Journal of Clinical Neuroscience 20 (2013) 406–409

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Relationship between ischemic stroke location and autonomic cardiac function

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ARTICLE INFO

Article history:
Received 12 March 2011
Accepted 11 February 2012

Keywords:
Acute ischemic stroke
Cardiac autonomic dysfunction
Heart rate variability

ABSTRACT

Autonomic cardiac dysfunction is a common complication after acute ischemic stroke (IS). We recruited 75 patients with acute IS with measurements of autonomic cardiac function, including heart rate variability (HRV) and associated parameters, and compared them with 81controls. Of the 75 patients, 28 had right hemispheric infarctions (RH), 29 had left hemispheric infarctions (LH), and 18 had brainstem infarctions (BS). A comparison of HRV in all patients with stroke and in control subjects showed significant differences between IS subgroups and controls in low frequency (LF), high frequency (HF), normalized LF, normalized HF, and LF/HF ranges. A post-hoc comparison identified significant differences between patients with IS with BS infarctions and the control group in LF, HF, and LF/HF ranges. BS infarction may cause a much greater increase in sympathetic modulation and reduced vagal activity compared to RH or LH infarction. Our findings provide evidence that acute IS causes significant damage to the cardiovascular autonomic system, manifesting as abnormalities of HRV. BS stroke might correlate with a significant reduction in parasympathetic and an increase in sympathetic influence on HRV.

1. Introduction

Sudden cardiac death is a leading cause of mortality, accounting for approximately 50% of all cardiovascular mortality and 12% of all deaths.[1] Severe acute neurologic conditions, including large infarcts, subarachnoid hemorrhage, intracerebral hematoma, brain tumors, intracranial hypertension, and status epilepticus may be associated with severe cardiovascular manifestations, including cardiac arrhythmia, myocardial injury, severe hypertension, and neurogenic pulmonary edema.[2] These manifestations may occur in the absence of previous underlying cardiovascular disease, may produce diagnostic confusion, and are generally associated with a poor prognosis. In particular, insular cortex involvement is associated with a more pronounced autonomic imbalance, leading to life-threatening arrhythmias and sudden death.[3] Cardiac arrhythmias are the most urgent life-threatening cardiovascular complication of central nervous system disease and may account for the high incidence of sudden death.[2]

The comparison of heart rate variability (HRV) in right- or left-sided hemispheric strokes has attracted much attention. Considerable evidence exists regarding the role of forebrain lateralization in cardiovascular autonomic regulation in patients with ischemic and hemorrhagic stroke. A study of patients with first-ever acute ischemic stroke (IS) who had no pre-existing cardiac disease demonstrated a more pronounced decrease in HRV measurements in patients with right-sided insular involvement, indicating the significant role of the right insular cortex in the pathogenesis of cerebrogenic cardiac disturbance.[4] Right hemispheric stroke increases nocturnal blood pressure, reduces circadian blood pressure variability, and is associated with both a higher norepinephrine level and reduced HRV, compared with left hemisphere infarcts, indicating the role of lateralization of the human forebrain in cardiovascular autonomic control.[4,5] However, Laowattana et al. showed increased rates of cardiac events in patients with left insular infarction compared to other strokes.[6] Thus, frequency of cardiac autonomic derangements relating to right- compared to left-hemispheric infarctions remains controversial. In addition, studies comparing cardiac autonomic function between brainstem and hemispheric stroke are few. Only a few studies, all with small sample size, compare cardiac autonomic dysfunction between brain stem and hemispheric stroke.[7–9] It is important therefore to undertake further investigations to compare brainstem and hemispheric stroke in terms of their effect on autonomic cardiac function.

Frequency-domain analysis of HRV has gained popularity with broad application as a functional indicator of the autonomic

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0967-5868/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jocn.2012.02.047

nervous system (ANS), because it is a non-invasive and accessible tool. The standard procedure and interpretation of HRV analysis was described in 1996.[10] HRV has been categorized into high-frequency (HF), low-frequency (LF), and very-low frequency (VLF) ranges.[10] HF is equivalent to the well-known respiratory sinus arrhythmia and is considered to represent vagal control of the heart rate (HR).[11] Both vagal and sympathetic activities jointly contribute to LF HRV.[12] Normalized LF (LF%) and the ratio LF/HF are considered by some investigators to mirror the sympathovagal balance[13] or to reflect sympathetic modulations.[10,13] In previous reports, central lesions, such as insular damage, have been associated with complex arrhythmias, including ventricular tachycardia (VT), nonsustained VT, and supraventricular tachycardia.[2,14,15] HRV can provide an objective method to detect the effect of cardiac autonomic function after acute IS.

We sought to evaluate the ANS using resting HRV and associated cardiovascular parameters in patients with acute IS on the basis of short-term (5 min) recordings of an electrocardiogram (ECG) acquired in a well-controlled environment. The aim of this study was to demonstrate the impact of brain infarction location on autonomic cardiovascular function in the acute stroke phase.

2. Methods

2.1. Study population

The study was carried out from March 2007 to March 2009 in the Department of Neurology, Kaohsiung Municipal Hsiaokang Hospital. The protocol was approved by the Ethics Committee of the Medical Faculty of Kaohsiung Municipal Hsiaokang Hospital and informed consent was obtained from each participant or a legal representative. The study enrolled 75 consecutive eligible patients with acute IS (46 men and 29 women; mean age, 59.6 ± 11.7 years). Inclusion criteria were admission for acute IS; evidence of acute ischemic lesions consistent with clinical manifestations, as determined by neuroimaging studies (MRI); absence of any clinically relevant arrhythmia on admission, including atrial fibrillation; absence of diabetes mellitus or any concomitant central nervous system, cardiac, or pulmonary disease that could possibly affect the ANS and HRV; absence of any pharmacological treatment, including beta-blockers, that could possibly affect the ANS and HRV; absence of any major concurrent medical disease, including end-stage renal disease and malignancy; and absence of fever, hypoxia, severe hypertension, or any relevant hemodynamic compromise on admission.

Patients underwent neuroimaging studies to confirm brain infarct size and localization as well as clinical, neurological, and functional examinations. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score.[16] The presumed etiology of stroke was defined by the attending physician on the basis of clinical judgment and laboratory features, and subsequently classified according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[17]

For comparison, 81 age-matched normal controls (37 men and 44 women; mean age 56.8 ± 8.4 years) were recruited from the hospital and general community. They were carefully screened to have no clinical history of diabetes mellitus, stroke or manifestations of any nervous system, cardiac, or pulmonary disease, and were not using medications known to affect the ANS and HRV. In particular, congestive heart failure, moderate-to-severe valvular dysfunction, any form of cardiomyopathy, and previous acute myocardial infarction were ruled out by a comprehensive clinical evaluation, which included history, physical examination, 12-lead electrocardiography and echocardiography.

2.2. Recorded variables

Measurements of HRV and associated cardiovascular parameters, including supine and head-up tilt blood pressure and heart rate (HR), were performed for both control subjects and stroke patients. Brachial artery pressure was measured by sphygmomanometry. Differences in systolic blood pressure (SBP) and HR were calculated by the value of head-up tilt SBP and HR minus supine SBP and HR, respectively.

2.3. Electrocardiogram signal processing

Detailed procedures for HRV analysis have been reported previously.[18–20] In brief, a pericardial ECG was taken for 5 min in the day (between 8 a.m. and 5 p.m.) with the subject laying quietly and breathing normally in the supine position for at least 10 min. HRV measurement was performed for all patients within 10 days (median 5 days) from stroke onset as described previously.[21] ECG signals were recorded using an HRV analyzer (SS1C, Enjoy Research, Taipei, Taiwan) with an analog-to-digital converter and sampling rate of 256 Hz. Digitized ECG signals were analyzed online and were simultaneously stored on a hard disk for off-line verification. Signal acquisition, storage, and processing were performed on an IBM-compatible portable personal computer. The computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template. Stationary R–R values were resampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain.[19]

2.4. HRV frequency-domain analysis

Frequency-domain analysis was performed using a non-parametric method of fast Fourier transformation (FFT). The direct current component was deleted, and a Hamming window was used to attenuate the leakage effect.[22] For each time segment (288 s; 2048 data points), our algorithm estimated the power spectrum density based on FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency-domain measurements as defined previously,[10] including total variance, HF (0.15–0.40 Hz), LF (0.04–0.15 Hz), VLF (0.003–0.04 Hz), and LF/HF HRV. HF, LF, and LF/HF were logarithmically transformed to correct for the skewness of the distribution.[19] LF was normalized by the percentage of total power, except for VLF (total power VLF), to detect the sympathetic influence on HRV (LF% = LF/(total power-VLF) $*$ 100). A similar procedure was applied to HF (HF% = HF/(total power-VLF) $*$ 100). All HRV parameters were expressed in original, square root, and natural logarithmic form to demonstrate and correct possible skewness.[10]

2.5. Statistical analysis

Numeric values were expressed as means ± standard deviation (SD). Comparisons of categorical variables between stroke patients and control subjects were performed using Chi-squared tests. The analysis of variance (ANOVA) was used for comparing HRV measurements among groups with different infarct location, and post-hoc comparisons were performed for patients with IS compared to controls. Multiple regression analysis was used to adjust for the differences in age, gender, and hypertension. Data differences were considered statistically significant at $p < 0.05$.