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Changes in heart rate variability at rest and during exercise in patients after a stroke: a feasibility study

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Abstract

The aim of this study was to evaluate the feasibility of using a biofeedback-enhanced robotics-assisted tilt table (RATT) to investigate time- and intensity-dependent changes in heart rate variability (HRV) at rest and during heart rate-controlled exercise in patients recovering from a stroke. Twelve patients (age 55.3 years ± 15.6 years, 7 women) completed two separate measurement sessions. The first involved familiarization and system identification to determine parameters of a feedback system for automatic control of heart rate (HR). The second comprised 14 min of rest and 21 min of active exercise during which HR was held constant using feedback control to eliminate cardiovascular drift. HR data were collected using a chest-belt HR sensor, and raw RR intervals were employed for HRV analysis during periods of rest (0–7 min and 7–14 min) and exercise (5–13 min and 13–21 min). A biofeedback-enhanced, robotics-assisted tilt table can be successfully employed to perform heart rate-controlled exercises in patients after a stroke. All HRV metrics were substantially lower during exercise compared to rest. In the rest period, HRV values during 0–7 min were lower than during 7–14 min, in line with a slight HR decrease over the entire rest period. During exercise, HRV values during 5–13 min were higher than during 13–21 min, suggesting a time-dependent HRV decrease. All HRV metrics exhibited intensity- and time-dependent changes: higher HRV at rest and decreasing HRV over time. Understanding these HRV characteristics will support the development of heart rate-controlled exercise regimens and protocols for examining HRV changes during exercise in patients.

Introduction

The autonomic nervous system (ANS) maintains homeostasis by regulating the cardiovascular and pulmonary systems, as well as performing other visceral activities [1]. The ANS is intricately controlled and modulated by the central autonomic network located in multiple areas of the brain, such as the insular cortex, the anterior cingulate gyrus, the hypothalamus, the brain stem, and the spinal cord [2–4]. The integrity of the autonomic network is critically important for the normal function of the ANS [2]. Autonomic output from the central nervous system (CNS) is divided into the sympathetic and

parasympathetic nervous systems: the sympathetic nervous system is crucial for blood pressure regulation, regional blood flow allocation, and thermoregulation, while the parasympathetic system is responsible for controlling the sinoatrial (SA) node automatism and other visceral activities, such as micturition or defecation [3].

It has been observed that some specific brain regions are associated with higher levels of autonomic disturbance, e.g., right hemispheric and insular cortex lesions [5–7]. In addition, strokes in other areas of the brain have been found to cause autonomic dysfunction. Although the mechanisms remain unclear, it is proposed that strokes disrupt the brain network, resulting in asymmetry in ANS modulation between both hemispheres, leading to central autonomic disturbances [8, 9]. Multiple studies have shown that autonomic dysfunction is highly prevalent in patients after stroke, with prevalence rates varying from 10 to 100% depending on the tests conducted [9, 10]. Furthermore, multiple studies have demonstrated that the presence of autonomic dysfunction is related to poor outcomes after stroke [5, 11].

Heart rate variability (HRV) refers to the variation in the time intervals between consecutive heartbeats generated by the SA node located in the right atrium of the heart [12]. Given that disruption in autonomic function can directly affect cardiac function, HRV may provide a non-invasive diagnostic tool to reflect autonomic activity after stroke. HRV can be assessed in the time-domain, the frequency-domain and using nonlinear analysis [12]. Common HRV time-domain metrics include the standard deviation of all normal-to-normal R–R intervals (SDNN) and the root-mean-square value of differences between successive R–R intervals (RMSSD). In the frequency domain, the primary outcomes are high frequency power (HF), low frequency power (LF), very low frequency power (VLF), ultra-low-frequency power (ULF) and total power (TP). Studies have indicated that patients after a stroke exhibit significantly lower HRV values compared to their able-bodied counterparts [6, 10].

During exercise, higher brain centres send descending commands to the cardiovascular centre in the brainstem to reset the baroreflex to a higher operating point. This triggers a rapid increase in heart rate, which is initially mediated by parasympathetic withdrawal. The sympathetic nervous system is also activated due to the loading of the baroreceptors [13]. Both the sympathetic and parasympathetic nervous systems work in harmony to regulate heart rate throughout exercise, with parasympathetic dominance at rest and low exercise intensity, shifting to sympathetic control primarily at higher exercise intensities [14]. Changes in autonomic control of the heart result in alterations of HRV during exercise, with healthy persons typically showing a decrease in all time- and frequency domain metrics during exercise [15–17].

Previous research on HRV in patients after a stroke has primarily focused on short-term resting HRV or 24-h recordings [6, 10, 18–21]. While resting HRV is a parameter of interest in most HRV research and may provide prognostic value [19, 20, 22–24], HRV changes in responses to exercise could elucidate additional information about autonomic dysfunction which may be unnoticed at rest. There is limited literature on the characteristics of HRV during exercise in patients after a stroke across a wide range of disability levels. One possible reason is the physical limitation of patients to use conventional exercise modalities such as treadmills or cycle ergometers. To enable patients with different levels of disability to exercise, we augmented a robotics-assisted tilt table

(RATT), which is initially aimed at the early stage of rehabilitation in patients with neurological disorders, with force sensors and a visual feedback screen, thus allowing them to exercise at a prescribed work rate. The choice of the RATT as the exercise modality for this study, therefore, allowed inclusion of patients who would not be able to exercise using conventional devices. Furthermore, we have implemented a feedback control system for heart rate control to facilitate the maintenance of a constant heart rate during exercise, aiming to achieve a stable heart rate and minimize or eliminate the impact of cardiovascular drift during prolonged exercise [25].

The aim of this feasibility study was to investigate time- and intensity-dependent changes in heart rate variability at rest and during exercise in patients after a stroke using a biofeedback-enhanced robotics-assisted tilt table, with heart rate being stabilised during the exercise using feedback control. The novelty of this study lies in the analysis of HRV responses during exercise (and not only at rest), the use of a robotics-assisted tilt table to allow inclusion of patients with severe disability, and the implementation of feedback control of heart rate to exclude cardiovascular drift.

Results

Twelve patients (aged 55.3 years ± 15.6 years, 7 women) were enrolled. Most of them suffered from ischaemic stroke (83.3%) and had left hemiparesis (58.3%). Approximately one-third of them were dependent in ambulation (33.3%) (Table 1).

Rest

When comparing rest windows 1 and 2 (RW1 and RW2), HRV metrics in RW2 generally showed slightly higher HRV values, in line with a slight HR decrease over the entire rest period. Frequency domain metrics showed a higher magnitude of change compared to time domain metrics, in particular for HF, VLF and TP (Table 2). For illustration, RR intervals during the resting measurement for one patient are shown in Fig. 1. The orange horizontal bar marked "eval" depicts the time period from 0 to 14 min (0–840 s) during which the overall resting HRV outcomes were evaluated.

Exercise

Overall, the mean target heart rate was 94 bpm, which corresponds to 57% of the mean age-predicted maximum heart rate of 220—age. This falls within the light exercise intensity range according to ACSM norms [26]. One patient could not complete the exercise from 5 to 21 min because of difficulty in maintaining the work rate at the target level. All other patients completed the test and achieved constant heart rate exercise with a root-mean-square-error HR tracking error of 1.8 bpm. For illustration, the feedback control test for one patient is shown in Fig. 2. The orange horizontal bar marked "eval" depicts the time period from 5 to 21 min (300–1260 s) during which the overall HRV outcomes for active exercise were evaluated.

When comparing the overall resting measurement with the overall exercise measurement, there were uniformly large decreases in all time domain and frequency domain metrics during exercise. Furthermore, all HRV values decreased slightly during the second phase of exercise (EW2) when compared to the first phase (EW1) (Table 2, Figs. 3 and 4).

Table 1 Characteristics and demographic data of patients ($n = 12$)

Characteristic	Value
Age (years)	55.3 (15.6)
Sex, *n* (%)	
Male	5 (41.7%)
Female	7 (58.3%)
Height (m)	1.69 (0.1)
Body mass (kg)	77.9 (19.6)
Body mass index (kg/m^2)	27.2 (6.5)
Type of stroke, *n* (%)	
Ischaemic	10 (83.3%)
Haemorrhagic	2 (16.7%)
Hemiparetic side, *n* (%)	
Left	7 (58.3%)
Right	4 (33.3%)
No weakness	1 (8.3%)
Days post stroke, median (p25, p75)	82 (22.5, 460.5)
NIHSS, *n* (%)	
1–5	9 (75.0%)
6–14	3 (25.0%)
MRS, *n* (%)	
1–2	8 (66.7%)
3–5	4 (33.3%)
FAC, *n* (%)	
1–3	4 (33.3%)
4–5	8 (66.7%)
Comorbidities, *n* (%)	
Hypertension	7 (58.3%)
Dyslipidemia	5 (41.7%)
None	3 (25.0%)
Antihypertensive medications, *n* (%)	
ACE inhibitors	3 (25.0%)
Calcium channel blockers	2 (16.7%)
Renin–angiotensin–aldosterone system inhibitors	4 (33.3%)
None	5 (41.7%)

Values are mean (standard deviation) unless otherwise indicated

n number, *IQR* interquartile range, *FAC* functional ambulation category, *ACE* angiotensin-converting-enzyme, *p25* 25th percentile, *p75* 75th percentile

Discussion

The aim of this feasibility study was to investigate time- and intensity-dependent changes in heart rate variability at rest and during exercise in patients after a stroke using a biofeedback-enhanced robotics-assisted tilt table; to avoid cardiovascular drift, heart rate was stabilised during the exercise using feedback control. We found that a biofeedback-enhanced, robotics-assisted tilt table can be successfully employed to perform heart rate-controlled exercises in patients after a stroke, thus, confirming the feasibility of the approach. We found that HRV decreased during exercise compared to rest. Furthermore, HRV decreased over time during exercise. Thus, intensity- and time-dependent decreases in HRV exist in patients after a stroke.

Table 2 Summary of outcome variables for resting and exercise evaluation windows

Variables	Rest			Exercise		
	RW1	RW2	Total rest period	EW1	EW2	Total exercise period
RRi (s)	865.1 (127.2)	886.2 (128.9)	876.4 (128.3)	650.1 (72.6)	647.6 (69.0)	648.8 (70.7)
HR (bpm)	70.86 (10.6)	69.2 (10.3)	70.0 (10.5)	93.4 (10.3)	93.7 (9.9)	93.5 (10.1)
SDNN (ms)	31.1 (15.5)	34.0 (18.8)	35.3 (17.0)	16.9 (7.7)	15.3 (7.8)	16.7 (7.5)
RMSSD (ms)	20.0 (15.3)	21.4 (17.6)	21.0 (16.6)	9.2 (6.2)	8.0 (4.4)	8.7 (5.2)
HF (ms^2)	250 (443)	328 (601)	291 (530)	27 (33)	21 (25)	23 (26)
LF (ms^2)	301 (307)	338 (379)	318 (339)	93 (97)	78 (70)	84 (78)
VLF (ms^2)	621 (681)	757 (940)	695 (852)	174 (165)	165 (201)	167 (178)
ULF (ms2)	106 (130)	116 (101)	265 (278)	32 (46)	13 (16)	41 (65)
TP (ms^2)	1205 (1356)	1509 (1875)	1546 (1669)	315 (250)	270 (286)	311 (262)

Values are mean (standard deviation)

RW1/2 rest window 1 or 2, *EW1/2* exercise window 1 or 2, *RRi* RR intervals, *HR* heart rate, *SDNN* standard deviation of all normal-to-normal R–R intervals, *RMSSD* root mean square of successive differences between normal heartbeats, *HF* high frequency power, *LF* low frequency power, *VLF* very low frequency power, *ULF* ultra-low frequency power, *TP* total power

In general, the resting HRV values of time-domain and frequency-domain metrics from patients in this study were lower than data from able-bodied healthy individuals reported elsewhere [27, 28]. SDNN and RMSSD in the rest period in this study were 35.3 ms ± 17.0 ms and 21.0 ms ± 16.6 ms, respectively, while the values were 50 ms ± 16 ms and 42 ms ± 15 ms in able-bodied participants [27]. In addition, HF, LF and TP reported in this study (291 $ms^2 \pm 530$ ms^2, 318 $ms^2 \pm 339$ ms^2 and 695 $ms^2 \pm 852$ ms^2, respectively), Table 2, were much lower compared to the respective values of 975 $ms^2 \pm 203$ ms^2, 1170 $ms^2 \pm 416$ ms^2 and 3466 $ms^2 \pm 1018$ ms^2 in healthy participants [27, 28]. This aligns with previous research indicating that patients after stroke exhibit lower HRV values at rest compared to healthy individuals [6, 10]. For example, Tokgözoglu et al. [6] found significantly lower SDNN, HF and LF values in patients after stroke compared to age- and sex-matched controls. Similarly, Xiong et al. [10] demonstrated that patients with acute or chronic stroke exhibited significantly lower LF compared to a control group. Although there were trends showing a decrease in the values of HF, VLF and TP in both acute and chronic cases, these differences were not significant. We also found that HRV in the second window of the rest period was slightly higher than the first part of the rest period, which may be due to a slight decrease in heart rate in the latter half of the rest period.

In line with findings reported for healthy participants, we found a decrease in all time- and frequency domain metrics during exercise compared to rest [15–17, 29, 30]. Raimundo et al. found an increase in LF as well as a decrease in SDNN and HF among ambulatory patients after stroke exercising at moderate intensity on a treadmill when compared to rest [31]. This elevation in LF contrasts with this study and numerous previous studies. The difference may be due to the disparities in study methodologies and HRV analysis techniques, as highlighted in [13].

The decreases in RMSSD and HF (which reflects cardiac parasympathetic activity) during exercise when compared to rest may reflect the dynamics of parasympathetic withdrawal during the exercise. It was hypothesized that an increase in heart rate at the onset of exercise is because of a reduction in parasympathetic activity [14].

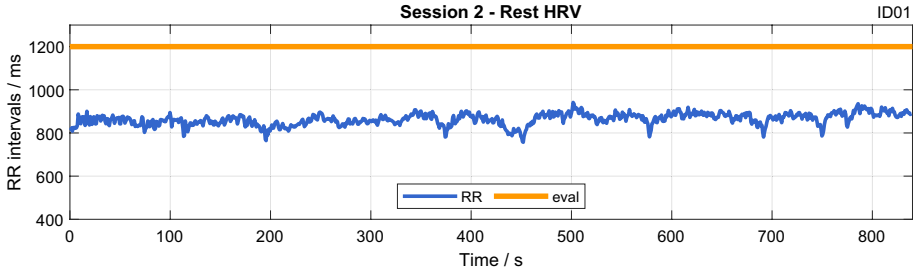

Fig. 1 Original data for RR intervals of patient ID01 at rest. The orange horizontal bar marked "eval" depicts the time period from 0 to 14 min (0–840 s) during which the resting HRV outcomes were evaluated

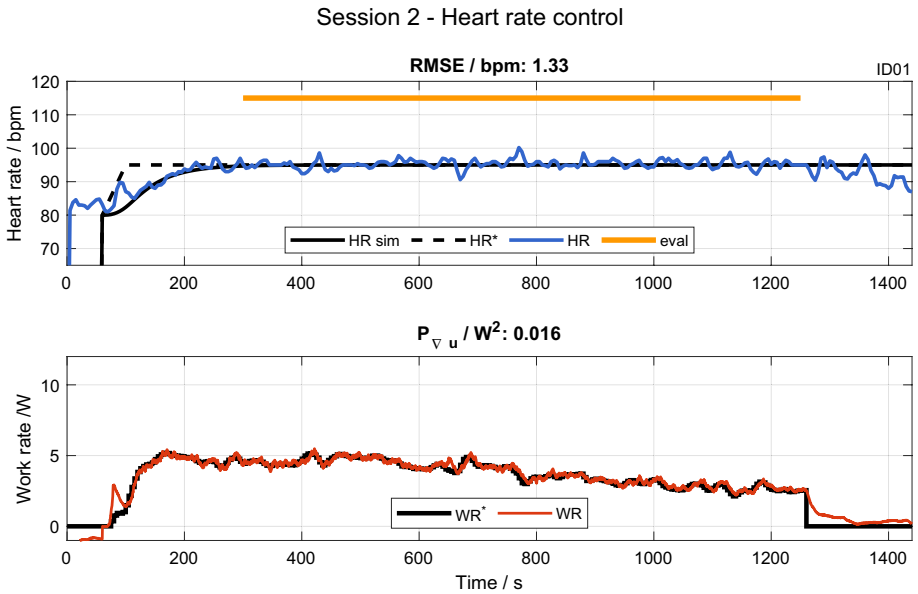

Fig. 2 Original data for HR and work rate during the regimen of constant heart rate exercise in patient ID01. Upper plot: the black dashed line denotes the target heart rate HR* and the blue line is the actual heart rate HR; the continuous black line is the nominal, simulated HR, HR_{sim}; the orange horizontal bar marked "eval" depicts the time period from 5 to 21 min (300 s to 1260 s) during which the HRV outcomes for active exercise were evaluated. Lower plot: the black line denotes the target work rate WR*, which is computed from the heart rate control system, and the red line demonstrates the actual work rate, WR, achieved by the patient

The interpretation of other HRV metrics is limited due to their dependence on multiple factors. For example, LF is influenced by both the sympathetic and parasympathetic components together with blood pressure regulation via baroreceptors [32]. Thus, it was proposed that decreases in LF may reflect a shift in the balance between sympathetic and parasympathetic activity, with an up-regulation of baroreceptor mechanisms [33]. Furthermore, marked inter-individual variation in the relationship between HRV and parasympathetic/sympathetic effect was also found [34, 35]. Thus, the direct interpretation of some HRV metrics such as LF as markers of sympathetic effect may be an oversimplification.

Regarding VLF and ULF, these metrics are less well studied. VLF was proposed to be generated from the heart's intrinsic nervous system and the influences of thermoregulation, the renin–angiotensin system, the parasympathetic nervous system and physical

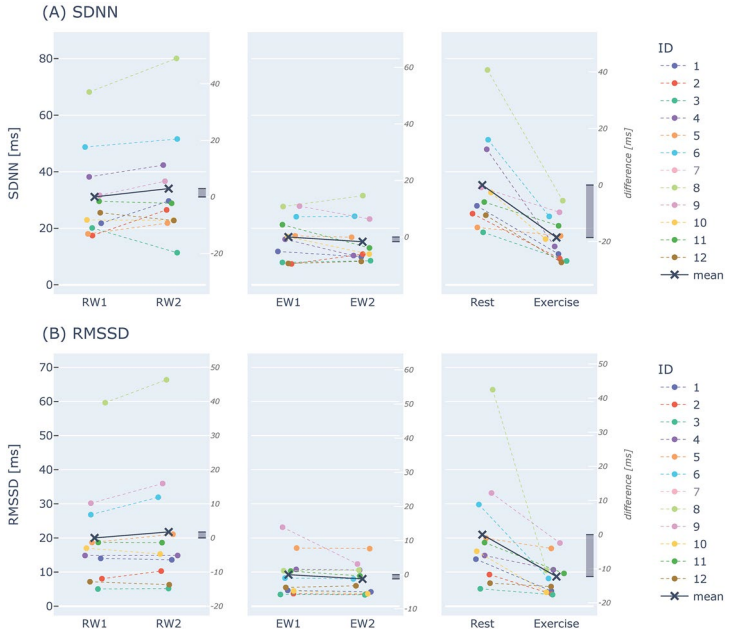

Fig. 3 Gardner–Altman comparison plots showing the heart rate and time domain HRV measures, **A** SDNN and **B** RMSSD for all patients. Different colours display the individual data-paired set of observations from the same patient connected by a line. Black lines connect mean values. EW1/2: exercise window 1 or 2; exercise: overall exercise period; rest: overall rest period; RW1/2: rest window 1 or 2; RMSSD: root mean square of successive RR interval differences; SDNN: standard deviation of all normal-to-normal R–R intervals

activity [12, 36]. It has been proposed that circadian rhythms are the primary drivers of the ULF component, and core body temperature, metabolism, and the renin–angiotensin system may also contribute to this frequency band [12]. Similar to other HRV variables observed here, we found the decrement pattern over time in both the VLF and ULF frequency bands [16]. However, in view of the window durations employed in the present study (7–8 min), and because the upper bound of VLF periods is 5 min, the VLF and ULF outcomes may have limited validity and can only be considered as preliminary values.

In view of the effect of exercise duration on HRV, we attempted to overcome two factors which limit the investigation of this issue, as stated by Michael et al. [13]. First, since the intensity of exercise has a strong effect on HRV and most HRV measures reach a minimum at or above moderate intensity [13], we employed a low level of intensity. Second, after a certain time of exercise at the same intensity, heart rate generally increases. This phenomenon is called cardiovascular drift, and it can occur even within 15 min of exercise onset. The mechanism of this phenomenon is multifactorial, and has been proposed to be due to the increase in skin blood flow during exercise leading to a progressive decline in stroke volume, reduction in ventricular filling time due to the increase in heart rate, the negative cardiac force–frequency relationship, temperature, dehydration and exercise intensity [37]. Cardiovascular drift hinders the study of the direct effect of exercise duration on HRV, because HRV is primarily dependent on heart rate [13, 38]. Thus, other previous studies mostly focused on the effects of exercise intensity or the effects of exercise duration on recovery HRV [13]. Only a limited number of studies can be used for the interpretation of the effect of exercise duration on HRV. For example,

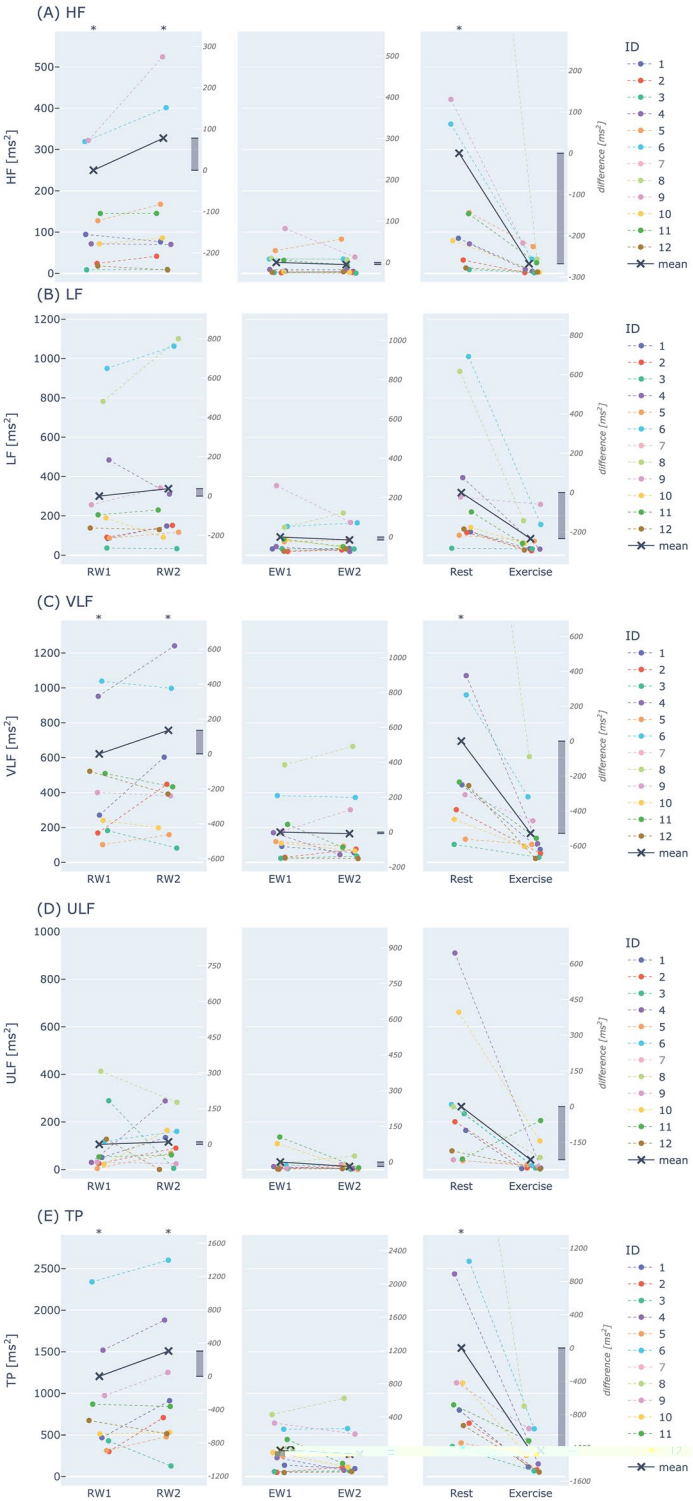

Fig. 4 Gardner–Altman comparison plots showing the frequency domain HRV measures for all patients, **A** HF, **B** LF, **C** VLF, **D** ULF, and **E** TP. Different colours display the individual data-paired set of observations from the same patient connected by a line. Black lines connect mean values. *Indicates cropped, out-of-scope values. HF: high frequency; EW1/2: exercise window 1 or 2; exercise: overall exercise period; RRi: RR intervals; LF: low frequency; rest: overall rest period; RW1/2: rest window 1 or 2; TP: total power; ULF: ultra-low frequency; VLF: very low frequency

Moreno et al. found that several HRV metrics (SDNN, RMSSD, LF and HF) showed a time dependent decrease during moderate intensity exercise (60% of peak oxygen uptake) when measured during the periods of 25–30 min, 55–60 min, and 85–90 min of exercise. However, HR also increased throughout the 90 min of exercise, thus it is difficult to separate the effects of exercise duration from the confounding increase in heart rate [29]. To address both limitations, we employed a feedback control system which continuously adjusted the target work rate to keep heart rate constant throughout the exercise. Full details of the implementation of the feedback control system can be found in a companion paper [25]. Regarding the effect of exercise duration on HRV, our results confirmed that all HRV metrics decrease over time. This is consistent with previous findings in able-bodied participants which demonstrated that HRV decreases over time during treadmill training, while the heart rate is kept constant using feedback control [15].

We recruited 12 patients as appropriate to the design of a feasibility study, but we recognise that the relatively small sample size may not be fully representative of all patients after a stroke. Although we enrolled patients with mild-to-severe physical disability, our inclusion and exclusion criteria may not reflect the broader stroke population. The inclusion and exclusion criteria were set to minimize the potential effect of certain known comorbidities that influence cardiac autonomic control. For example, excluding patients with underlying diseases such as atrial fibrillation, previous myocardial infarction, or those taking medications that could affect the cardiovascular response to exercise might result in an over-representation of younger and healthier patients, thereby limiting the generalizability of our findings. In addition, there was heterogeneity among patients in terms of medication use, level of physical activity, mood, menstrual cycle, time since stroke and stroke location, all of which may influence HRV metrics and the HRV response to exercise [6, 39–41].

Exercise intensity characterised using age-predicted maximal heart rate may not be as accurate as using a percentage of maximal oxygen uptake. Furthermore, we did not measure the tidal volume and breathing frequency, each of which may affect HRV [12]; however, with light intensity and constant heart rate control, we propose that the breathing frequency should theoretically be similar over the period of exercise. In addition, although the Polar H10 has been found to be valid and can be recommended for recording heart rate and RR intervals for practitioners [42], and while the device is extremely convenient for application in the clinical setting, there are some disadvantages to recording RR intervals without continuous ECG monitoring. This limitation may affect the ability to detect ECG morphology changes in cases where cardiac arrhythmias occur [12, 43].

HRV responses during exercise may provide additional insights into autonomic function beyond what is observed at rest. This is because exercise alters the balance between sympathetic and parasympathetic activity, making subtle derangements in autonomic nervous system activity more apparent through changes in HRV. However, to achieve reliable results, the test must be standardized, ensuring that heart rate does not fluctuate, as such changes could confound HRV interpretations. The implementation of a biofeedback system can facilitate a precisely controlled and standardized test. In addition, the use of a robotics-assisted tilt table could expand the test's applicability, enabling even

severely disabled patients to participate. In this feasibility study, we found a decrease in all time- and frequency domain metrics during exercise compared to rest and found a further decrease in HRV metrics over time. Thus, changes in HRV metrics should be considered when developing heart rate control systems for exercise [16]. Further studies relating to HRV changes over longer durations of exercise and the impact of different exercise durations or modes on HRV outcomes during exercise should be explored. For example, evaluating whether HRV continues to decrease for longer exercise durations and whether HRV values reach similar minimum levels at different exercise intensities or modes would be valuable. The inclusion of age- and sex-matched able-bodied controls would enable more insightful comparison of responses. A larger and more homogeneous sample together with standardized exercise protocols in terms of intensity and duration would improve the comparability of results among studies. In addition, while it has been demonstrated in sedentary middle-aged adults that HRV changes after regular exercise [44], confirmatory results in patients after stroke are lacking. Examining the predictive validity of HRV to determine whether improvements in HRV values are associated with better functional outcomes, reduced risk of cardiovascular events, or other clinically important endpoints in patients after stroke would have significant clinical implications. Incorporating measures such as non-linear analysis of HRV may provide additional information [45]. Systolic time intervals, which are a good measure of cardiac sympathetic activity, may be used to complement HRV measures of cardiac parasympathetic activity to provide a more comprehensive insight into cardiac autonomic regulation [13].

Conclusion

All HRV metrics exhibited intensity-dependent changes—lower HRV at higher intensity, i.e., exercise vs. rest—and time-dependent changes—decreasing HRV over time when cardiovascular drift is eliminated. The attribution of a reduction in HRV during exercise to time, and not to HR, was facilitated by the employment of a feedback system that maintained HR at a constant level throughout the exercise session. Understanding these HRV characteristics will support the development of heart rate-controlled exercise regimens and protocols for examining HRV changes during exercise in patients.

Methods

Study design and patients

This descriptive, cross-sectional feasibility study was conducted at Reha Rheinfelden, a rehabilitation centre in the northwest of Switzerland, from January 2023 to June 2023. Ethical approval was obtained from the Ethics Committee of Northwestern and Central Switzerland (Ref. 2022-01935) and the study was carried out in accordance with relevant guidelines and regulations. Recruitment was conducted by reviewing the medical records of patients who were admitted or were undergoing post-stroke rehabilitation at Reha Rheinfelden. During this review, researchers identified potentially eligible participants by screening for specific inclusion and exclusion criteria. All patients gave their written informed consent before participating in the study.

The sample size of $n = 12$ for this feasibility study was selected a priori in the approved study protocol based on formal guidelines for feasibility trials in consideration of aspects

including feasibility, precision about the mean and variance, and regulatory conditions [46].

Patient inclusion criteria were: (1) a diagnosis of first-ever stroke, either ischaemic or intracerebral haemorrhage; (2) clinically stable; (3) > 18 years; (4) can communicate well, can sustain attention and can follow commands; (5) has the capacity of judgement; and (6) willing to cooperate in the study and able to attend all testing sessions. Exclusion criteria were: (1) any contraindications to exercise testing according to the American College of Sports Medicine guidelines (ACSM) [26] or having cardiac arrhythmia such as atrial fibrillation or myocardial infarction; (2) taking medication that interferes with heart rate response during exercise such as beta-blockers; (3) severe aphasia other severe cognitive problems; (4) any contraindications for the RATT based on guidelines from the manufacturer; and (5) severe orthopaedic lower extremity problems that may hinder exercise.

Robotics-assisted tilt table (RATT)

The RATT system (Erigo, Hocoma AG, Switzerland) was adapted to facilitate active participation during exercise. The RATT is a motorized tilt table equipped with a body harness to provide body support, and two motor drives to generate cyclical movement of the legs. Two thigh cuffs fix the legs and interface to the leg drives, and two-foot plates support the feet. The RATT is primarily designed for early rehabilitation in patients with neurological impairments to provide early mobilization and to deliver intensive sensorimotor stimulation. In addition, it can enhance cardiovascular function by cyclic leg loading. During the therapy, the RATT can be tilted up from 0° to 90° and the cyclic leg

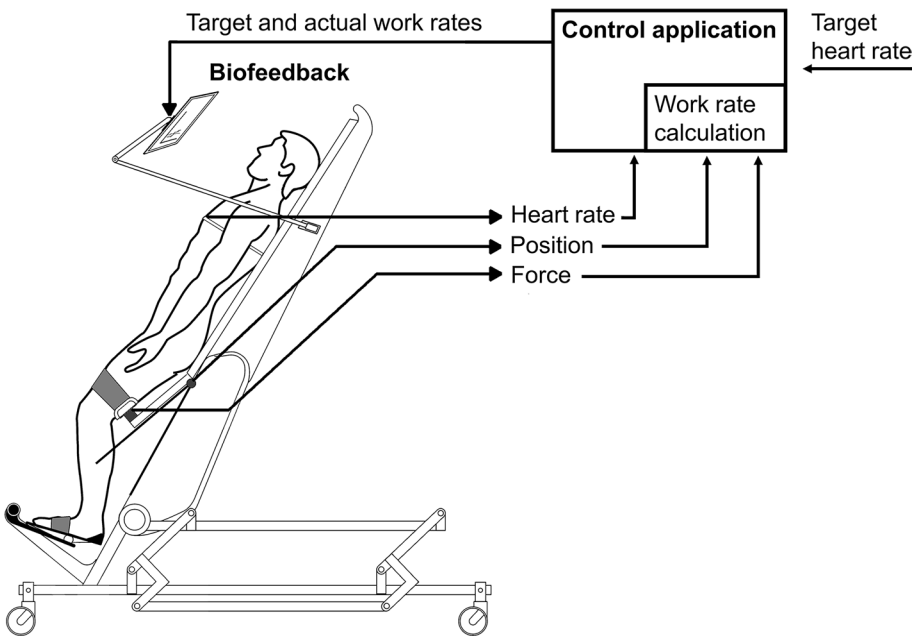

Fig. 5 Modified robotics-assisted tilt table (RATT) with force sensors under the thigh cuffs, visual feedback system and a heart rate feedback control system (modified from [54])

movement can be set to a stepping cadence between 8 and 80 steps/min. In the present study, the tilt angle was set to 60° and the cadence to the maximum of 80 steps/min.

With the augmented RATT system, patients can see their estimated exercise work rate together with a target work rate [47]. This was achieved by the incorporation of individual force sensors for the left and right leg cuffs, a work rate estimation algorithm and a real time visual feedback system (Fig. 5). Patients were instructed to adapt their voluntary leg effort to follow the work rate target. Active engagement in exercise was achieved by the patient exerting forces into the leg cuffs in synchronization with the movement of the RATT.

Experimental procedures

Patients took part in two test sessions, each separated by a minimum of 24 h. The HRV analysis conducted in the present work used data recorded from the second session where heart rate was controlled by feedback; the first session served to allow calculation of the feedback controller parameters. Patients were instructed to avoid strenuous activity within the 24 h before the test sessions and not to consume a large meal, caffeine or nicotine in 3 h prior to testing [48]. Testing was conducted at the same time of day for each patient, and the laboratory environment remained consistent for all tests.

For each test, the patient was first transferred and secured to the RATT in accordance with the manufacturer's guidelines. Then the physiological measurement systems (i.e., heart rate chest-belt sensor and automatic blood pressure monitoring) were fitted. The patient was then tilted up to 60° and the stepping cadence was set at 80 steps/min.

The first session comprised familiarization and system identification phases. The familiarization phase aimed to instruct patients regarding the RATT and the test procedures. The patient learned to adjust their leg movement and forces to remain as close as possible to the target work rate shown on the screen for 8 min. Then, after 15 min of rest, the system identification phase followed. This aimed to obtain the data necessary to calculate the parameters of the feedback control system used for constant heart rate exercise in the second session (below). In this phase, patients followed a square-wave target work rate profile for 15 min (5 block of 3 min). Further details of system identification and control design procedures can be found in reference [25]: "The target HR level was determined for each patient individually by evaluating the HR values measured during the system identification test, and initially setting HR* within the observed range. In practice, it was found necessary in 6 of 12 cases to adjust HR* manually during the first few minutes of the active phase of the feedback control tests to ensure patients could maintain the target and/or to keep the exercise intensity within the desired range. This is likely due to fatigue or other factors that affected patients' performance" [25].

The second session, which generated data for the HRV analysis, comprised two contiguous phases (Fig. 6): a rest phase of 14 min and an exercise phase lasting 27 min. The rest phase was conducted in a supine position to facilitate resting HRV analysis. The exercise phase, which started immediately at conclusion of rest, was conducted at a tilt angle of 60° and had three parts: 3 min of passive movement during which the patient's legs were moved by the RATT without active participation of the patient; then, during an active exercise phase lasting 21 min, patients were instructed to move their legs to follow the work rate target, which was calculated by the feedback control system to achieve the

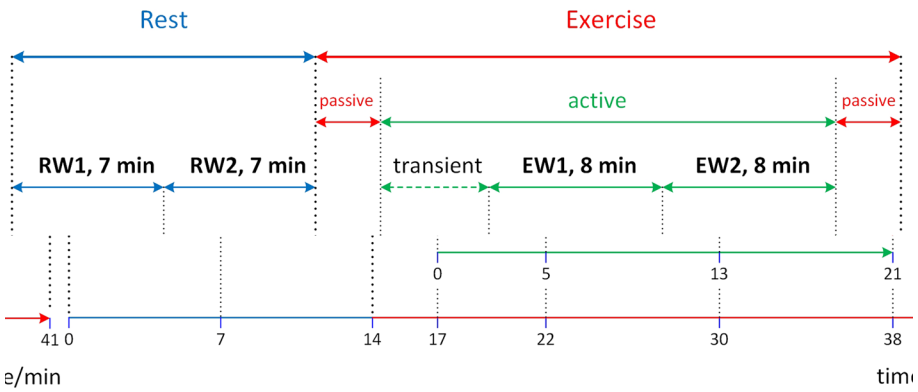

Fig. 6 Timeline of the experiment. This comprises two contiguous phases: rest and exercise. For HRV outcome analysis during Rest, the rest phase is split into two windows, each with a duration of 7 min: rest window 1 (RW1) and rest window 2 (RW2). The Exercise phase comprises an active period of duration 21 min that is preceded and followed by 3 min of passive movement. For HRV outcome analysis during Exercise, the active exercise phase is split into two windows, each with a duration of 8 min: exercise window 1 (EW1) and exercise window 2 (EW2). The first 5 min of the active exercise period, denoted "transient", was not included in the analysis due to the non-stationary increase in heart rate up to a new steady-state level at the onset of active exercise

constant heart rate target, while they were continuously encouraged to remain as close to the target work rate as possible; 3 min of passive movement then followed.

We employed a chest-strap-mounted sensor (H10, Polar Electro Oy, Finland) to record heart rate and raw RR intervals. The Polar H10 uses a sampling rate of 1 kHz and has previously been validated for HRV analysis, e.g., [42]. That study found strong agreement in HRV outcomes when comparing the Polar H10 with ECG recording.

Outcome measures

Data from the second test session described above were used for the HRV analysis. Raw RR intervals were imported to a custom-written HRV analysis tool that we implemented using Matlab and its Signal Processing Toolbox (The Mathworks, Inc., USA). All data sets were preprocessed to check for and to remove artifacts by defining bounds for plausible RR values and maximal deviation between successive intervals. The time-domain metrics used were standard deviation of all normal-to-normal R–R intervals (SDNN) and the root-mean-square value of the differences between successive R–R intervals (RMSSD). Power in the high frequency (HF, 0.15 Hz to 0.4 Hz), low frequency (LF, 0.04 Hz to 0.15 Hz), very low frequency (VLF, 0.0033 Hz to 0.04 Hz), ultra-low frequency (ULF, <0.0033 Hz) ranges, and total power (TP) were reported for frequency-domain analysis. This choice of HRV metrics is based upon contemporary standards for HRV analysis in general [12, 49] and when applied to patients after a stroke [22]. Frequency-domain outcomes were obtained using the Lomb–Scargle method for estimation of power spectra, which is optimised for non-uniformly-spaced data such as RR intervals and has recently been applied in HRV studies, e.g., [50]. The latter reference is a recent review that provides a systematic analysis of the applicability of Lomb–Scargle in the clinical HRV analysis setting. Time-dependence analysis was performed by calculating and comparing HRV metrics for two-time windows (Fig. 6). For the rest period, which had a total duration of 14 min, the HRV data was split into two time windows of equal

duration: rest window 1 (RW1), which lasted from 0 to 7 min; and rest window 2 (RW2), from 7 to 14 min. HRV in the active exercise period, which had a duration of 21 min, was analysed for two windows of equal duration (Fig. 6): exercise window 1 (EW1), from 5 to 13 min; and exercise window 2 (EW2) from 13 to 21 min. The first 5 min of active exercise was not included in the analysis due to the non-stationary increase in heart rate up to a new steady-state level at the onset of active exercise.

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation. Data analysis was based upon estimation statistics [51, 52] and the associated robust statistical visualization of outcomes using Gardner–Altman plots [53]. This paradigm focuses on estimation of effect sizes and their uncertainty rather than on null hypothesis significance testing: this approach is deemed appropriate because of the feasibility nature of the study and the chosen sample size ($n = 12$). Statistical calculations were implemented in the Matlab Statistics and Machine Learning Toolbox (The Mathworks, Inc., USA).

Author contributions

All authors were responsible for the research conceptualization and study design, and drafting and final approval of the manuscript. J.S., L.B. and K.H. were also involved in data collection, analysis and interpretation.

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Data availability

The datasets generated and/or analysed during the current study are publicly available in the OLOS repository: https://doi.org/10.34914/olos:2zknihrcvbg6heuq3e4ipoh76q.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethics Committee of Northwestern and Central Switzerland (***Ethikkommission Nordwest- und Zentralschweiz***, Ref. No.: 2022-01935). We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. All patients provided written informed consent prior to participation.

Competing interests

The authors declare no competing interests.

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