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Heart Rate Variability as a Possible Biomarker of Cognitive-Motor Integration in Post-Stroke Patients

Rachele Penati[1*], Alessandro Robustelli[1*], Giulio Gasperini[1], Alessandro Specchia[1], Valeria Paleari[1], Eleonora Guanziroli[1] and Franco Molteni[1]

Abstract
Heart Rate Variability (HRV) refers to variation in time intervals between consecutive heartbeats, indicating autonomic nervous system's control over the heart. Time and frequency analysis of HRV could serve as predictors for severity and functional outcome in stroke. Aim of this study is to verify if HRV, measured during cognitive and sensorimotor upper limb (UL) tasks, can be used as a biomarker of cognitive-motor interaction in post-stroke patients. Forty-six patients with unilateral brain injury following stroke were enrolled: 27 (58.7%) ischemic, 19 hemorrhagic, 24 (52.2%) subacute (<6 months), and 22 chronic. Mean age at evaluation was 61 years. Right side was affected in 16 subjects (34.8%). Each patient underwent HRV recording in the following conditions: (1) Rest (5 minutes); (2) Visuomotor simulation training of the affected upper limb (UL) using Dessintey IVS3 (DE, 5 minutes); (3) Motor Imagery of the affected UL (MI, 5 minutes). UL functional outcome measures were collected for both affected and less affected sides. All patients showed reduced HRV in time and frequency domains and sympathetic tone predominance at rest. During DE and MI, a significant reduction in time domain was observed. In frequency domains, low frequency decreases during DE, with parasympathetic tone predominance. In the subgroup analyses for lesion side, only right hemiparetic patients showed parasympathetic predominance during mental tasks of the upper limb (DE and MI. No correlation was found between HRV parameters and UL functional scales. Different HRV response in time and frequency domains to mental task was observed between right and left hemiparetic subjects. This could be explained by different anatomical-functional substrates between right and left hemisphere and could reflect different behaviors during UL cognitive-motor tasks. HRV parameters were not correlated with clinical functional assessment scales, likely meaning that they possible exploring different domains.

Keywords
stroke, autonomic nervous system, cognitive flexibility, upper limb, action observation

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Introduction

Stroke is the second leading cause of death and one of the leading causes of disability worldwide. In Europe it has an incidence of 1.1 million people every year and a prevalence of about 9.5 million people, both destined to increase in the coming decades.[1]

Approximately two-thirds of patients who survive a stroke are affected by neurological deficits, which negatively affect both quality of life and independence in performing activities of daily living (ADL); impairment of upper limb (UL) occurs in more than half of stroke survivors.[2]

Several rehabilitation strategies are used in UL rehabilitation of stroke patients, such as robot-assisted therapy, constraint-induced movement therapy (CIMT), mirror therapy (MT),[3] motor imagery (MI),[4] and virtual reality-based rehabilitation.[5] These treatments improve UL motor functions, inducing neuroplasticity at brain level.[5] In this sense, the rehabilitation techniques that exploit the principles of MT and MI would allow to activate the cortical areas involved in the motor execution and in the visuo-spatial exploration and would allow to carry

[1]Villa Beretta Rehabilitation Center, Valduce Hospital, Costa Masnaga, Lecco, Italy

[*]These authors contributed equally to this work.

Corresponding author:
Eleonora Guanziroli, Villa Beretta Rehabilitation Center, Valduce Hospital, Via N. Sauro 17, Costa Masnaga, Lecco 23845, Italy.
Email: eleonora.guanziroli@gmail.com

out UL rehabilitation treatments even for patients with severe hemiparesis.[6,7]

Associated with motor deficits, alterations of the Autonomic Nervous System (ANS) are relatively frequent after stroke[8] and may play a role in predicting risk of recurrence and functional recovery.[9] The analysis of Heart Rate Variability (HRV) is a simple and non-invasive method to evaluate autonomic functions. HRV represents the oscillations of the interval between heartbeats, calculated by measuring time variations between 2 consecutive QRS complexes (RR interval) on the ECG. It reflects the autonomic modulation of cardiac activity, mediated by the parasympathetic vagal and sympathetic fibers interacting on the sinus node. HRV analysis could be of large use in rehabilitation, considering the complex interactions occurring between the ANS and the Central Nervous System (CNS).

According to the Neurovisceral Integration Model (NIM),[10] the CNS and the ANS are deeply interconnected, and reciprocally modulate their activities. This model defines a Central Autonomic Network (CAN), which includes the prefrontal cortex (PFC), together with the cingulate cortex, insula, and amygdala, modulating the activity of the pontine centers, which in turn regulate the parasympathetic and sympathetic fibers that modulate sinoatrial node activity, finally determining the Heart Rate (HR). In this sense, HRV may represent a window to indirectly investigate the functioning of cortical and subcortical areas and their interactions with other neuronal structures, as a measure of the adaptability of the brain-body system.

The link between HRV and cognitive performances has gained increasing interest in recent years. Studies in healthy people have revealed correlations between resting HRV and cognitive functions such as inhibitory control, working memory, and cognitive flexibility.[11] As shown in a study by Ohira et al,[12] a higher parasympathetic tone at rest is associated with more flexible "top-down" brain regulation, while an imbalance favoring sympathetic activity is linked to poorer cognitive performance. Furthermore, a recent research[13] has demonstrated that high HRV positively influences cognitive functions, particularly executive functions, memory, and language. This effect is likely due to the efficient functioning of prefrontal-subcortical inhibitory circuits, which facilitate flexible and adaptive responses to environmental demands. Resting HRV parameters have also been correlated with the response to cognitive-motor training programs, reflecting executive functions in older adults.[14]

Several studies have tested the neurovisceral integration model, showing that elevated resting vagus-mediated HRV is related to better functioning of prefrontal-subcortical inhibitory circuits, modulating flexible and adaptive responses to environmental demands.[10] Greater HRV at rest is therefore predictive of enhanced cognitive flexibility and improved task-switching ability.[10] These findings highlight the importance of the relationship between HRV and cognitive-motor integration abilities in neurorehabilitation, as they can influence the patient's ability to learn new motor and cognitive strategies and respond effectively to rehabilitation treatments.[15]

While there are many studies in the literature that have evaluated the correlation between resting HRV and different cognitive or motor functions, few instead have measured HRV while performing specific tasks.[16,17] Between these, to date, no studies have measured task-related HRV in a population of subjects affected by stroke.

The aim of the present study was to verify if HRV can be used as a biomarker of cognitive-motor integration in stroke patients, during the execution of UL-related tasks. To do this, a thorough functional assessment of patients was performed and HRV was measured at rest and during cognitive-motor tasks performed with the paretic UL, involving computerized MT and MI exercises, to identify possible changes between the different conditions. The study protocol was designed under the hypothesis that short-term modulation of HRV in response to cognitive-motor tasks of the upper limb would be observed within a 5-minute measurement interval.

Materials and Methods

The study has been approved by the institutional research ethics committee before experiment was started (CE Sezione "IRCCS Fondazione Don Carlo Gnocchi," Comitato Etico IRCCS Regione Lombardia, Via Capecelatro, 66, 20148, Milano), with the following ID 03_08/02/2023. The study has been conducted in accordance with the principles set forth in the Helsinki Declaration and patients have given their informed consent for participation in the research study.

The study design was a cross-sectional observational study. Post-stroke patients admitted at the Neurorehabilitation Unit of Villa Beretta Hospital, Costa Masnaga (LC) were enrolled between March 2022 and September 2022.

Criteria of inclusion were: (1) age between 18 and 80 years; (2) unilateral ischemic or hemorrhagic stroke; (3) post-stroke sub-acute (less than 6 months) or chronic phase (more than 6 months); (4) ability to understand simple commands; and (5) Mini-Mental State Examination $\geqslant$23. Criteria of exclusion were: (1) poor or absent trunk control; (2) permanent atrial fibrillation; (3) ongoing clinical acute conditions; (4) obesity (obese patients were excluded because they couldn't fit the smart shirts); and (5) severe hemineglect.

At the admission, patients underwent the following evaluation: (1) clinical and anamnestic data collection and general and neuromotor clinical examination; (2) Mini Mental State Examination (MMSE)[18]; (3) Trunk Control Test (TCT)[19]; and (4) upper limb functional evaluation scales, chosen according to ICF, to investigate both body structure and capacity (Box and Block Test [BBT][20]); Action Research Arm Test (ARAT)[21]; Nine-Hole Peg Test (9HPT)[22]; Fugl-Meyer Upper Limb;[23] and Motricity Index – subscore for the upper limb.[19]

ECG was collected with X10X and X10Y wearable shirts (©L.I.F.E. CORPORATION S.A) and HRV was extracted using a custom-made Matlab Software (Matlab R2020a). Obese patients were excluded because they couldn't fit the smart shirts. Evaluations were performed during the following consecutive conditions: (1) 5 minutes at rest, patient positioned with eyes open, sitting on a chair with back rest; (2) 5 minutes of computerized MT exercise using Dessintey IVS3 with the paretic/plegic limb; and (3) 5 minutes performing an upper limb MI task, asking the patient to imagine the movement of the paretic UL observed during the previous MT exercise. Each patient underwent HRV evaluations in a quiet environment of the rehabilitation gym, at least 2 hours from meals, performed by the same physiotherapist.

For each patient the following parameters were recorded:

- Mean heart rate (HR) and mean interval between 2 R-R peaks (RRI);
- Time domains: Standard deviation of normal-to-normal intervals (SDNN) and Root mean square of successive RR interval differences (RMSSD).
  SDNN specifically measures the overall variability in heart rate over a period of time. It provides information about both sympathetic and parasympathetic influences on the heart, with higher SDNN values generally indicating greater overall HRV. RMSSD reflects the short-term fluctuations in heart rate and is primarily influenced by the parasympathetic nervous system; it is often used as a marker of vagally mediated HRV[24];
- Frequency-domains: low-frequency (LF) area, high-frequency (HF) area, and LF/HF ratio. The LF band (0.04-0.15 Hz) reflect the combined activity of both the sympathetic and parasympathetic branches of the autonomic nervous system, although it is often considered to predominantly represent sympathetic activity. However, it is important to note that LF power can also be influenced by other factors such as baroreceptor activity and respiratory patterns. The HF (0.15-0.4 Hz) component primarily reflects parasympathetic activity. Therefore, the LF/HF is often used as an indicator of sympathovagal balance, reflecting the relative contributions of sympathetic and parasympathetic activity to HR regulation. A higher LF/HF ratio is often associated with sympathetic dominance, while a lower ratio suggests parasympathetic dominance.[24]

Procedures

For the computerized mirror therapy, patients used the Dessintey – Intensive Visual Simulation (IVS-3) device. This system allows the patient to perform an "intensive visuomotor simulation" task, in which the image of the paretic arm is replaced with a mirrored video reproduction of the movement performed by the contralateral UL. This training modality combines the principles of mirror therapy and action observation treatment, where the patient is able to observe the movement of his/her paretic/plegic arm previously recorded with the unaffected arm. The IVS3 system stimulates the activation of the mirror neuron system and brain plasticity and allows patients and therapists to work specifically on motor action intention and planning. The visual feedback provided favors motor relearning and movement programming,[25] even in patients with severe paresis or plegia of the UL.

All evaluations were performed by the same trained physiotherapist. At first, the subjects were asked to perform a movement of flexion-extension of the fingers of the non-paretic hand, keeping the elbow semi-flexed while resting on the table. The IVS3 system recorded a video of the movement performed and then played it, mirrored, on the half of the screen corresponding to the paretic side. The patient was then instructed to observe the movement played on the screen, creating an illusion of movement of the paretic limb, for 5 minutes. For what regards the motor imagery task, patients were asked to repeatedly imagine the gesture they just saw in the previous MT session performed by the paretic hand, with the elbow resting on the table, in a neutral pronosupination position, at the same speed of video. The total duration of the task was 5 minutes. The therapist gave the patient verbal instructions for the imagery task only once, before starting. The activity was carried out with eyes closed, in order to reduce potential distractions and maximize the patient's capacity for imagination.

Statistical Analysis

Data were tested for normality of distribution by the Kolmogorov-Smirnov test and log-transformed to correct for skewness. All data analyzed Obese patients were excluded because they couldn't fit the smart shirts resulted normally distributed. Repeated measures analysis of variance (ANOVA) was used to evaluate the interaction between conditions (Rest-Dessintey-Motor Imagery) for each HRV variables. Furthermore, for each variable, possible differences between groups were evaluated (Right hemiparesis versus Left hemiparesis Subacute vs Chronic, Ischemic vs Hemorrhagic). Correlations analyses were calculated with the Pearson's coefficient. P values lower than 0.05 were considered significant. The post hoc analysis was performed with the least significant difference (LSD) test. All statistical tests were performed using the software SPSS. Significance in the graphs is represented as: $*P < 0.05$, $**P < .01$, and $***P < .001$.

In order to determine sample size, we utilized the method described by Charan and Biswas.[26] We used the following formula with a confidence interval of 99%:

$N = \frac{1{,}96^2 * P * (1-P)}{D^2}$ with P = expected proportion and D = absolute error or precision desired.

Considering the absence of literature data, we hypothesized a P of 50% and a D of 20%, obtaining a sample size of N = 41. Considering the possibility of drop out of around 10%, we enrolled a total of 46 subjects.

Data Availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

A total of 46 subjects were enrolled, of which 12 females (26.1%). Mean age and standard deviation at enrolment was 61 years ± 15.6 (see Table 1). All patients had right-hand dominance. Twenty-four patients (52.2%) in the subacute phase after stroke (5 days-6 months after the event) and 22 patients (47.8%) in the chronic phase after stroke (>6 months) were included in the study. A total of 27 (58.7%) patients had an ischemic stroke while the remaining had a hemorrhagic stroke. Each patient underwent intensive rehabilitation treatment of both affected and non-affected limbs according to a tailored rehabilitation program. The latter included: passive, active-assisted and active mobilizations; proprioceptive and muscle strengthening exercises; treatment with robotic devices aimed at recovering the distal and proximal region and, where indicated by the neuropsychologist, cognitive training. In terms of affected upper limb strength, 4 patients (8.7%) had no muscular activity in the upper limb. Motor functional characteristics of the enrolled patients are shown in Table 2.

A total of 46 subjects were analyzed, on whom we performed the entire HRV analysis. Mean and standard deviation values for each parameter at rest evaluated in the patients enrolled are displayed in Table 3, compared to healthy subjects (Normal absolute values in healthy adults).[27]

Mean HR

No significant differences were found between the 3 conditions in the different comparisons (Supplemental 1, Supplemental Table S1.1; Supplemental 2, Supplemental Graph 2.1).

Mean RRI

No significant differences were found between the 3 conditions in the different comparisons (Supplemental 1, Supplemental Table S1.2; Supplemental 2, Supplemental Graph 2.2).

SDNN

A significant difference between the 3 conditions (RE-DE-MI, Supplemental 1, Supplemental Table S1.3) was found at the analysis over the overall population. In detail, a significant difference was found between RE and DE (post hoc, $P = .0002$) and RE and MI (post hoc, $P = .029$; Figure 1).

Comparing right and left hemiparesis, ANOVA analysis revealed a significant difference between the 3 conditions. Post hoc analysis revealed a significant difference between RE and DE ($P = .001$) and RE and MI ($P = .023$) in patients with right hemiparesis.

In the comparison of subacute versus chronic stroke, there was a significant difference between the 3 conditions. Post hoc analysis revealed a significant difference between RE and DE ($P = .0003$) in the subacute group.

Table 1. Demographic characteristic of the enrolled patients.

Characteristics	n (%)
Total patients	46
Males	34 (73.9)
Females	12 (26.1)
Age (years)	
Mean ± standard dev.	61 ± 15.6
Median	62
Range	24-88
Hemiparetic side	
Right	16 (34.8)
Left	30 (65.2)
Type of stroke	
Ischemic	27 (58.7)
Hemorrhagic	19 (41.3)
Stroke stage	
Subacute	24 (52.2)
Time from the event (days)	
Mean ± standard dev.	62 ± 38.5
Chronic	22 (47.8)
Time from the event (days)	
Mean ± standard dev.	1219 ± 1363

The column on the right represents the overall population enrolled.

Table 2. Clinical functional measures.

Clinical functional measures	Affected side	Non-affected side
MOtricity index		
Mean ± Stand. Dev.	52.6 ± 30.2	100
Median	58.5	/
Range	1-100	/
Fugl-meyer		
Mean ± Stand. Dev.	34.7 ± 29.1	66
Median	32	/
Range	0-66	/
ARAT		
Mean ± Stand. Dev.	27.0 ± 25.5	57
Median	24	/
Range	0-57	/
Box and block (no. blocks/min)	(normative 71 ± 8 blocks/min)	
Mean ± Stand. Dev.	17.1 ± 19.2	44.6 ± 11.5
Median	9	44.5
Range	0-64	22-66
9-Hole PEG test (s)	(normative 20 ± 2 s)	
Mean ± Stand. Dev.	50.8 ± 22.3	32.2 ± 11.9
Median	44.5	30
Range	29-101	19-49

Finally, between ischemic and hemorrhagic stroke, a significant difference between the 3 conditions was observed. Post hoc analysis revealed a significant difference between RE and DE ($P = .002$) and DE and MI ($P = .008$) in ischemic patients and a significant difference between RE and DE ($P = .024$) and DE and MI ($P = .044$) in the hemorrhagic stroke.

Table 3. HRV data at rest.

	RRI		SDNN (ms)		RMSSD (ms)		LF (ms^2)		HF (ms^2)		LF/HF	
Stat.	Pts	Norm.	Pts	Norm.	Pts	Norm.	Pts	Norm.	Pts	Norm.	Pts	Norm.
Mean	823.6	*926*	26.2	*50*	28.6	*42*	158.1	*519*	83.3	*657*	2.0	*2.8*
SD	163.3	*90*	13.1	*16*	2.9	*15*	347.4	*291*	92.9	*777*	3.1	*2.6*

Abbreviations: Norm., normal absolute values in healthy adults; Pts, patients; SD, standard deviation.[27]

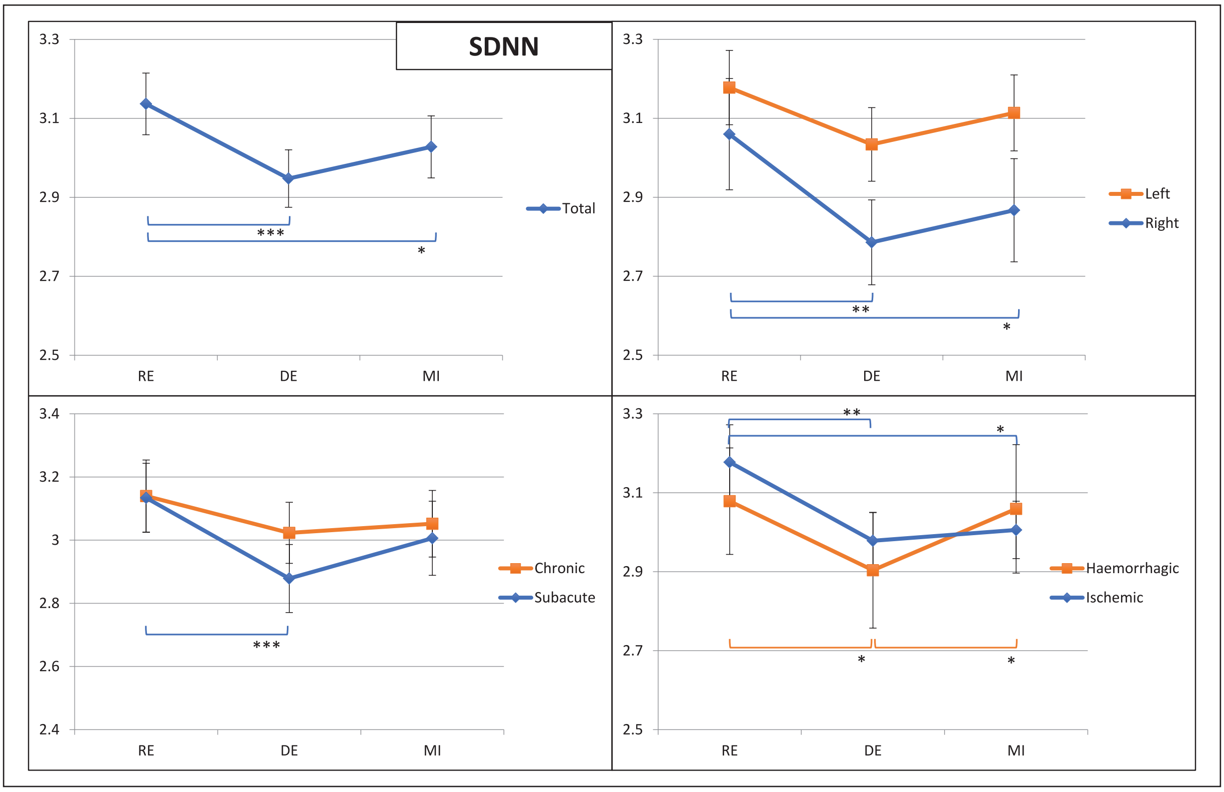

Figure 1. SDNN representations for overall population and subgroups analysis.

RMSSD

No significant differences were found between the 3 conditions in the different comparisons (Supplemental 1, Supplemental Table S1.4; Supplemental 2, Supplemental Graph 2.4).

LF AREA

No significant differences were found between the 3 conditions (RE-DE-MI, Supplemental 1, Supplemental Table S1.5) at the analysis over the overall population (Figure 2).

Comparing right and left hemiparetic patients, there was no significant difference between the 3 conditions. A significant interaction between condition and side was found. Post hoc analysis revealed a significant difference between RE and DE (P = .0048) and RE and MI (P = .0113) in the right hemiparesis group.

Instead, no significant differences were found in the analysis between subacute/chronic stroke and between ischemic/hemorrhagic stroke in the LF area.

HF AREA

No significant differences were found between the 3 conditions in the different comparisons (Supplemental 1, Supplemental Table S1.6; Supplemental 2, Supplemental Graph 2.6).

LF/HF Ratio

No significant difference between the 3 conditions (RE-DE-MI, Supplemental 1, Supplemental Table S1.7, Supplemental 2, Supplemental Graph 2.7) at the analysis over the overall population (Figure 3) was found.

Comparing right and left hemiparesis, there was a significant difference between the 3 conditions. Post hoc analysis revealed a significant difference between RE and DE (P = .0003) and RE and MI (P = .001) in the right hemiparetic patients.

Instead, no significant differences were found in the analysis between subacute/chronic stroke and between ischemic/hemorrhagic stroke in the LF area.

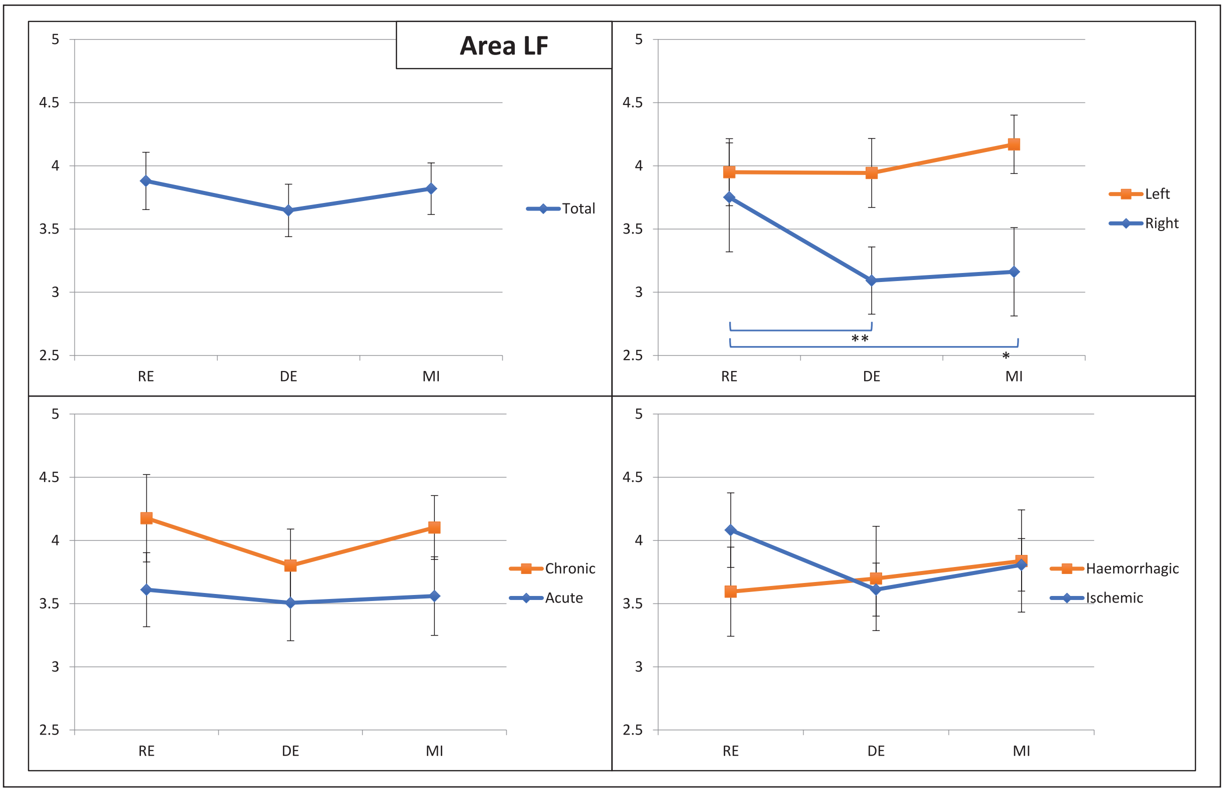

Figure 2. LF AREA representations for overall population and subgroups analysis.

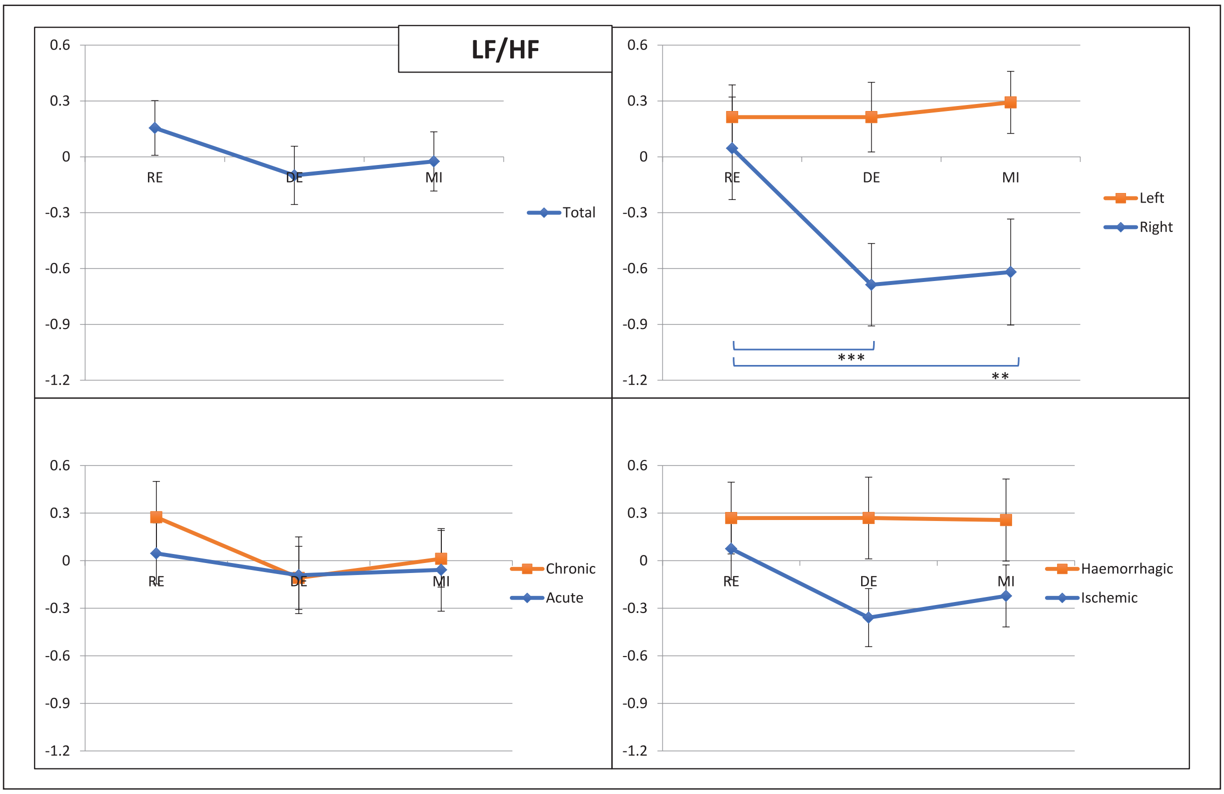

Figure 3. LF/HF representations for overall population and subgroups analysis.

Correlations Between HRV Parameters and Clinical Functional Assessment Scales

Additionally, correlation analyses were conducted between HRV parameters in the time and frequency domains at rest (average heart rate, average R-R interval, SDNN, RMSSD, LF, HF, and LF/HF ratio) and clinical functional assessment scales of the upper limb (Motricity Index, Fugl-Meyer Upper Extremity, ARAT, Box and Block, and 9-Hole Peg Test) and the Barthel Index.

No statistically significant correlation was observed in any of the comparisons made.

Discussion

It has been shown that in patients suffering from stroke, autonomic dysfunctions are often present.[28] HRV analysis is used as a non-invasive method to assess these dysfunctions in the clinical setting. In addition, any fluctuations in the ANS activity modulated by the CAN could potentially be detected with HRV measurement.

According to this, the purpose of the present exploratory study was to evaluate whether HRV can be used as a biomarker of motor-cognitive interaction in post-stroke patients during upper limb rehabilitation. To this end, linear parameters of short-term HRV in patients with stroke sequelae were analyzed in resting conditions and during the execution of cognitive-motor tasks related to the upper limb.

First, the patients enrolled in the study showed lower HRV at rest than the normative data for healthy subjects,[27] both in time (RRI, SDNN, and RMSSD) and frequency domains (LF and HF area). These data confirm what has been widely demonstrated in the literature in relation to post-stroke patients, who showed reduced HRV and an imbalance between the sympathetic and parasympathetic tone, compared to healthy subjects.[29,30] These changes persist over time and are often considered predictors of recurrence of stroke, mortality, poor functional outcome, and increased need for care.[31,32] It should be noted that vagal imbalance in post-stroke patients is often due to an inhibition of parasympathetic activity, rather than from sympathetic hyperactivity, which shifts the sympathetic-vagal balance in favor of the former. As reported in the literature in young and older adults, autonomic imbalance and reduced HRV are often associated with an altered cognitive functionality, with less efficient performance in executive functions.[33] Conversely, it is well known how elevated vagal-mediated HRV at rest is associated with a proper functioning of prefrontal-subcortical inhibitory circuits, which modulate flexible responses and adapt to environmental demands.[10]

To confirm this, Eggenberger et al,[14] demonstrated in older adults a correlation between some parameters of resting HRV (SDNN, RMSSD, and HF area) and the subjects' response to a motor-cognitive training program, which reflected executive functional abilities. Consistent with these studies, it has been demonstrated how high vagally mediated resting-state HRV is associated with a higher efficiency of neural resources.[34] It was also demonstrated that a higher HRV at rest (expressed by an increased RMSSD value) is associated with a better ability to maintain attention.[35] While all these studies have examined the relationship between resting HRV and different cognitive or motor functions, there has been limited research on HRV during task performance. Specifically, to date, no studies have investigated task-related HRV in individuals affected by stroke. Task-related HRV refers to the variations that occur during the performance of cognitive, emotional, or physical tasks.[36] These fluctuations reflect the real-time dynamic regulation of the autonomic nervous system in response to the demands of the task. It is known that when people are exposed to direct stress, and when the metabolic demands are important, there is a marked reduction of vagal parasympathetic drive, resulting in increase in sympathetic tone, associated with better chances of self-regulation.[37] In reverse, when the task relies primarily on cognitive functioning and requires a low level of metabolic activity, an increase of vagal tone reflects a more efficient adaptation of the autonomic responses.[38]

Considering the entire study population, there was a statistically significant difference only for the SDNN, between the RE condition and those of DE (Dessintey) and MI (Motor Imagery), but not between DE and MI. This demonstrates that, despite the autonomic imbalance and HRV reduction observed in stroke patients, they were able to modulate their autonomic responses from rest condition to cognitive-motor tasks involving the upper limb (UL). Additionally, the HRV measurement conducted effectively detected these fluctuations.

In the subgroup analysis, a different trend was observed mostly in the comparison between right hemiparetic and left hemiparetic subjects, with significant modifications in HRV parameters between the 3 conditions in right hemiparetic subjects. In particular, a statistically significant reduction in the time domain (SDNN) and in the frequency domain (LF and LF/HF ratio) between rest and the DE and MI conditions was found only in right hemiparetic patients, while left hemiparetic subjects did not showed significant differences. This would indicate a reduction in overall HRV and a relative vagal predominance during the execution of the UL tasks in in patients with right hemiparesis. The differences in HRV observed between right and left hemiparetic patients could also be explained by different anatomical-functional substrates present in the 2 cerebral hemispheres. It is known that right and left hemispheres are involved differently in the control of cardiac functions and that cardiac autonomic innervation has an asymmetric anatomical distribution.[39]

In the last years, numerous works have studied the cortical asymmetry in the regulation of cardiac frequency and cardiovascular functions; it has been proved how the stimulation of the right insula increases the sympathetic vascular tone, while the stimulation of the left one increases the vagal tone.[40] In healthy subjects, the influences of the hemispheres on the sympathetic and parasympathetic modulation are in balance.[39] This equilibrium can be compromised in patients after a unilateral brain lesion, leading to different autonomic dysfunctions depending on the lesion side. Naver et al[41] have shown a significant decrease in HRV at rest in patients with right hemispheric stroke, with a reduction in the RRI compared to healthy subjects. According to these results, in a study by Colivicchi et al[42] left hemiparetic patients with right-sided insular damage presented higher autonomic imbalance and a more pronounced sympathetic tone predominance at rest.

It should be noted how the differences encountered in this study between right and left hemiparetic patients were statistically significant only for those involving the DE and MI imagery task, while no significant difference was found between the 2 groups at rest.

Another possible explanation of the differences encountered between right and left strokes could be the presence of subclinical neglect in left hemiparetic patients. As previously discussed, patients with severe hemineglect were excluded from this study; nevertheless, no specific neuropsychological evaluation of neglect were performed, thus mild neglect patients may have been enrolled (see "Limitations" paragraph).

Usually, hemineglect and spatial working memory deficits are associated to right hemispheric lesions, particularly those of the right parietal cortex, inferior right parietal lobe, temporo-parietal junction,[43] and right frontal lobe.[44]

The projected image of the upper limb and the imagination task envisaged in the study both referred to the paretic limb. For this reason, a reduced capacity to explore personal and peri-personal space in the left hemiparetic side may have influenced the actual execution of tasks in these patients. In this perspective, the absence of changes in HRV observed during DE and MI tasks in left hemiparetic subjects could reflect both a reduced ability to perform cognitive-motor tasks of action observation and motor imagination, and a lower capacity of engagement with the required task. Autonomic activation occurs in many situations involving a higher attentive-cognitive state of vigilance ("cognitive arousal").[45] For this reason, it can be hypothesized that the degree of autonomic activation during motor imagination should be proportional to the effort of imagination exerted. Wang et al[46] demonstrated that the imagination of movements leads to a significant increase in ventilation and systolic blood pressure, similarly to what would occur during physical exercise. Our results may suggest a reduced response in left hemiparetic patients to rehabilitative techniques that exploit the principles of mirror therapy/action observation and motor imagery in the contralateral hemiparetic side, consistent with the findings found in a study by Kemlin et al[47] However, systematic review by Zhang et al[48] demonstrated that mirror therapy could improve hemineglect regardless of lesion laterality in stroke patients. Finally, in a study by Waller and Whitall,[49] no differences in basic motor function emerged between subjects with left and right hemispheric lesions; nevertheless, a clear advantage in terms of motor recovery was noted for right hemiparetic patients after completing 6 weeks of bilateral upper limb training, perhaps reflecting a better motor learning capacity in such individuals. In this context, the different behavior of HRV during the execution of DE and MI tasks shown by right and left hemiparetic patients enrolled, who may have different anatomical-functional substrates, could reflect a better capacity for cognitive-motor interaction in right hemiparetic patients, due to different anatomical functional substrates.

The results obtained in the comparisons between subgroups "subacute versus chronic stroke" and "ischemic versus hemorrhagic stroke" show less consistent differences. The only significant differences were observed in the time domain with a significant reduction in SDNN in subacute strokes compared to RE versus DE and in SDNN in the ischemic stroke group compared to RE versus DE and RE versus MI, while no significance emerged in the hemorrhagic stroke group.

Finally, a possible correlation between resting HRV variables and functional assessment scales of the paretic upper limb (Motricity Index, Fugl-Meyer, ARAT, Box and Block, and 9-hole peg test) and the Barthel Index was evaluated. Our results did not show any correlation in all the comparisons made; furthermore, no correlation was found between UL motor impairment and HRV parameters. This result supports the hypothesis that HRV assessment explores a different domain of UL functionality compared to tools currently available in clinical practice. This may allow for precise characterization of individual patients by observing their real-time autonomic responses to tasks performed. In this regard, task-related HRV analysis wouldn't just be an adjunctive tool to the various scales commonly used in clinical practice to assess UL impairment following a stroke and predict rehabilitation outcomes. Instead, it would provide a new functional perspective in evaluating post-stroke patients and become a specific tool to study autonomic response, thus assessing the cognitive-motor interaction ability of these patients. HRV assessment could therefore enable physiatrists to examine each patient's autonomic response not just before or after, but also during the execution of specific therapeutic exercises at different phases of the rehabilitation process, allowing for further adaptation and personalization of the rehabilitative treatment. Even more, it could offer clinicians a valuable tool to assess the autonomic response of stroke patients to specific high-tech enhanced treatment, allowing for a tailored application based on real-time physiological feedback. By integrating HRV assessment into rehabilitation, treatment strategies could be further individualized, optimizing therapeutic interventions, and potentially improving functional outcomes. Additionally, this approach could help differentiate rehabilitation strategies based on lesion laterality, for example emphasizing exploratory and spatial navigation exercises in patients with left hemiparesis, while prioritizing task-specific, goal-directed activities in those with right hemiparesis.

Limitations

This study has some limitations, which should be noted. First, the study did not include the recruitment of a control group to assess the behavior and modulation of HRV parameters in healthy subjects during the different proposed tasks.

Additionally, subjects performed the motor imagery task but no imagination questionnaire to evaluate their abilities to imagine the upper limb movement was applied, since in literature there are no validated questionnaires in Italian language for imagination in the post-stroke population. Another limitation is that during motor imagery the command was given at the beginning and not systematically during the entire session of 5 minutes. It is thus possible that stroke patients, who are known to have subtle cognitive deficits or concentration deficits, may lose focus during the exercise and thus HRV may not represent the full 5 minutes testing. Moreover, no additional analysis was conducted to correlate the brain lesion location with factors other than right/left hemisphere. Finally, the cognitive evaluations performed for each patient were not standardized and no neuropsychological tests which evaluate cognitive flexibility were performed.

Conclusions

This work represents an observational preliminary study that opens the door to numerous possible new developments and research, such as the evaluation of the potential predictive value of HRV regarding the patient's engagement capacity during the execution of therapeutic exercise. This may allow physicians to personalize the rehabilitative treatment based on the patient's HRV response to various tasks and therapeutic exercises proposed.

ORCID iD

Rachele Penati https://orcid.org/0000-0002-1684-3518

Ethical Considerations

The study has been approved by the institutional research ethics committee before experiment was started (CE Sezione "IRCCS Fondazione Don Carlo Gnocchi" Comitato Etico IRCCS Regione Lombardia, Via Capecelatro, 66, 20148, Milano), with the following ID 03_08/02/2023.

Consent to Participate

The study has been conducted in accordance with the principles set forth in the Helsinki Declaration and patients have given their informed consent for participation in the research study.

Author Contributions

RP, AR, FM, and EG have given substantial contributions to the conception or the design of the manuscript, RP, AR, VP, and EG to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author AS and GG revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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