 2). However, there was no significant difference in the occurrence of sudden death in patients with left and right stroke (6.3% versus 16.7%, $P=0.186$). Moreover, the occurrence was not significantly increased in patients with or without insular involvement (14.6% versus 0%, $P=0.149$). When the parameters of HRV in patients who died suddenly were compared with those of survivors, the SDNN, LF, and HF were found to be lower in those who died and except for SDNN, failed to reach a statistical significance (Table 3). The ratio of LF to HF was greater in patients in the sudden death group than the survival group but failed to reach a statistical significance ($P=0.487$)

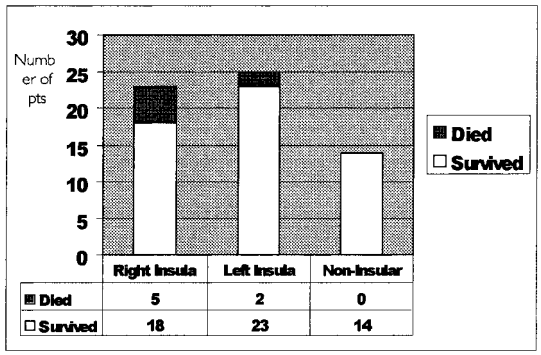

Figure 2. Sudden deaths during hospitalization according to localization of stroke.

Discussion

In humans, stroke in both hemispheres has been shown to produce changes in autonomic mechanisms, which leads to myocardial necrosis, arrhythmias, and even sudden death through related mechanisms. However, the localization of stroke may have differential effects. Lane et al[17] have shown that right hemisphere infarction is associated with a greater number of supraventricular tachycardia, and they speculated that a decrease in cardiac parasympathetic activity in right-sided infarction may cause the probable reciprocal rise in the sympathetic tone. Experimental and clinical studies indicate that certain parts of the cerebral hemisphere, such as the insula, amygdala, and lateral hypothalamus exert influence in the autonomic control of the heart.[6] Of these, the insular cortex within the MCA territory is the most important cortical area that controls both parasympathetic- and sympathetic-mediated cardiovascular regulation. The insula is frequently involved in stroke because of MCA occlusion, which is a frequent cause of ischemic stroke.

We found the SDNN to be decreased in all the patients with stroke. More importantly, all the components of the power spectrum HRV were suppressed in our stroke patients versus controls. This has been shown in previous studies to indicate that both sympathetic and parasympathetic autonomic cardiovascular regulatory systems are impaired in acute stroke.[18] We also found evidence in support of cortical asymmetry in autonomic control with right-sided stroke having lower parameters on PSA.

It has been shown that focal cerebral ischemia in rats leads to transient elevations in blood pressure and heart rate only if the insular cortex is involved.[19] This suggests that involvement of the insular cortex in stroke may have more important implications than involvement of other localizations. However, this has been documented previously in only a few human stroke studies.[20,21] An interesting finding in our study was that lesions that included the right insula had the lowest SDNN, LF, and HF amplitudes of all the patients. We also found a decrease in the powers of LF and HF in patients who died suddenly, but this decrease failed to reach statistical significance. This possibly relates to the power of analysis because the sudden death group included only 7 patients. Importantly, the size of infarct and the degree of neurological involvement were not different between groups; therefore, the difference could not be explained by other factors. This finding is in accordance with human[22] and animal[23] studies that have shown that stimulation of the different locations of insular cortex reveals different cardiac autonomic response. No deaths were observed in 14 patients with lesions that did not involve the insula: sudden death occurred only in patients with insular lesions in our group of patients. Five of 7 deaths occurred with right-sided insular lesions. Although this is not statistically significant, because the group was small, we think that it is a relevant finding to have all the patients who died to have their lesion in one anatomic location. These findings suggest that insula (especially the right insula) may be an important anatomic location in the control of autonomic tone. Ischemia caused by stroke in this area can impair the autonomic tone and increase the likelihood of sudden death. The importance of insula on sympathovagal balance has been highlighted previously in other studies.[20,21] We found that the ratio of LF to HF was significantly greater in patients with stroke than control subjects ($P<0.001$). This finding suggests that there was a shift toward to sympathetic predominance in patients with stroke. Factors that increase sympathetic or decrease parasympathetic nervous system activity increase the likelihood of ventricular arrhythmias.[24,25] Impaired HRV also is related to an increased risk of cardiac arrhythmias and

TABLE 3. Data of Patients who Died Suddenly or Survived

	Sudden Death (+)	Sudden Death (−)	*P*
n	7	55	
Age, y	62.4±10.4	60.1±10.7	0.62
Respiration rate, min	16.1±3.8	15.7±2.3	0.67
Male/Female ratio	2/5	23/32	0.50
Right/Left ratio	5/2	25/30	0.186
Insula/other ratio	7/0	41/14	0.149
NIH score	18.4±4.9	16.7±5.9	0.48
LF/HF	4.76±4.88	3.82±3.12	0.487
LF (ms^2/Hz)	119.6±116.9	263.6±176.2	0.06
HF (ms^2/Hz)	53.1±52.6	86.7±89.9	0.272
SDNN	22.4±13.0	33.3±11.2	0.026

to sudden death after myocardial infarction according to previous studies.[26,27] These findings may explain why stroke patients have increased susceptibility to sudden death. However, we also found that the lateralization of stroke and the involvement of the insular region had no significant effect on sympathovagal balance (LF/HF ratio) of spectral HRV, although sympathetic shift remains the same level as the control group.

Additional confirmation of our finding that the risk of autonomic imbalance and sudden death increases in insular stroke in larger numbers of patients may have important clinical implications. Patients with insular strokes, especially right location, may require more intensive monitoring or prophylactic treatment to prevent sudden death.

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