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Autonomic dysfunction in different subtypes of post-acute ischemic stroke

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ABSTRACT

Objectives: Central autonomic impairment is frequent in ischemic stroke at acute or chronic stages. The mechanism by which these symptoms occur in patients with ischemic stroke has not been elucidated. This study sought to investigate cardiovascular autonomic function in patients with different subtypes of post-acute ischemic stroke.

Methods: 77 ischemic stroke patients [50 patients with large-artery atherosclerosis (LAA) and 27 patients with small-vessel occlusion (SVO), average 6 months after stroke onset] and 37 elderly controls were recruited. All performed Ewing's battery autonomic function tests and power spectral analysis of heart rate variability (HRV).

Results: Stroke patients with both LAA and SVO had significantly lower low frequency power spectral density than controls. The prevalence of autonomic dysfunction in both groups (82.0% patients with LAA and 63.0% with SVO) was higher than that in controls (21.6%). Patients with LAA showed impairment of all parasympathetic tests (all $P < 0.05$) and one of the sympathetic tests (mean fall in systolic blood pressure on standing: $P = 0.058$) and those with SVO only showed impairment in two parasympathetic tests (heart rate response to deep breathing: $P = 0.010$; heart rate response to standing: $P = 0.004$) in comparison with controls. Patients with LAA had significantly more impairment than those with SVO in some autonomic parameters (Valsalva ratio: $P = 0.039$; mean fall in systolic blood pressure on standing: $P = 0.015$).

Conclusions: Irrespective of the subtype of the ischemia, post-acute stroke patients showed a parasympathetic cardiac deficit. Additionally, parasympathetic and sympathetic cardiovascular modulations were more severely impaired in patients with LAA.

1. Introduction

Impaired autonomic function is frequently seen in patients with ischemic stroke [1–3]. Decreased heart rate variability (HRV) was an independent predictor of 1-year mortality of patients with first-ever acute ischemic stroke [4]. In addition, reduced baroreflex sensitivity (BRS) in the acute phase of stroke was an independent predictor for all-cause mortality during a median 4-year follow-up [5]. Despite these important implications of impaired autonomic function, the mechanism by which these symptoms occur in ischemic stroke patients has not been elucidated. In prior studies, ischemic stroke patients have depressed parasympathetic activity at acute or chronic stages, but the results of sympathetic activity were conflicting [1,4,6]. Sympathetic activity was similar between patients with acute ischemic stroke and normal controls in a study by Korpelainen et al. [6], but it was increased in other studies [1,4]. To the best of our knowledge, acute ischemic stroke is heterogeneous in risk factors, pathogenesis, clinical features and outcome among different subtypes [7,8]. The conflicting results in sympathetic activity in these studies might be caused by heterogeneity of stroke subtypes.

However, there are only a few studies of cardiovascular autonomic function comparing the most common subtypes in ischemic stroke [9,10]. The results of these studies are also conflicting. Kwon et al. found that there was no significant association between impaired autonomic function and subtypes of acute ischemic stroke [10], whereas Chen et al. demonstrated that patients with acute large-artery atherosclerotic infarction had lower parasympathetic activity and higher sympathetic activity than those with acute lacunar infarction [9]. Therefore, in our study, we further sought to investigate cardiovascular autonomic function in patients with different subtypes of post-acute ischemic stroke.

2. Material and methods

2.1. Participant recruitment and inclusion criteria

Stroke patients were recruited from patients on stroke registry in Prince of Wales Hospital in Hong Kong between January 2007 and April 2009. The patient cohort was assessed at a minimum of 3 months after stroke onset (mean 6 months after stroke onset). Inclusion criteria

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were as follows: 1) age ≥18 years old; 2) computed tomography (CT) or magnetic resonance imaging (MRI) showed cerebral ischemic stroke. None of the patients had insular involvement of their stroke lesions. Diagnosis of ischemic stroke was defined by the World Health Organization (WHO) definition. 3) the presumed etiology of stroke was classified as large-artery atherosclerosis (LAA) or small-vessel occlusion (SVO) based on the criteria from the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) study [11]. Exclusion criteria are as follows: 1) dementia; 2) any clinically relevant arrhythmia on admission, including atrial fibrillation; 3) any major concurrent illness, including renal failure and malignancies; and 4) fever, hypoxia, alterations in consciousness, or any relevant hemodynamic compromise on admission. On admission, stroke severity of patients was assessed by the National Institutes of Health Stroke Scale (NIHSS) [12]. The diagnosis of carotid artery stenosis was made by gray-scale, color Doppler, and spectral Doppler ultrasonography. The degree of carotid artery stenosis was determined using the widely accepted criteria reported by Grant et al. [13]. Therefore, we specified no less than 50% stenosis of the carotid arteries as carotid stenosis including moderate and severe stenosis. We categorized all the participating patients into two groups based on the different subtypes of ischemic stroke according to the TOAST criteria [11]: group 1 had LAA, and group 2 had SVO.

Case controls were elderly volunteers living in the community. They had no previous history of transient ischemic attack or stroke and no evidence of dementia.

2.2. Ethics statement

All subjects gave their written informed consent for this study, which was approved by the Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

2.3. Measurement of heart rate variability

Continuous monitoring of heart rate (HR), BP and respiration was recorded using a Task Force Monitor 3040i (CNSystems Medizintechnik AG Graz, Austria). All participants were asked to refrain from caffeine ingestion on the day of the investigations and to take only a light breakfast. All investigations were performed between 9:00 AM to 11:00 AM in a warm, quiet room. After an adjustment period of at least 10 min, we monitored HR, BP and respiration during a 5-minute resting period with a respiration targeting a frequency of 15 cycles per minute (cpm) to minimize bias due to individually different breathing patterns. To achieve the targeted breathing rate, patients and controls were instructed to follow the movements of a bar on a computer screen with their eyes. Patients were to inspire as long as the bar was moving upward and they expire as long as the bar was moving downward on the computer screen. Patients were familiarized with this breathing instruction during a 5-minute training session before this assessment. BP was measured in the supine position through finger cuffs on the index fingers and the middle fingers of left hands, and appropriate cuff size (small, medium, or large) was chosen depending on the size of hand. HR, BP and respiratory signals were first edited automatically, then sampled digitally and transferred from the Task Force Monitor 3040i system to a computer for analysis of HRV using time domain and spectral methods.

2.4. Time domain analysis

HR was recorder as R–R interval (RRI) (milliseconds). Mean RRI was chosen as the time domain indices of HRV [14].

2.5. Frequency domain analysis

For spectral analysis, 120-second recordings of RRI recorded in patients and controls were cleaned of artifacts, resampled at 4 Hz, and then taken for spectral processing using an autoregressive algorithm suggested by Berger et al. [15]. The power spectra were quantified by measuring the areas in the following frequency power bands: the very low (VLF; <0.04 Hz), low (LF; 0.04–0.15 Hz) and high (HF; 0.15–0.40 Hz) frequency bands and also total spectral power (<0.40 Hz), as recommended by the international guidelines [14]. The magnitude of these components was determined as the integral under the power spectral density curves of RRI (ms^2/Hz) for these frequency bands and expressed as power of RRI (ms^2) [16–18].

HF component of HRV correlates with respiratory rhythm and has 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. VLF component accounts for long term regulatory mechanisms mainly related to humoral factors and thermoregulation, and its physiological correlate is still unknown. In addition, the LF/HF ratio appears to be an accurate marker of the shifts in sympathovagal balance [16–18].

2.6. Ewing's battery assessment

Clinical autonomic function tests were carried out according to Ewing's battery [19]: after pioneering much of the development work of cardiovascular autonomic function tests, the authors adopted a battery of five tests (three predominantly parasympathetic tests: mean max/min ratio during three Valsalva maneuvers; mean max/min HR difference during six deep breaths; the 30:15 ratio after standing; two predominantly sympathetic tests: the systolic BP fall after standing; and the diastolic BP rise during sustained handgrip) with a sixth test (standard deviation of the RR) during quiet breathing for five-minutes available for research purpose. In a review article in the British Medical Journal in 1982, they proposed the battery of five tests (three predominantly parasympathetic and two predominantly sympathetic) as an assessment of autonomic dysfunction for simple bedside use [20]. The advantage of using such a battery is to allow classification of autonomic dysfunction according to severity in which patients were divided into five groups depending on the number of abnormal or borderline results [19]. Ewing's battery of autonomic function tests was widely used for peripheral autonomic disorders. Recently, we have demonstrated that this method can also be used to assess the cardiovascular autonomic regulation for central autonomic failures [21–23].

There was a 2-minute rest phase after individual rests.

2.6.1. Parasympathetic tests

2.6.1.1. Valsalva maneuver. The Valsalva maneuver was performed by having the participant exhale for 15 s, while maintaining an expiratory pressure of 40 mm Hg. Expiratory pressure can be measured by having the patient blow into a mouthpiece connected to a pressure transducer. The maneuver was performed at least three times in order to maximize participant compliance and ensure reproducibility. The Valsalva ratio was an index of HR changes that occur during a Valsalva maneuver. The Valsalva ratio was taken as the maximum RRI in the 15 s following expiration divided by the minimum RRI during the maneuver.

2.6.1.2. Deep breathing. Respiratory sinus arrhythmia was assessed by performance of 6 deep breaths per minute at a frequency of 0.1 Hz. Participants were given adequate rehearsal to achieve the required frequency and counted through the 6 breaths with slow inhalation and exhalation (5 s each). The timed breathing was performed with the aid of verbal coaching and a time indicator. The response was taken as the mean of the differences between the maximum and minimum instantaneous HR for each cycle. A minimum of 3 breaths was required for inclusion.