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Linear and nonlinear parameters of heart rate variability in ischemic stroke patients

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ABSTRACT

Introduction: Cardiovascular system presents cortical modulation. Post-stroke outcome can be highly influenced by autonomic nervous system disruption. Heart rate variability (HRV) analysis is a simple non-invasive method to assess sympatho-vagal balance.
Objectives: The purpose of this study was to investigate cardiac autonomic activity in ischemic stroke patients and to asses HRV nonlinear parameters beside linear ones.
Methods: We analyzed HRV parameters in 15 right and 15 left middle cerebral artery ischemic stroke patients, in rest condition and during challenge (standing and deep breathing). Data were compared with 15 age- and sex-matched healthy controls.
Results: There was an asymmetric response after autonomic stimulation tests depending on the cortical lateralization in ischemic stroke patients. In resting state, left hemisphere stroke patients presented enhanced parasympathetic control of the heart rate (higher values for RMSSD, pNN50 and HF in normalized units). Right hemisphere ischemic stroke patients displayed a reduced cardiac parasympathetic modulation during deep breathing test. Beside time and frequency domain, using short-term ECG monitoring, cardiac parasympathetic modulation can also be assessed by nonlinear parameter SD1, that presented strong positive correlation with time and frequency domain parameters RMSSD, pNN50, HFnu, while DFA $\alpha 1$ index presented negative correlation with the same indices and positive correlation with the LFnu and LF/HF ratio, indicating a positive association with the sympatho-vagal balance.
Conclusions: Cardiac monitoring in clinical routine using HRV analysis in order to identify autonomic imbalance may highlight cardiac dysfunctions, thus helping preventing

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potential cardiovascular complications, especially in right hemisphere ischemic stroke patients with sympathetic hyperactivation.

1. Introduction

Cardiac dysautonomia is a common complication of stroke [1–3]. Post stroke autonomic nervous system dysregulation has attracted significant interest in the last couple of decades. Many facts involved in short term evolution and prognostic still need to be clarified.

Cardiovascular system presents cortical modulation. Both human studies and experimental data revealed that insular cortex, anterior cingulate gyrus, hypothalamus and amygdala may be involved in central autonomic nervous system regulation [4–6]. Lesions at these levels might be held responsible of cardiac arrhythmias. After acute cerebrovascular events arrhythmias and electrocardiographic abnormalities are common, even in the absence of structural heart disease, with a high incidence of dysautonomia [7].

Studies about heart–brain connections proposed the concept of neurogenic cardiac disease, clinically and pathogenically different from the actual cardiac disease [8–11].

Identifying high risk patients prone to develop neurogenic cardiac complications, by better understanding dysautonomia pathophysiology, and further implementation of adequate prophylactic and therapeutic measures, may significantly reduce mortality rate in stroke patients. The influence of stroke's hemispheric lateralization in cardiovascular autonomic dysregulation [12] has been illustrated using modern neuroimaging data, including positron emission tomography and functional magnetic resonance imaging data [13].

An acute ischemic lesion involving the cortical network controlling the activity of the autonomic nervous system may imbalance autonomic responses at cardiac level and lead to an increased risk of arrhythmia [14]. Insular cortex, a complex structure supplied by the middle cerebral artery (MCA), was often used as a model to illustrate the possible lateralization impact on sympatho-vagal balance, depending on the hemispheric localization of the stroke. It has been reported that cardiosympathetic centers are located in the anterior, medial and superior parts of the insula, while posterior insula and inferior parietal lobe are responsible for inhibiting and modulating the cardiosympathetic outflow of the other parts of the insula [15]. Autonomic imbalance associating increased sympathetic activity may be reflected in cardiovascular impairment post insular stroke [1].

Among different variables assessing the autonomic response, heart rate variability (HRV) quantifies sympatho-vagal modulation at sino-atrial level. It has been shown that a reduction of HRV may be an indicator of general illness, including acute stroke, and it correlates with enhanced sympathetic or reduced vagal tone, which may predispose to higher risk of arrhythmia [16,17] and increased risk of sudden cardiac death. HRV might provide prognostic information in ischemic stroke. Graff and collaborators [18] underlined the contribution of HRV in-depth analysis to stroke prognosis and stated that while HRV assessed by linear methods may provide long-term prognostic value, complex, non-linear measures of HRV may rather assess the impact of the neurological state on temporary patterns of heart rate post stroke [18]. In the same line of evidence, it has been recently shown that acute ischemic stroke patients had a significant reduced complexity of HRV. Early assessment of HRV by nonlinear methods can be a potential predictor of stroke-in-evolution in newly admitted non- atrial fibrillation ischemic stroke patients [19].

In addition to linear parameters, nonlinear parameters of HRV might be useful to identify patients prone to cardiac arrhythmia, thus a prognostic marker of cardiac function.

The Poincaré plot is a visual representation of the dependence between successive RR intervals, first used as a qualitative tool [20] by fitting an ellipse to the shape of the Poincaré plot in order to calculate HRV indices [21]. This geometrical technique can be used to assess the dynamics of HRV by a representation of the values of each pair of R–R intervals into a simplified phase space, describing the dynamics of a phenomenon that can recognize the hidden correlation patterns of a time series signal [22,23]. Each pair of successive elements in a time series (tachogram) is pictured into a simplified Cartesian plane [24,25]. Series of these points at successive times outline a trajectory. This describes the system's evolution and therefore is commonly applied to assess the dynamics of HRV. Using this technique, SD1 and SD2 are the semi-axis of this ellipse. SD1 is related to the fast beat-to-beat variability, while SD2 describes the longer-term variability, SD1/SD2 showing the ratio of short-term to long-term interval variation. This quantitative method of analysis is based on the notion of different temporal effects of changes in the vagal and sympathetic modulation of the HR on the subsequent R–R intervals without a requirement for a stationary quality of the data [22,24,26,27].

SD1 is considered a parasympathetic index of sinus node control being a measure of rapid changes in R–R intervals, because vagal effects on the sinus node are known to develop faster than sympathetically mediated effects [28,29] and SD2 is influenced by both parasympathetic and sympathetic tonus [30].

Other useful parameter is approximate entropy (ApEn), a measure of the disorder in the HR signal which quantifies the regularity and complexity of time series. Sample entropy (SampEn) is a less biased measure derived from approximate entropy [23,31], which quantifies signal complexity robustly within short time segments [32]. The name refers to the applicability to time series data sampled from a continuous process and the algorithm suggests ways to employ sample statistics to evaluate the results [33]. It measures system complexity and unpredictability [34] and is the negative natural logarithm of the conditional probability that two

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