Stroke patients and a non-linear analysis of Heart Rate Variability

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***Abstract*—** Cerebrovascular diseases represent one of the major cause of death and disability in western countries. Considering the projection in older population by 2100, life expectancy is expected to vary across countries from 66 to 97 years, and by 2300 from 87 to 106 years. Beyond the demographic window, population ageing becomes a predominant demographic feature. The analysis of heart rate variability is a well recognized non-invasive tool to investigate the cardiovascular autonomic control but only limited data are available on the autonomic imbalance assessment of stroke patients by heart rate variability changes after a prior single stroke, using time- and frequency-domain linear methods. To evaluate the relationship between lesion's severity and Poincarè' Plots features, 20 first-ever stroke subjects, divided on the basis of presence of a single or multiple medium cerebral artery lesion, and 10 healthy subjects were studied. All subjects underwent to a 24-hour ECG recording analysed by Poincarè' Plots, spectral and time-domain techniques. The Poincarè' Plots were quantified by computer-generated indexes, namely the length (L), wideness (W) and area (A) of 2D plots and the number of peaks (Np) and the length of the radii of inertia (Px,y,z) of the 3D plots. Power spectral density was estimated on 5 minutes sequences by the Blackman-Tukey method in the VLF, LF and HF band by numerical integration. SDNN, PNN50, MSSD time-domain parameters were also evaluated. Statistical analyses were performed by the Kruskal-Wallis and Dunn's post hoc test for multiple comparisons. A direct relationship between increasing lesion's severity and progressive collapsing of both 2D and 3D Poincarè' plots was observed. L, A and Np, showed the highest significant differences between all groups, while lower significance was found for spectral and time-domain parameters. These data suggest that Poincarè' Plots analysis contains relevant information related to different heart rate variability dynamics in normal and stroke subjects with different lesion's severity.

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I. Introduction

Cerebrovascular diseases represent one of the major cause of death and disability in western countries. Considering the projection in older population by 2100, life expectancy is expected to vary across countries from 66 to 97 years, and by 2300 from 87 to 106 years. Beyond the demographic window, population ageing becomes a predominant demographic feature.

Between 2100 and 2300, the proportion of world population 65 years and older will increase by one-third (from 24 to 32 per cent); the proportion 80 years and older will double (from 8.5 to 17 per cent); and the proportion 100 years and older will increase nine times (from 0.2 to 1.8 percent) [1]. The prevalence of silent cerebral infarction is estimated to range from 6% to 28%, with higher prevalence with increasing age.

An impaired cardiovascular autonomic regulation has been described in stroke patients with dysfunction that often complicate the clinical course of these pathology.

Brainstem stroke, damaging the baroreflex relay nuclei, is typically associated with baroreflex failure and blood pressure instability [2]. However, hemispheric lesions altering the widespread central autonomic network may impair the baroreflex function as well [3].

Disease manifestations that may indicate baroreceptor reflex dysfunction, such as hypertensive crises or high blood pressure variability, often accompany the acute phase of ischemic or hemorrhagic stroke [4]. Indeed, baroreflex impairment has been repeatedly shown to be present in acute ischemic and hemorrhagic stroke [3-8].

It has been hypothesized that these abnormalities are mediated by the central nervous system as a result of the cerebrovascular event, whereas the mechanism of this phenomenon is not fully understood [9,10].

Since changes in the sympathetic and vagal traffic to the sinoatrial node alter the natural frequency of the cardiac pacemaker inducing a corresponding change in heart rate, the measurement of the latter would be the simplest way of appraising the autonomic control of the heart and, more specifically, the sympatho-vagal balance.

The interaction between heart rate, the intrinsic frequency of the pacemaker and the levels of vagal and sympathetic outflows to the heart has been model as a multiplicative relationship. Hence, given the intrinsic frequency, the net effect of the sympatho-vagal balance at any instance is expressed by the current heart rate.

Unfortunately, however, the intrinsic frequency changes between individuals and its measurement requires a complete autonomic blockade. As a consequence, the measurement of heart rate provides only an uncalibrated quantification of the sympatho-vagal balance.

Beat-to-beat spontaneous fluctuations of heart rate do occur continuously in every human subject with an intact heart and reflect corresponding fluctuations in neural traffic of efferent vagal and sympathetic nerves. The fluctuation of heart rate around its mean has commonly been referred to as heart rate variability (HRV).

In fact, many ECGs variations has been the subject of numerous clinical studies investigating a wide spectrum of cardiological and non-cardiological diseases and clinical conditions [11-14].

The analysis of HRV is a well recognized non-invasive tool to investigate the cardiovascular autonomic control [11-17] but only limited data are available on the autonomic imbalance assessment of stroke patients by heart rate variability changes after a prior single stroke, using time- and frequency-domain linear methods [18-22].

Recently non-linear analysis of heart rate variability has been suggested to provide more valuable information for physiological interpretation of heart rate fluctuation and for the risk assessment [23].

The popular technique used to quantify the Poincaré plot is fitting an ellipse to the shape of the Poincaré plot and measure the dispersion along the major and minor axis of the ellipse. This technique was first proposed by Tulppo et. al. [24] in which they have defined two standard descriptors of the plot SD1 and SD2 for quantification of the Poincaré plot geometry.

Later, the description of SD1 and SD2 in terms of linear statistics, given by Brennan et. al. [25], showed that the standard descriptors guide the visual inspection of the distribution. In case of heart rate variability, it reveals a useful visual pattern of the RR interval data by representing both short and long term variations of the signal [24,25].

Poincarè's plots analysis of beat-to-beat time series is one of the few methods that have been tested in clinical settings in the last year, allowing to detect patterns resulting from non-linear processes that may not be observable by time- and frequency-domain analysis [26,27].

It has been shown that Poincarè plots of heart rate variability allows quantitative display of parasympathetic nervous activity [28,29] and that quantitative descriptors of Poincarè plots are better predictors of mortality in cardiac patients than time-domain conventional indexes [30].

Several Poincarè plots analysis' methods have been proposed in literature, but it has clearly been shown that most of them bring back to existing linear measure of heart rate variability [31] and only nongeometric techniques, such as scanning parameters [32], allow to detect patterns resulting from non-linear processes that cannot be detectable by time- and frequency-domain analysis.

The aim of the paper was to evaluate the relationship between the lesion's severity of stroke patients and Poincarè plots novel computer-generated quantitative indexes, comparing results with the traditional time- and frequency-domain linear parameters of heart rate variability.

II. Study Population

The study population consisted of 20 patients consecutively admitted to Neurology Rehabilitation Division of "Salvatore Maugeri" Foundation. All subjects enrolled were over 45 years old, with a positive past medical history for previous first-ever stroke (ischemic and/or hemorrhagic), presence of neuromotor monolateral deficit at physical examination.

Moreover to confirm the presence of a neurological impairment was used the Functional Independence Measure (FIM) score.

This tool contains 18 items composed of: 13 motor tasks and 5 cognitive tasks (considered basic activities of daily living). Tasks are rated on a 7 point ordinal scale that ranges from total assistance (or complete dependence) to complete independence. Scores range from 18 (lowest) to 126 (highest) indicating level of function. When assessing deficit-severity using the FIM, several groups of researchers use the functional groups <40, 40-60, 61-80, or >80 for the total FIM score.

In these study we considered patients with a FIM score between 40 and 60, that assess a moderate functional impairment.

Patients with manifestations of other nervous system lesions and patients with any other disease or medication known to affect the autonomic nervous system were excluded. Patients with acute congestive cardiac failure as well as patients with previous cardiac or pulmonary diseases were also excluded.

Patients with congestive heart failure (in IV NYHA functional class), renal, hepatic or pulmonary failures, cerebral neoplasm, severe cranial trauma, psychosis, FIM score <40 or >60, atrial fibrillation were excluded.

The study population was divided in two groups. Each group included 10 patients with an evidence, in according to a CT finding, of medium cerebral artery single (SL, mean-age 65±15 yo) or multiple (ML, mean-age 68±7 yo) lesion. The control group (N) consisted of 10 healthy subjects (mean-age 42±6 yo).

Table 1 shows some variables considered in SL and ML-SP groups.

III. Holter Analysis

The study population underwent to a 24-hour Holter ECG recording by a portable three-channel tape recorder, processed by a Marquette 8000 T system with a sampling frequency of 128 Hz.

All recordings were performed at admission: after the preparation of the skin, self-adhesive electrodes were placed in the positions usually used for three-leads Holter monitoring, and recording was started between 9.00 and 9.30 AM.

During the recording period the patients were allowed to standing or sitting next to their beds, while other activities were not allowed.

In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable RR intervals in sinus rhythm. Moreover, this period had to include at least half of the nighttime (from 00:00 AM trough to 5:00 AM) and half of the daytime (from 7:30 AM trough to 11:30 PM) [33].

Tab. 1: Some variables in the SL and ML groups

	SL-SP	ML-SP	p
Age	65.05±15.23	68.38±7.55	ns
Height	163.52±6.18	165.13±7.79	ns
BMI	27.84±3.96	26.42±3.77	ns
SBP	138.82±14.95	136.15±21.03	ns
DBP	87.65±9.03	79.23±25.32	ns
Hb	13.12±1.35	13.49±1.87	ns
Cholesterol	220.15±48.19	178.57±30.68	<0.01
ADL	4.62±1.94	5.19±1.72	ns
IADL	7.24±2.43	6.75±1.91	ns
Diabetes (%)	2 (9.5)	1 (6.3)	ns
Hyp (%)	9 (42.9)	6 (37.5)	ns
EF	56.49±11.41	56.29±7.94	ns
NYHA class	1.90±0.72	2.19±0.66	ns

Values are mean ±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ADL, activity daily living; IADL, instrumental activity daily living; Hyp, hypertension; EF, ejection fraction; NYHA, New York Heart Association.

Each beat was labeled as normal or aberrant according to recognition by the algorithm for tape analysis and after an investigator's verification.

All RR time series were analysed by PPlots, spectral- and time-domain techniques.

IV. Poincarè Plots Analysis

The Poincare plot, is a technique taken from nonlinear dynamics and portrays the nature of RR interval fluctuations.

It is a plot in which each RR interval plotted as a function of the previous RR interval. Poincare plot analysis is an emerging quantitative-visual technique, whereby the shape of the plot is based on the analysis of the maps constructed by plotting each RR interval against the preceding one.

The plot provides summary information as well as detailed beat-to-beat information on the behavior of the heart.

The markings of the plot are gathered around a line of unitary slope passing through the origin. Quantitative analysis of a plot entails fitting an ellipse to the plot, with its center coinciding with the center point of the markings.

Usually bi-dimensional (2D) Poincarè plots are visually classified into three typical patterns [18]: a comet-shaped pattern (C), with an increasing heart rate variability at lower heart rates, a torpedo-shaped pattern (T), with a reduced heart rate dispersion on the whole distribution, and a fan-shaped pattern (F), with a great dispersion in a narrow range of frequencies. One major limitation of this visual classification is the subjective evaluation of the plots.

To overcome this problem, the automatic quantification of Poincarè plots have been recently proposed by our group.

Moreover our maps plotted the RR couple repetition's number as the third dimension. of the plot (see Fig. 1).

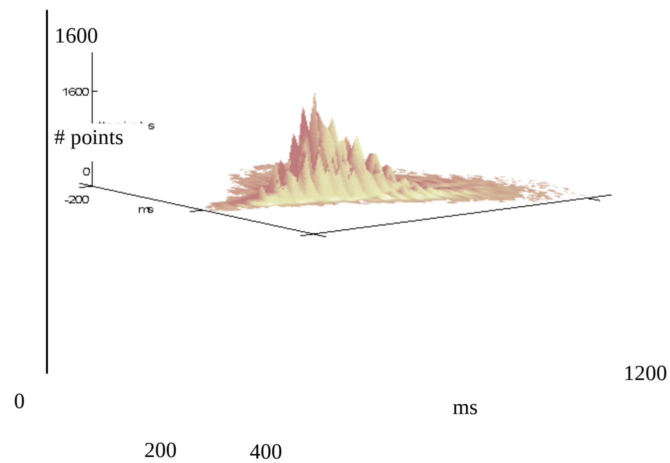

Fig. 1. 3D Poincarè plots analysis

A dedicated software developed by the authors allowed to automatically calculate the main morphological characteristics of bi and three-dimensional (3D) maps.

Technical details on the procedure have been described elsewhere and excellent reproducibility of obtained indexes has been previously demonstrated [32].

Only normal classified QRS complexes were considered in the analysis, excluding RR intervals preceding or following not-normal beats and plotting only time-closed RR couples.

The most meaningful parameters extracted from 2D PPlots are measures of the extension and dispersion of the ellipsoidal cloud of points around the bisecting line, namely the length (L), the area (A), the highest variability extension (HVE), that can be obtained scanning the plot with a vertical line and generating a curve which represent the measure of scatterplot width at different RR intervals, and percentage of length which corresponds the maximum plot wideness (P) (see Fig. 2).

The most interesting parameters extracted from 3D PPlots are measures related to the plot's height, taking into account the RR couples' repetition number, namely the peaks' number

(Np), the mean peaks' distance from the bisecting line (Dp), and the length of the three radii of of inertia (Px, Py, Pz) of the semi-ellipsoidal three-dimensional cloud of points (see Fig. 2).

V. Linear Analysis

Spectral analysis was performed by an homemade software [34] on 5 minutes RR sequences extracted from 24-hours holter recordings. From each 5 min sequence

HRV indexes were computed, and their mean value across the whole 24 h recording and during daytime and nighttime was obtained.

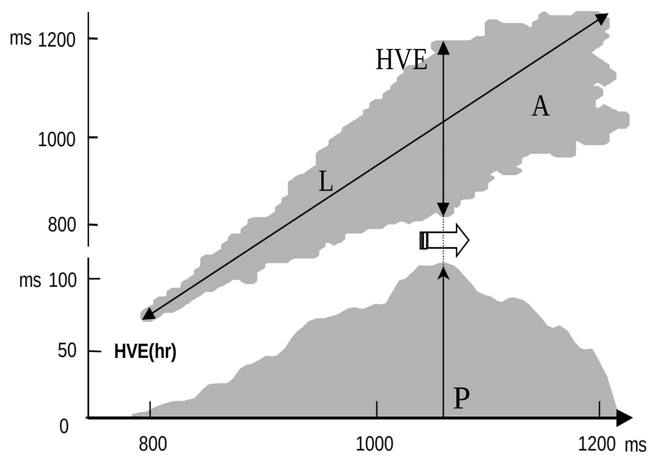

Fig. 2. 2D Poincarè plots parameters

Identified RR time series were preprocessed according to the following criteria: (1) RR intervals associated with single ectopic beats were replaced by their mean value, (2) artifacts and runs of tachycardic beats were replaced by N values equal to the mean RR, in such a way that N # mean RR was less than or equal to the substituted value, (3) RR values differing from the preceding one more than 30% (absolute value) were replaced in the same way as for artifacts.

The mean RR was computed as a moving average centered on the beat to correct, with a buffer of ±3 beats labeled as normal.

The sequences containing artifacts or large transients or containing over 4% of ectopies were automatically discarding.

The few ectopic beats present in accepted sequences were automatically corrected by an interpolating algorithm.

The original and the corrected 5 minutes sequences were then plotted superimposed and the analyst could decide whether to accept or to discard the resulting series.

Power spectral density, a highly reproducible tool to assess the functional balance between parasympathetic and sympathetic domains of the autonomic nervous system activity and to decompose the total variation of a data series into its frequency components, was estimated by the Blackman-Tukey method in all accepted segments after linear trend removal.

The total power and the power in the low frequency band (LF, 0.04-0.15 Hz) and high frequency band (HF, 0.15-0.45 Hz) were then computed by numerical integration of the spectral density function. The LF/HF ratio was also calculated.

Only normalized LF, HF, and LF/HF values were considered in the analysis and expressed as normalized units.

The most commonly used time-domain parameters were derived from normal RR intervals (NN).

Among these, the square root of the mean squared differences of successive RR intervals (RMSSD) is associated with respiratory effects on heart rate and modulated by both parasympathetic and sympathetic activity, the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms (NN50) by the total number of NN intervals (pNN50) reflects rapid adjustments, and the standard deviation of NN (SDNN) express overall HRV regulation.

The most important time-domain parameters (SDNN, PNN50, MSSD) were also evaluated for all RR time series.

VI. Statistical Analysis

The results are expressed as the mean±standard deviation (SD).

Statistical analyses were performed for all parameters by the Kruskal-Wallis test and the Dunn's post test for multiple comparisons.

A p value <0.05 was considered statistically significant.

VII. Results

We observed a direct relationship between the increasing lesion’s severity of SP and a progressive collapsing of both 2D and 3D PPlots, indicating a progressive impairment of cardiac autonomic control.

L, A and Np parameters showed the highest significant differences between the three study groups (Table 1), while lower significance levels were found for spectral parameters. There were no significant differences using time-domain indexes (only SDNN is shown in Tab. 2).

Tab. 2. Measurements in Normals and patients with Single and Multiple lesion of medium cerebral artery.

Index	N	SL-SP	ML-SP	p
L	803±108	518±103 °	436±87 **	<0.0001
A	16890±6357	16330±7071	9229±2840 **†	<0.01
Np	44±21	23±9	11±5 **†	<0.0001
VLF	684±202	1924±1221 °	1355±672	<0.005
LF	988±422	888±516	453±344 *	<0.05
SDNN	53±10	72±20	56±12	ns

Values are mean ± SD. ° SL *vs* N p<0.01; * ML *vs* N p<0.05; ** ML *vs* N p<0.01; †ML *vs* SL p<0.05.

VIII. Discussion

Several time- and frequency-domain indexes have been extracted from the HRV signal using digital signal processing techniques, and experimental evidence has been provided that known changes in sympathetic and vagal outflows to the heart associated with physiological maneuvers, drug administration, disease or increased risk for lethal arrhythmias are accompanied by well-defined changes in HRV parameter.

It has been thus hypothesized that spontaneous cardiovascular fluctuations can be exploited to provide quantitative indexes of cardiac autonomic control mechanisms. More recently, several investigators have shown that heart rate fluctuations share some basic properties of processes with nonlinear dynamics and chaotic determinism.

Nonlinear phenomena involved in the genesis of HRV are thought to be determined by the complex interaction of hemodynamic, electrophysiological and humoral variables as well as by reflex and central regulatory mechanisms involved in cardiovascular regulation.

It has been speculated that analysis of HRV based on methods of nonlinear dynamics may provide valuable information for the physiological interpretation of HRV and for prognostic stratification of cardiac and non cardiac disease patients.

Recently it has been demonstrated that reduced nighttime HRV is associated with increased stroke risk in apparently healthy subjects with no previous history of stroke or cardiovascular disease.

Binici et al. [35] demonstrated that twenty-four-hour SDNN and MeanNN were associated with all-cause mortality, but not with stroke. The author suggested that the observed increased risk associated with low nighttime HRV seems to be beyond conventional risk factors.

As fist major finding our data clearly indicate that Poincarè plots indexes, in particular L, A and Np parameters are more sensitive than other heart rate variability linear indexes in identification of autonomic nervous system imbalance in patients after single stroke event.

As second consideration it is interesting to observe that Poincarè plots indexes seem to be significantly changed in relation to different lesion’s severity, suggesting a possible important role of the heart rate variability analysis also in the assessment of medium cerebral artery involvement after first-ever stroke.

On the other hand only few studies of heart rate variability spectral analysis [36-41] found strong correlation between stroke and abnormal values of spectral content (VLF, LF, HF) as well as a correlation with functional capabilities.

A third consideration may be done regarding the Poincarè plots technique that has been used.

Previously heart rate variability has been shown to be reduced as a consequence of both hemispheric [38,42] and brain stem cerebral infarction [16] by using conventional time and frequency domain measuring techniques based on the linear fluctuation of heart rate variability.

However, there is increasing evidence to suggest that the heart is not a periodic oscillator under normal physiological conditions, and commonly used measures of heart rate variability are insufficient to detect the changes in heart rate dynamics.

Therefore, new methods based on nonlinear dynamics and fractal analysis have been developed to quantify complex heart rate dynamics and to complement conventional measures of heart rate variability.

These new methods have already provided clinically useful information on patients with impaired left ventricular function, as well as on patients vulnerable to life-threatening arrhythmias, but their prognostic value has not been definitively proven in the risk stratification of patients with other cardiological or neurological diseases.

Korpelainen et al. suggested that not only the traditional time and frequency domain measures of heart rate variability but also the Poincare´ measures of heart rate variability may be suppressed in stroke patients, emphasizing the usefulness of this tool in quantifying abnormalities of cardiovascular autonomic dysfunction in stroke [18].

By using provocative cardiovascular reflex tests [37,42] such as deep breathing and the Valsalva maneuver, as well as with the use of the time domain and frequency domain measures of heart rate variability from 24-hour ECG recordings, both hemispheric and brain stem strokes show the suppression of heart rate variability. Moreover, all the spectral components of HR variability have been shown to be abolished or significantly decreased in patients with cerebral damage [36].

Oppenheimer et al. [43] investigated the effects of left insular lesion on ApEn and correlation dimension and found that acute left insular stroke may result in a decrease in randomness of heart rate variability, manifesting as suppressed correlation dimension.

It was demonstrated that the "width” of the Poincaré plot is a measure of parasympathetic nervous system activity [27].

Many authors that used Poncarè's plots technique just paid their attention to the bi-dimensional indexes of the maps.

In fact, Korpelainen et al. [18] found that cerebral infarction located either at the hemispheric level of the brain or in the medulla oblongata seems to alter the regulation of heart rate dynamics. The authors concluded that traditional time and frequency domain measures of heart rate variability and the 2-dimensional vector analysis of Poincare´ plots are sensitive to detect abnormalities of heart rate fluctuation, whereas information provided by the novel complexity and fractal measures only has a limited value.

Another aspect that should be considered in studying the sympathetic-parasympatethic balance is related to the blood pressure fluctuations.

Systolic blood pressure variability assessed by the SD of beat-to-beat blood pressure recordings, reflecting beat-to-beat variability in systolic blood pressure, has been previously demonstrated to significantly increase after acute stroke [44,45]. The possible explanations of this can be related to the short-term increase in blood pressure variability.

This phenomenon may be inversely related to cardiac baroreceptor sensitivity [46-48].

For instance a greater blood pressure variability is related to a less sensitive of the baroreceptors.

A possible limitation of our study could be in considering only the Poincarè' plots analysis of heart rate variability, as expression of an imbalance of sympathetic-parasympathetic system.

In fact, another tool to assess this aspect is the absolute levels and variability of blood pressure that are an important consequence of abnormalities of cardiovascular autonomic control after acute ischemic stroke and an important variable in the interpretation of other cardiovascular data that should be considered.

In fact, Robinson et al. demonstrated that impaired cardiac baroreceptor sensitivity is associated with increased long-term mortality after acute ischemic stroke, irrespective of age, sex, stroke type, and blood pressure [49]. This may reflect cardiac arrhythmias, but the mechanisms underlying this association are unknown, although therapies that improve cardiac baroreceptor sensitivity after stroke warrant further investigation.

The underlying mechanisms of pathogenesis and etiology of changes in HRV in relation to stroke are not completely resolved and remain unclear; however, several mechanisms may be involved, with hypertension most probably being one of them.

Some studies have found a strong correlation between HRV and blood pressure [50-53].

In our study no differences were detected in systolic and diastolic blood pressure in the two groups, on the basis of the different lesions, whereas no suitable equipment was available for ambulatory blood pressure measurements in our laboratory. Therefore, data about blood pressure variability could not be presented.

Depending on the different estimation's methods, the class of parameters considered can be related to existing linear measures of heart rate variability, hence the intrinsic ability of Poincarè' plot to identify non-linear beat-to-beat structure is not completely exploited by bi-dimensional maps alone.

An evidence of this consideration can be found in the statistical significance of the peaks' number (Np), one of the three-dimensional Poincarè plots indexes extracted, and in its discrimination power between the study groups.

This suggest future improvements in the evaluation of other multi-dimensional Poincarè plot indexes.

Moreover, recently Günther et al. demonstrated that HRV indices are also candidates for early markers of developing post-stroke infections, preceding routine blood samples.

In particular, the authors found that an increased HF, reduced LF and LF/HF at day and reduced LF and VLF on night are hlighly predictive of sub-acute post-stroke infection in patients without clinical or paraclinical signs of infection in the acute period.

Thus, HRV-based early diagnosis of post-stroke infection may have implications as a novel tool for timely and appropriate treatment [54], and may represent another reason to use HRV variability as mean in the assessment of stroke patients.

IX. Conclusions

In conclusion in the present study, heart rate variability was shown to be most markedly depressed in the patients with severe neurological deficits (in terms of multiple lesion vs single lesion) of medium cerebral artery and comparing both groups to normal.

Whereas the pathophysiological mechanisms by which changes in heart rate variability could be involved or responsible of different physiological responses are still unclear, the sympathetic activity probably stimulates enlargement of the left ventricle, thereby causing ventricular hypertrophy and arterial stiffness. This phenomenon is responsible of increasing vascular resistance [51], that, in turn is a well recognized risk factor for stroke.

On the other hand the reduced parasympathetic tone may enhance hypercoagulation or increase blood viscosity, possibly triggering episodes of bradychardia and inducing arrhythmias [51].

All these changes could at least partially explain the impact of the modifications in heart rate variability on many cardiovascular conditions (i.e. hypertension, atherosclerosis, and cardiovascular diseases).

Therefore, by considering the importance in predictability of neurological impairment, Poincarè plot indexes, particularly L, A and Np parameters, were the most sensitive markers of abnormal heart rate variability in our patients, compared to traditional spectral- and time-domain indexes.

Although further and wider investigations are needed for confirmation, these results clearly indicate that Poincarè plots analysis contains relevant information related to different heart rate variability dynamics of normal and stroke subjects with different lesion's severity and suggest the possible role of the HRV analysis in the prognostic assessment of patients with stroke.

Finally, a corresponding continuous HRV-based risk assessment using the ECG provided by the routine stroke monitoring system would be possible without any additional burden for patients and staff.

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