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# Serial heart rate variability testing for the evaluation of autonomic dysfunction after stroke

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## Abstract

**Background and purpose—**Autonomic dysfunction has been described as a frequent complication of stroke that could involve the cardiac, respiratory, sudomotor, and sexual systems. Cardiac autonomic dysfunction after stroke is one of the most recognized and has been described to increase the rate of mortality and morbidity.

**Methods—**We report two cases of stroke—one hemorrhagic and one ischemic—and describe heart rate variability during the patients' hospitalizations with improvement reported for each patient several days after stroke onset.

**Results—**The first case demonstrated autonomic dysfunction with severe reduction of HRV after a right parietal hemorrhagic stroke. The second case demonstrated similar findings in a patient with acute ischemic stroke. In both cases, normalization of heart rate variability occurred several weeks after stroke symptoms onset and was paralleled by a dramatic improvement of the clinical status.

**Conclusion—**Our data established that serial HRV testing is a noninvasive tool that could be utilized as a marker to evaluate the dynamics of acute stroke.

### Keywords

stroke; autonomic dysfunction; heart rate variability

## Introduction

Autonomic dysfunction has been described as a frequent complication of stroke [1–3] and could involve the cardiac, respiratory, sudomotor, and sexual systems [4]. Cardiac autonomic dysfunction after stroke is one of the most recognized and has been described to increase the rate of mortality and morbidity [5].

We report two cases of stroke—one hemorrhagic and one ischemic—and describe heart rate variability (HRV) during the patients' hospitalizations with improvement reported for each patient several days after stroke onset.

## Methods

HRV was recorded, using a 6 mm stainless steel disk electrode, in two patients in the supine position. The recording electrode was placed at the level of the left fourth or fifth intercostal space at a line perpendicular to mid clavicle. The reference electrode was placed 2–4 cm apart at the same intercostal space toward the left anterior axillary line. The ground electrode was placed on the dorsum of one hand. The bandpass was 16–80 Hz; sensitivity was 200–500 μV per division, and sweep duration was 200 ms. Using the triggering mode and delay line, the oscilloscope display was adjusted by regulating the trigger sensitivity and sweep speed so that two QRS complexes were displayed on the screen. The first displayed complex is the triggering potential, and the variation in timing of the second complex represents variation in the R–R interval. Five groups of 20 sweeps were recorded at rest. The recordings and calculations were performed by TECA Synergy EMG system (Cardinal Health, Philadelphia, PA). The following algorithm was used to analyze R–R variation: $(RR_{max} - RR_{min}) \times$

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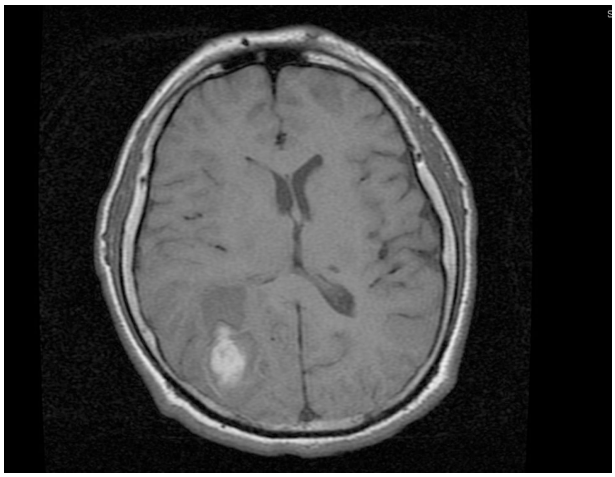

**Figure 1. MRI of the brain, T1-weighted image, showed a right parietal hematoma with vasogenic edema and mass effect on the lateral ventricle.**

$100/RR_{mean}$, which is the difference between the shortest and longest RR intervals during 1 min, given as a percentage of the mean of all maximal and minimal peaks. RR interval variation (RRIV) responses at rest were considered abnormal when less than 10% [6]. We measured average RRIV from five measurements of 20 RR intervals, each using continuous electrocardiographic monitoring by TECA Synergy EMG system.

## Results

### Case 1

A previously healthy 44-year-old right-handed man presented to our Emergency Department complaining of severe headache and blurred vision of 12 h duration. His neurological examination was significant for left homonymous hemianopsia and mild left deltoid weakness. Computed tomography (CT) of the head without contrast, performed on the day of admission, demonstrated an intraparenchymal hemorrhage within the right parietal lobe with mass effect and edema but no midline shift (images not shown). Cerebral angiogram performed within the first 24 h after symptoms onset was unremarkable.

Two days after admission, the patient developed severe dysarthria and left-side weakness of the face, arm, and leg. A repeated head CT without contrast showed no interval change in the hemorrhage but worsening mass effect and a new midline shift. Brain magnetic resonance imaging (MRI), performed 4 days after admission, demonstrated early subacute right parietal hemorrhage with edema and a 4-mm midline shift (Figure 1).

Autonomic testing was performed 23 days after admission. The neurological examination was significant for left facial droop, left hemiplegia, and left hemisensory loss with a National Institute of Health Stroke Scale (NIHSS) [7] of 18. Average heart rate variability (RR) was 5.5% (Figure 2). A nerve conduction study did not show any signs of a large-fiber neuropathy. Collectively, these findings suggest that the autonomic dysfunction is of a central origin.

The patient's neurological condition gradually improved. Neurological examination 45 days after admission showed an improvement in the left facial droop and left-sided weakness, with an NIHSS of 8. Followup autonomic testing demonstrated an improvement in the average heart rate variability at 18.75% (Figure 3).

### Case 2

A previously healthy 48-year-old right-handed man was brought to our hospital after a witnessed fall at work. Coworkers reported a sudden onset of change in mental status as well as right-sided weakness. On initial examination, he was found to be obtundent with right-sided hemiplegia. NIHSS was 18. CT of the head without contrast was normal. The patient was treated with intravenous tissue plasminogen activator (tPA) with no clinical improvement. A cerebral angiogram showed a 70% stenosis at the origin of the left vertebral artery. The patient was treated with intra-arterial tPA and mechanical thrombectomy, with partial resolution of the left vertebral artery stenosis to 40%.

An MRI of the brain was performed 2 days after admission and demonstrated an area of restricted diffusion in

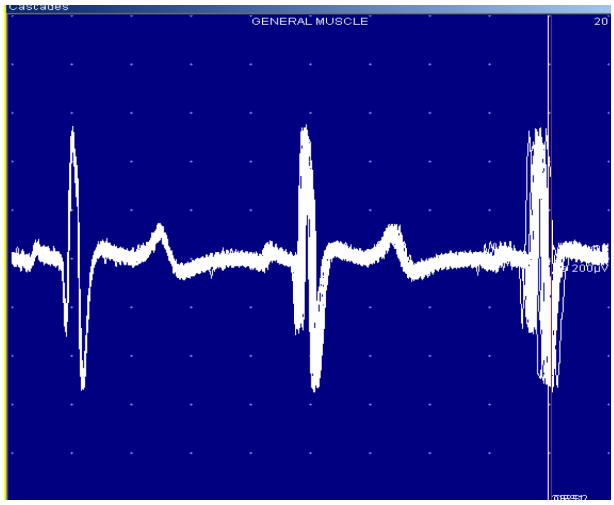


**Figure 2. Reduced average HRV (5.5%) on autonomic testing performed 23 days after admission.**

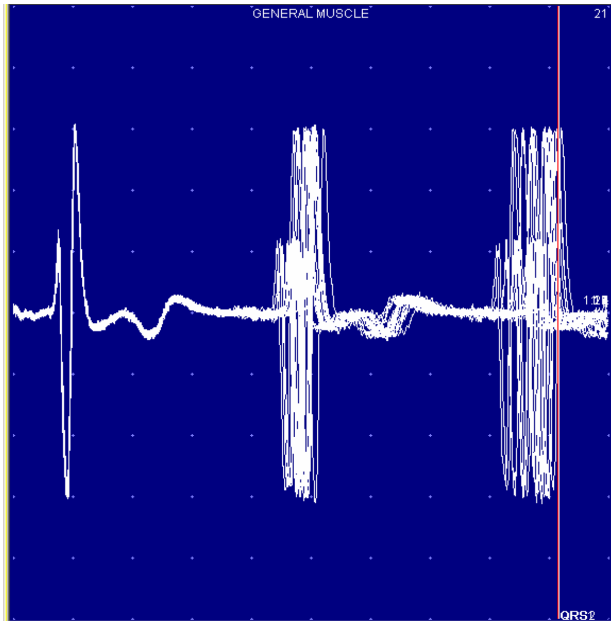


**Figure 3. Improved average HRV (18.7%) on autonomic testing performed 45 days after admission.**

the posterior limb of the left internal capsule. There was also an area of subtle hyperintensity in the medulla at the level of the inferior olive, but with no restriction of diffusion (Figure 4).

The patient underwent autonomic testing 2 days after admission. Neurological examination at that time showed no response to verbal, physical, or painful stimulation. Brain stem reflexes were intact. Autonomic testing showed an average HRV of 4.75% (Figure 5).

The patient showed gradual clinical improvement over the following 9 weeks. Forty-five days after admission, he was able to communicate by eye movements and move the right side of his body. Followup autonomic testing showed an improvement of average HRV to 13% (Figure 6).

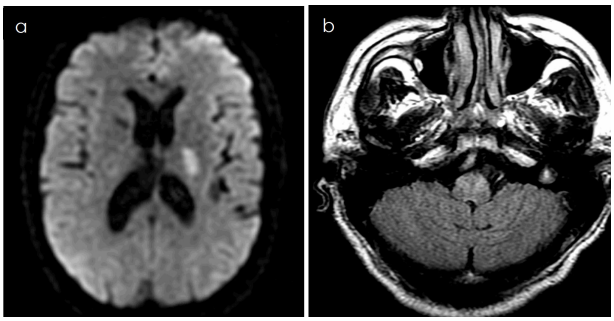


**Figure 4. (a) Brain MRI showed increased diffusion-weighted imaging signal in the left internal capsule. (b) Increased signal in the left ventral lateral medulla on fluid-attenuated inversion recovery (FLAIR) MRI.**

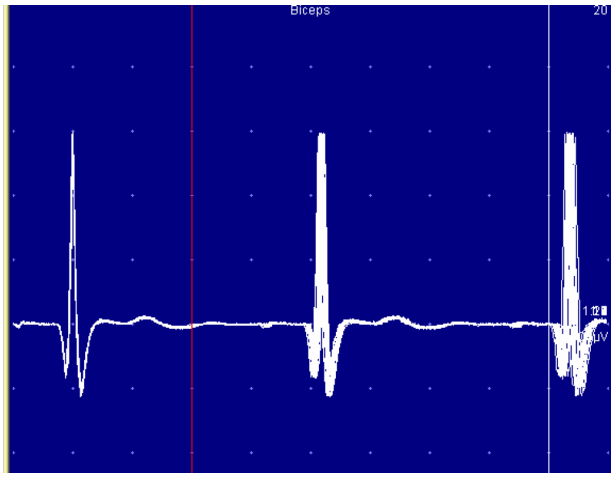


**Figure 5. Reduced average HRV (4.75%) on autonomic testing performed 2 days after admission.**

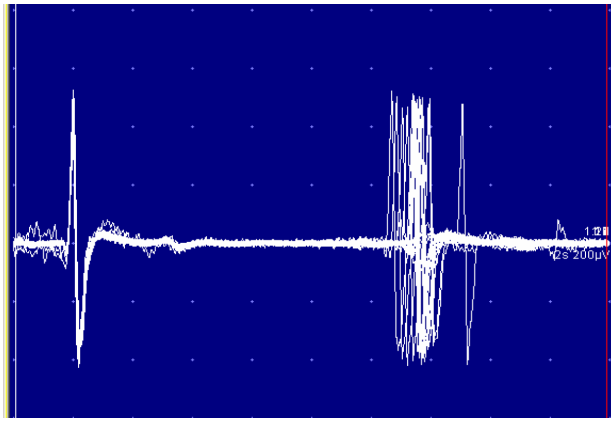

**Figure 6. Improvement of average HRV (13%) on autonomic testing performed 44 days after admission.**

## Discussion

HRV reflects a balance between the sympathetic and parasympathetic nervous systems and denotes the quantity of heart rate fluctuation around the mean heart rate. HRV has been utilized extensively to evaluate the alteration of autonomic function after stroke [8–15]. Decreased HRV has been associated with a higher risk of arrhythmia and sudden death in acute stroke patients [16,17]. Multiple and different anatomical regions of the brain have been suggested to be involved in autonomic dysfunction following stroke. Several studies reported an association between autonomic dysfunction and insular damage [1,18,19], and others described it following stroke in several other hemispheric locations, with no lateralization [19,20].

The patient presented in case 1 developed autonomic dysfunction with severe reduction of HRV after a right parietal hemorrhagic stroke. He had no history of arrhythmia or primary cardiovascular disease. Parietal stroke has been previously described to affect autonomic function [19,21]. With a secondary analysis of the Northern Manhattan study, Rincon *et al* [19] found an increased risk of cardiac death and myocardial infarction following parietal lobe strokes (left hemispheric greater than right). It is postulated that the cardiosympathetic centers are located in the anterior, medial, and superior parts of the insula. Furthermore, the posterior insula and inferior parietal lobe are responsible for inhibiting and modulating the cardiosympathetic outflow of other parts of the insula. A stroke involving the inferior parietal and posterior insula is more likely to disrupt the connection between the parietal lobe and autonomic centers in the brain, causing an autonomic imbalance and possible activation of the cardiosympathetic system, which leads to cardiac strain and increased risk of cardiac events [19].

In another study, conducted by Ay *et al* [21], the correlation between anatomical location of stroke and myocardial injury was analyzed. Patients with the diagnosis of stroke (documented clinically and radiographically) who had elevated cardiac troponin enzymes (cTnT) were compared with patients with stroke but no elevation of cardiac enzymes. Infarction sites on the MRI were mapped and correlated with the elevation of cTnT, demonstrating that the largest clusters of voxels that correlated with elevated troponin levels were found in the right posterior insular cortex and inferior parietal lobe. The authors suggested that the inferior parietal lobe is fed by the same branch of the middle cerebral artery and may have been included as a bystander. The insular cardiosympathetic cortex could be spared, while its parietal connections are disturbed, releasing the insula from some tonic source of inhibition [21].

In the second case described above, there was clinical and radiological evidence suggesting that the patient developed an acute stroke in at least two vascular territories: the medulla, supplied by the vertebrobasilar system, and the left internal capsule, supplied by branches of the middle cerebral artery. A stroke in either of these two anatomical regions has been shown to mediate autonomic dysfunction. Medullary stroke was reported to affect HRV more than any other brain stem region. In a prospective study conducted in Finland, patients with medullary stroke were found to have a lower HRV compared with other brain stem region infarcts [22]. Furthermore, left middle cerebral artery stroke may have a bystander effect on the left insula by releasing it from parietal connections.

In both patients presented above, normalization of HRV occurred several weeks after stroke symptoms onset and was paralleled by a dramatic improvement of the clinical status. This may potentially be related to resolution of brain edema observed during the acute phase, rescue of brain tissue in the penumbra area, and the activation of brain repair mechanisms. HRV testing reflected the dynamic changes in the neurological deficit and brain damage repair during the first weeks after an acute stroke. Our patients have a relatively good prognosis despite an initial reduced HRV. Several studies have considered abnormal HRV as a strong predictor of poor prognosis in stroke patients [9–12]. Our study challenges this finding and suggests that HRV, similar to brain tissue repair, is a dynamic process. A reduction in HRV during the acute or subacute phase of stroke may have a different prognosis than does a stroke of a comparable size, but with reversible changes of edema and penumbra when the mechanisms of tissue repair are more effective.

Our data demonstrated that serial HRV testing is a noninvasive tool that could be utilized as a marker to evaluate the dynamics of acute stroke. Larger controlled studies are needed to validate whether serial HRV testing is a more sensitive and cost-effective marker than single HRV testing or other markers in the assessment of the dynamics and prognosis of acute stroke.

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