The hemisphere of the brain in which a stroke has occurred visible in the heart rate variability

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The hemisphere of the brain in which a stroke has occurred visible in the heart rate variability

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ABSTRACT

Objective: Can the localization of an ischemic stroke in the hemisphere of the brain be assessed on the basis of the heart rate variability? Is there a difference in heart rate variability between people with right hemisphere stroke and people with left hemisphere stroke?

Methods: 24h analysis of RR intervals of people in the acute phase of stroke. The research group consisted of 25 people after ischemic stroke of the right hemisphere and 39 people after ischemic stroke of the left hemisphere. Standard linear methods were used to analyze heart rate variability in the time and frequency domains, as well as nonlinear methods - Sample Entropy, Detrended Fluctuation Analysis and asymmetry measures.

Results: Statistically significant results between right and left hemispheric stroke subjects are shown for the pNN50 (p-value=0.028) and Sample Entropy (p-value=0.010). The results for the RMSSD (0.052) are also close to statistical significance. People with a right hemisphere stroke are characterized by reduced parasympathetic activity and a lower complexity of heart rate variability compared to the group of people with left hemispheric ischemic stroke.

Conclusion: Based on the heart rate variability in the acute phase of an ischemic stroke, it is possible to determine the location of the stroke in the right brain hemisphere or the left brain hemisphere.

Introduction

Stroke is a neurological disorder, however, the human body is not a collection of separate systems, but an integrated network of many physiological systems that constantly interact with each other. According to the postulate of the physiological network, research is currently being carried out in which the mutual interactions of two or more systems in the human body are observed1. In this paper, the relationship between the cardiovascular system and the nervous system will be presented. The study discusses whether a neurological disease such as stroke can be seen in the heart rate variability (HRV). Many publications have been written in which a correlation was found between the heart rate variability in stroke patients, their health condition prior to stroke2, mortality3,4, the patient’s prognosis for the future and the probability of developing other post-stroke diseases5,6. In this study, it was verified whether it is possible to recognise the stroke location (right hemisphere stroke or left hemisphere stroke) just using heart rate variability analysis.

The classic, commonly used methods of analyzing HRV are linear measures in the time and frequency domains7. However, it is postulated that the heart rate variability is characterized by cardiovascular regulation mechanisms which interact non-linearly8. Therefore, nonlinear analysis methods should be used. Nonlinear methods are a more reliable indicator of the performance of physiological systems9. In the literature, you can find articles on the changes seen in HRV in people with a stroke in the right or left hemisphere of the brain10. Some researchers indicate that certain measures of HRV analysis differ depending on which hemisphere the stroke was in11,12, other researchers argue that there are no statistically significant differences in HRV parameters in people depending on the location of the stroke in the hemisphere5,13.

Results

Analyzes of linear and non-linear parameters describing heart rate variability were performed on 24h records of RR intervals, the study included 67 people in the acute phase of ischemic stroke. The Table 1 shows the numeric results in the X (Y) format, where X is the group mean and Y is the standard deviation. The p-value column represents a Mann-Withey statistical test to compare the two groups with each other.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left hemisphere (n=39)</th>
<th>Right hemisphere (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-based analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeanRR [ms]</td>
<td>837 (120)</td>
<td>849 (173)</td>
<td>0.901</td>
</tr>
<tr>
<td>SDNN [ms]</td>
<td>142 (62)</td>
<td>117 (39)</td>
<td>0.117</td>
</tr>
<tr>
<td>RMSSD [ms]</td>
<td>135 (96)</td>
<td>93 (68)</td>
<td>0.052</td>
</tr>
<tr>
<td>pNN50 [%]</td>
<td>34.50 (28.47)</td>
<td>19.83 (23.89)</td>
<td>0.028</td>
</tr>
<tr>
<td>Frequency-based analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF [%]</td>
<td>55.71 (19.44)</td>
<td>49.45 (19.97)</td>
<td>0.221</td>
</tr>
<tr>
<td>LF [%]</td>
<td>44.29 (19.44)</td>
<td>50.55 (19.97)</td>
<td>0.221</td>
</tr>
<tr>
<td>Non-linear analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI [%]</td>
<td>55.87 (5.15)</td>
<td>57.19 (4.71)</td>
<td>0.242</td>
</tr>
<tr>
<td>PI [%]</td>
<td>51.19 (2.49)</td>
<td>52.09 (3.69)</td>
<td>0.500</td>
</tr>
<tr>
<td>Sample entropy</td>
<td>1.25 (0.53)</td>
<td>0.92 (0.46)</td>
<td>0.010</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>0.83 (0.26)</td>
<td>0.92 (0.27)</td>
<td>0.248</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>0.84 (0.24)</td>
<td>0.92 (0.23)</td>
<td>0.289</td>
</tr>
</tbody>
</table>

Table 1. Comparison of linear and non-linear parameters HRV analysis between the group with the left and the right hemisphere ischemic stroke.

**Discussion**

It is commonly believed that HRV analysis is a good way of describing the activity of the autonomic nervous system. In the articles, researchers observe correlations between heart rate variability and mortality in stroke patients\(^1\). They look for the relationship between HRV rates and the patient’s health condition after a stroke and the speed of return to daily functioning\(^2\).

In this article, it has been observed that there are differences in heart rate variability between people with right hemisphere stroke and people with left hemisphere stroke. It was also shown that there are statistically significant correlations between indicators such as pNN50 (p-value=0.028) and the Sample Entropy value (p-value=0.010). Additionally, it is worth paying attention to the RMSSD indicator (p-value=0.052). The root mean square successive differences between successive RR is not an indicator that differs within statistical significance (p-value<0.05). The p-value in this indicator is larger than 5%, but not much. Similar observations were made by Colivicchi et al\(^10\). In a 2004 article points out that right insula patients had lower SDNN and RMSSD values and higher LF/HF values than patients with right-sided, but non-insula and left-sided stroke. Colivicchi et al. as in this article analyzed RR intervals. Unfortunately, in the article from 2004 there are no other methods of linear analysis, e.g. pNN50 nor non-linear methods.

Here, we show that people with right hemispheric stroke had significantly lower pNN50 and Sample Entropy values than people with left-sided stroke. Group differences seen in the pNN50 and RMSSD indices but not in the meanRR, stdRR might suggest that there are some differences in local, short-range analysis involving several adjacent intervals between the two groups. The pNN50 and RMSSD indices describe short-range relationships. MeanRR and stdRR as well as frequency analysis focus on indicating long-range relationships in a signal. It is possible that the differences between persons with a stroke of the right hemisphere and the left hemisphere of the brain are visible on short time scales, and globally (e.g. by analyzing the mean and standard deviation) these properties are hidden by long-range correlations. Following this line of reasoning, also the parameter $\alpha_1$ in Detrended Fluctuation Analysis should be statistically significant. This parameter describes short-range correlations, but the results show that both $\alpha_1$ and $\alpha_2$ do not show statistically significantly different values for both groups.

The second direction of considerations may be the activities of the sympathetic and parasympathetic systems seen in the heart rhythm. According to Wittling et al.\(^14\) the right hemisphere of the brain is mainly responsible for sympathetic activity, while the left hemisphere of the brain is responsible for parasympathetic activity. In a 1998 paper, researchers analyzed the power spectrum of heart rhythm variability in a group of 45 healthy people who were shown film fragments for selective sensory stimulation of the hemispheres. The conclusion from this study was that there was a clear and consistent advantage in the left hemisphere in the control of parasympathetic cardiac modulation. Similar observations were published by Hilz et al.\(^15\) in a 2001 article. They studied a group of 15 people with drug-resistant epilepsy. Based on the analysis of the autonomic heart rate (HR) and blood pressure (BP) modulation and baroreflex sensitivity (BRS), they also observed sympathetic lateralization in the right hemisphere and the predominance of the parasympathetic system in the left hemisphere.

In a 1994 article, Barron et al.\(^16\) analyzed power spectra of short records (256 RR intervals). They observed that the parasympa-
thetetic innervation of the heart was reduced after both right and left brain stroke. However, a greater reduction in the heart’s parasympathetic innervation was seen in the right hemispheric stroke group. In Table 1, the RMSSD and pNN50 parameters in people with right-sided stroke are significantly lower than in people with left-sided stroke. This observation is consistent with the conclusions of Barron et al. The RMSSD and pNN50 measures show a decreased activity of the parasympathetic system in people with right-sided stroke compared to people after left hemispheric stroke who have higher RMSSD and pNN50. The lower the pNN50 and RMSSD parameters, the lower the parasympathetic activity of the autonomic nervous system.

The open question is why Sample Entropy differentiates these patients so well? When looking for an answer to the above question, it was checked whether the Sample Entropy parameter would still be after the removal of persons with atrial fibrillation. Analysis of normal-to-normal intervals, modification of ‘m’ and ‘r’ parameters, i.e., pattern length and tolerance, analysis of shorter time series (day or night only) it well differentiated patients with right hemisphere stroke from patients with left hemisphere stroke. The observations showed that Sample Entropy in each of the above-mentioned cases statistically significantly differentiated people with left hemisphere stroke from people with right hemisphere stroke. Right hemisphere stroke survivors have lower HRV complexity (lower Sample Entropy) than left hemisphere stroke survivors.

Summing up: analyzing the heart rate variability, it is possible to identify the location of the ischemic stroke in the hemisphere of the brain. Right-sided stroke patients are characterized by reduced parasympathetic activity (lower pNN50 and RMSSD) and lower heart rate variability complexity (lower Sample Entropy) compared to the left-sided stroke group.

Methods

Participants
The research group consists of 67 people with ischemic stroke. In 2010-2019, these people were patients of the Neurological Clinic of the Stroke Division of the Military Institute of Medicine in Warsaw. This analysis is a retrospective study, the data contained in the article come from routine tests performed on stroke patients staying at the Department of Neurology of the Military Institute of Medicine. We have conducted this study in accordance with the Declaration of Helsinki. The electronic database was decoded, and the patient identification data was scrambled to ensure confidentiality; the informed consent was thus exempted (approved by Institutional Review Board of Military Institute of Medicine in Warsaw (Komisja Bioetyczna przy Wojskowym Instytucie Medycznym), no.:20WIM/2020 at 22.04.2020). The evaluation of all the studies was blinded from the clinical data. This study was evaluated and approved as an internal study of Military Institute of Medicine in Warsaw (no.: 00574) and by the Institutional Review Board of Military Institute of Medicine in Warsaw (Komisja Bioetyczna przy Wojskowym Instytut Medycznych) (no.:20WIM/2020 at 22.04.2020). The exclusion criteria for patients were hemorrhagic or transient ischemic stroke (TIA). Patients qualified for the analyzes had to have a 24h Holter EKG examination performed in the acute phase of a stroke and a medical imaging examination (computed tomography and/or magnetic resonance) indicating in which hemisphere of the brain the stroke occurred. 3 people with brainstem stroke were excluded from the study due to the insufficient size of the group to properly perform statistical tests. Sixty-four patients were qualified for the final analyzes, including 25 patients with diagnosed right hemisphere stroke and 39 patients with left hemisphere stroke. The mean age among people with right-sided stroke was 64 ± 12, in the left hemisphere stroke group the mean age was 66 ± 13. The number of women with right hemisphere stroke was 13, and the number of men was 12. Left hemisphere stroke group was 20 women and 19 men. At the time of admission to the hospital, each person was rated using the National Institutes of Health Stroke Scale (NIHSS). Right hemispheric stroke subjects had mean NIHSS = 14 ± 5 (1 patient had no data), and left-sided stroke subjects averaged 15 ± 6 NIHSS scores (also 1 patient in this group was not rated on the NIHSS).

Heart rate variability
The 24-hour heart rate variability recordings were recorded by the Reynolds Medical Holter EKG Lifecard CF device. The sampling frequency was 128 Hz. The RR intervals were analyzed in the HRV analysis. The R wave detection process was performed automatically by Holter’s software. Both methods of linear analysis in the time and frequency domains as well as non-linear analysis were used in the work.

Linear methods

Time domain
In this paper shows linear analysis measures in the time domain, such as: meanRR, SDNN, RMSSD, pNN50. The first measure is the mean duration of the RR interval (meanRR) and is expressed in milliseconds, SDNN is the deviation of RR intervals relative to the meanRR and is expressed in milliseconds. The RMSSD measure is root mean square successive differences between successive RR intervals and pNN50 indicates the percentage share in the entire recording of such samples, where the difference between adjacent RR intervals is greater than 50 ms.
Frequency domain

Linear analysis was expressed as $HF_{nu}$ and $LF_{nu}$ measures. These are the power spectra in the high frequency range (0.15–0.4 Hz) and low frequency (0.04–0.15 Hz), respectively. Power spectra are given in normalized units, where the numerator is the corresponding power spectrum $HF$ or $LF$, and the denominator is the sum of both power spectra ($LF + HF$). Values are expressed as percentages.

Non-linear methods

Two measures of heart rhythm asymmetry were used in the study: the Guzik index [GI] and the Porta index [PI]. The Guzik Index calculates the distance between adjacent points above the identity line to the distance between adjacent points on the identity line, above and below the identity line in the Poincaré plot. The Porta Index, unlike the GI, does not consider points on the line of identity. The Porta Index describes the ratio of the number of points on the Poincaré chart above the identity line to the sum of the points above and below the identity line.

The article also presents the results of Sample Entropy. 0.2 * std was assumed as the tolerance parameter ‘r’, and the standard length ‘m’ was set as 2.

Another two measures of non-linear HRV analysis come from Detrended Fluctuation Analysis (DFA). In this method, two scaling factors $\alpha_1$ and $\alpha_2$ are determined. The first exponent contains information on short-range correlations (4-16 consecutive RR intervals). The exponent $\alpha_2$ evaluates long-range sequences (17-64 RR intervals).

Statistical analysis

For each of the analyzed variables, the Shapiro-Wilk test was performed in order to verify the normality of the variable distributions. The measures did not have normal distributions, so the non-parametric Mann-Whitney test was used for statistical analysis, the results $p<0.05$ were considered statistically significant. The results of the statistical tests are presented in Table 1.

The statistical analysis was performed in the Python 3.8 environment.

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Limitations of the Study

This study had several limitations. First, the sample size was small and the data came from one clinic. Secondly, in the paper it was decided to consider only the division of patients with left hemisphere stroke vs. with a stroke of the right hemisphere of the brain. Deeper analyzes, distinguishing areas in the brain that were affected by ischemia, could provide additional information.

Declarations

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Author contributions statement

J.A., J.S., J.Ż., A.D., A.P.-W. designed the study. J.S., A.D., A.P.-W. collected the data and were responsible for medical part of study. A.K., A. J. created the database with medical data. J.A. observed significant differences between the studied groups. J.A., J.Ż. were responsible for results presentation and interpretation. All authors participated in manuscript construction. All authors reviewed the manuscript. The authors declare that they have no conflict of interest.

References


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