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ORIGINAL ARTICLE

Physiological responses and perceived exertion during robot-assisted treadmill walking in non-ambulatory stroke survivors

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ABSTRACT

Purpose: To examine physiological responses and perceived exertion during robot-assisted treadmill walking in non-ambulatory stroke survivors; compare these outcomes with aerobic exercise recommendations; and investigate the effect of robotic assistance.

Materials and methods: Twelve non-ambulatory stroke survivors (67 ± 11 years-old, 84 ± 38 d post-stroke) participated. Subjects walked three times 20 min (1 session/day) in the Lokomat: once with conventional exercise parameters, once with 60% robotic assistance and once with 100% robotic assistance. Gas exchange and heart rate were monitored continuously. Perceived exertion was assessed every 3 min during walking.

Results: During conventional robot-assisted treadmill walking, net perceived exertion (0–14 scale) significantly increased between minute 6 (median = 2, interquartile range = 4) and 18 (median = 5, interquartile range = 4). Net physiological responses did not significantly change over time. Throughout exercise, percentage of predicted heart rate reserve was significantly below the 40% threshold (medians: 11–14%) and percentage of predicted maximum heart rate reached the 55% threshold (medians: 59–60%). Perceived exertion reached the 11-point threshold halfway. Net physiological responses and perceived exertion did not significantly differ between 60% and 100% robotic assistance.

Conclusions: The assistance level that non-ambulatory stroke survivors require at their highest tolerable walking speed seems too high to sufficiently stress the cardiorespiratory system during robot-assisted treadmill walking.

➤ **IMPLICATIONS FOR REHABILITATION**

- The exercise intensity of 20-minute conventional robot-assisted treadmill walking can be low, and might be too low to challenge the cardiorespiratory system of non-ambulatory stroke survivors.
- Lowering the level of robotic assistance from 100% to 60% does not seem to increase the exercise intensity of 20-minute robot-assisted treadmill walking.

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Energy metabolism; aerobic exercise; walking; exoskeleton devices; stroke

Introduction

Cardiorespiratory fitness after stroke is low. In the subacute stage, reported peak oxygen uptake levels range between 8 and 15 ml/kg/min (26–54% of that of age- and gender-matched healthy controls) [1]. Such poor fitness levels can contribute to a "neurorehabilitation ceiling" that restricts patients to partake in rehabilitation at a frequency and intensity high enough to stimulate recovery [2]. This ceiling stresses the importance of incorporating aerobic exercise already early in stroke rehabilitation.

Aerobic exercise can comprise various types of exercise, including (stationary) cycling, swimming, recumbent stepping, overground and treadmill walking (with or without body weight support (BWS)) [3]. However, to also impact walking function, aerobic exercise has to be task-specific. A recent meta-analysis with meta-regression highlighted that aerobic exercise involving walking also improves walking speed (pooled mean 0.09 m/s, 95% confidence interval (CI) 0.04–0.13) and 6-min walking distance (pooled mean 38 m, 95%CI 27–50), whereas seated aerobic exercise does not impact walking speed (pooled mean −0.05 m/s, 95%CI −0.14 to 0.05) nor endurance (pooled mean 4 m, 95%CI −11 to 19) [4]. Hence, in the rehabilitation of stroke survivors with reduced walking function, walking aerobic exercise may be preferred to seated.

Unfortunately, Stoller and colleagues already discussed the important issue that stroke-related impairments such as non-ambulatory status, limited trunk control and poor coordination of

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Supplemental data for this article can be accessed here.

the affected limbs restricts individuals to exercise using conventional devices such as cycle ergometers or treadmills [5]. Also physiotherapists indicate that patients' physical impairment is a barrier to incorporate aerobic exercise into rehabilitation early after stroke [6,7]. However, the use of robotic devices may offer a potential opening to facilitate walking aerobic exercise in patients who cannot walk at all or as long as needed to challenge the cardiorespiratory system (stroke guidelines suggest a minimum of 20 min or multiple 10-min sessions) [8].

However, to properly trigger the cardiorespiratory system, not only an adequate exercise duration but also an adequate exercise intensity is important. Aerobic exercise guidelines recommend stroke survivors to exercise at moderate intensity, meaning 40–70% of peak oxygen consumption or heart rate reserve (or 55–80% of maximum heart rate) and 11–14 rating of perceived exertion (RPE) [8]. However, a recent meta-analysis revealed that only very few studies consider the physiological responses during robot-assisted walking in persons with stroke [9], especially non-ambulatory patients in the subacute stage (the population that benefits the most of robot-assisted gait training[10]). To our knowledge, only one study reported the physiological responses in terms of aerobic exercise intensity during conventional robot-assisted treadmill walking (RATW) – focusing mainly on the gait pattern – in 7 subacute non-ambulatory stroke survivors [5]. The authors reported that the percentage of predicted heart rate reserve during training was around 14% (too low for aerobic exercise) [5]. Lee and colleagues also investigated the physiological responses during RATW in 10 subacute non-ambulatory stroke survivors, but the authors did not compare their results with aerobic training recommendations [11]. Hence, it is still unclear whether RATW adequately challenges the cardiorespiratory system in these patients.

One of the parameters that can be adjusted during RATW is the level of robotic assistance. When it is set to its maximum, patients have to strictly follow a predefined gait trajectory mostly moved by the robot; when it is decreased, patients are allowed to deviate from this trajectory and to physically contribute to the motion [12,13]. It is assumed that in this second case, in order to stick to a pre-set trajectory, patients have to walk more actively and therefore consume more energy. However, there is no evidence yet that lowering the robotic assistance increases the active contribution in terms of oxygen consumption. So far, lowering the robotic assistance (100–60%) either did not significantly change the level of oxygen consumption [14] or, in contrast with the authors' expectations, even decreased it [11]; in both cases, minor differences were experienced (0.15–1.12 ml/kg/min). However, in both studies, fixed levels of BWS (30% or 50%) and walking speed (up to 0.55 m/s) were used [11,14]. For some patients, such amount of BWS could have been too high (or such walking speed could have been too slow), which may have weakened the effect of changing robotic assistance. It is possible that lowering the robotic assistance has a larger effect on physiological parameters when other training parameters are individually adjusted (i.e., BWS as low as tolerable and walking speed as high as tolerable).

This study aimed to answer three research questions: (1) What is the exercise intensity of 20-min conventional RATW in non-ambulatory subacute stroke survivors?; (2) Does the exercise intensity of RATW comply with aerobic exercise recommendations for stroke survivors [8]?; and (3) Does lowering the level of robotic assistance increase the exercise intensity of RATW when walking speed and BWS are fixed, but individually adjusted?

Methods

Study design

This study was an experimental, one-group, bi-center trial with repeated measures design. The study protocol was pre-registered (NCT02995616) and approved by the medical ethics committees of the University Hospital Brussels (B.U.N. 143201526040), Jessa Hospital Hasselt (16.124/reva16.15) and Fondazione Santa Lucia in Rome (CE/PROG.630).

Participants

All persons with stroke, who stayed at the neurorehabilitation ward of the Jessa Hospital campus Sint-Ursula (between February and August 2017, and between January and December 2018) and the neurorehabilitation wards 1 and 4 of the Fondazione Santa Lucia (between September and December 2017), were screened for eligibility.

Included were adults in the early subacute (1 week–3 months) and late subacute (3–6 months) stage after stroke [15], who were non-ambulatory (score ≤ 2 on the 6-point functional ambulation category [16]), who were eligible to receive RATW training according to local therapists' criteria (able to bear full weight on the hemiplegic leg during a minimum of one gait cycle with manual help allowed to maintain balance), and who walked twice in a treadmill-based exoskeleton (Lokomat, Hocoma, Switzerland) prior to the beginning of the trial.

Excluded were persons with unstable cardiovascular conditions, lower limb musculoskeletal problems (unrelated to stroke), concurrent pulmonary diseases, concurrent neurological diseases, communicative or cognitive problems constraining the ability to comprehend and follow instructions, and other contra-indications for exoskeleton training [17].

All participants gave written consent.

Experimental procedure

Subjects participated in three RATW sessions each lasting 20 min. During the first session, participants walked in a treadmill-based exoskeleton (Lokomat, Hocoma, Switzerland) according to conventional training parameters (i.e., the therapist decreased the level of BWS and robotic assistance and increased the walking speed as much as tolerable throughout the training without negatively affecting the gait pattern or generating discomfort). During the second and third session, participants walked with two different levels of robotic assistance: one session 100% and one session 60% (randomized using a random number generator). Sixty percent was chosen because Krewer and colleagues reported that this level of assistance is frequently applied in the initial phase of therapy [14], and lower percentages of robotic assistance can cause the Lokomat to stop for safety reasons, especially in non-ambulatory patients with limited Lokomat experience (i.e., 3 sessions). Hence, to prevent dropout, 60% was chosen as lower bound. The level of BWS and walking speed were left unchanged with respect to the first session (conventional training). All operators were Lokomat-certified physiotherapists and the operator was the same across the three sessions.

At the start of each session, a flexible mouth mask, portable respiratory gas analysis system (MetaMax3B, Cortex, Germany) and heart rate belt (Polar H7, Polar, Finland) were fitted. Participants rested in their wheelchair for 5 min wearing the equipment, and were thereafter accommodated in the exoskeleton. Gas exchange and heart rate were monitored from the beginning of rest to the end of walking. At the end of seated rest and every 3 min during walking, participants were asked to rate their RPE by pointing on a 6–20 Borg Scale (no to maximal exertion). Gas and volume calibrations were performed in accordance with manufacturer's instructions before each session. Participants were asked not to consume food, alcohol, caffeine, or nicotine at least 3 h prior to the sessions, nor to perform additional strenuous activities (apart from their regular therapy) at least 12 h prior to the sessions [18]. Usual medication intake was allowed with small amounts of water [18,19]. The second and third session were performed on separate days (maximum 1 d in-between) and were controlled for time of day.

The Metamax 3B and Polar heart monitor have been proven reliable to measure oxygen consumption (intraclass correlation coefficient (ICC)=0.80), carbon dioxide production (ICC = 0.76), respiratory exchange ratio (ICC = 0.97), minute ventilation (ICC = 0.81) and heart rate (ICC = 0.92) during a 6-min overground walking test in people with chronic stroke [20].

Outcomes

Breath-by-breath data were handled as in our previous study (i.e., we calculated medians over 60-s intervals) [21]. We computed medians per minute instead of means, because medians are less affected by irrelevant outliers caused by coughing or talking unintentionally during RPE scoring. The first 5 min were used to reach a steady-state condition and were not used in the analyses [19].

Physiological measures of interest were: gross and net oxygen consumption (mL/kg/min), carbon dioxide production (mL/kg/min), respiratory exchange ratio (no unit), oxygen cost (mL/kg/m), heart rate (beats/min), minute ventilation (L/min), breathing frequency (breaths/min), and RPE (6–20 Borg scale). Net values were calculated as gross values minus resting values (median of minute 5). Oxygen cost (mL/kg/m) was calculated as oxygen consumption (mL/kg/min) divided by walking speed (m/min).

To compare with aerobic guidelines for stroke survivors (i.e., 55–80% maximum heart rate, 40–70% heart rate reserve and 11–14 rating of perceived exertion on the Borg scale [8]), percentage of predicted heart rate reserve $\{[(\text{Heart rate}_{walking} - \text{Heart rate}_{rest})/(\text{Maximum heart rate}_{predicted} - \text{Heart rate}_{rest})*100]\}$ and percentage of predicted maximum heart rate $[(\text{Heart rate}_{walking}/\text{Maximum heart rate}_{predicted})*100]$ were calculated offline. Maximum heart rate was predicted as 164 − 0.7*Age (for participants taking β-blockers [22]) or 206.9 − 0.67*Age (for participants not taking β-blockers [18]).

Statistical analysis

Statistical analyses were done using SPSS (version 25, IBM, Armonk, NY). The significance level was set at 5%. Related-samples Wilcoxon rank signed tests were conducted to compare net physiological responses and net RPE among minutes 6, 12, and 18 of conventional RATW. One-sample Wilcoxon signed rank tests were analyzed to check if percentage of heart rate reserve, percentage of predicted maximum heart rate and gross RPE were above minimum and below maximum threshold for aerobic exercise at minutes 6, 12, and 18. Related-samples Wilcoxon rank signed tests were performed to compare net physiological responses and net RPE between walking with 60% robotic assistance and walking with 100% robotic assistance. Comparisons were repeated for minutes 6, 12, and 18. Median and interquartile range (IQR) were calculated to describe physiological responses and RPE at minutes 6, 12, and 18 of RATW. To compare with other trials and for use in future meta-analyses, means, standard deviations and 95%CIs were reported in Supplemental Appendix S1 and S2.

Table 1. Demographic and clinical characteristics of included participants (n = 12).

	Median or number	IQR	Minimum	Maximum
Recruitment center (FSL/SU)	4/8	–	–	–
Sex (male/female)	8/4	–	–	–
Weight (kg)	73	17	50	85
Height (m)	1.66	0.09	1.50	1.85
BMI (kg/m^2)	24.4	6.5	21.2	30.9
Time since stroke (days)	80	60	24	134
Type of stroke (Ischemic/ Hemorrhagic/Unknown)	8/3/1	–	–	–
FAC (0/1/2)	2/3/7	–	–	–
β-blockers (yes/no)	4/8	–	–	–
Predicted HR_{max} (beats/min)	156	39	109	178
Predicted $HR_{reserve}$ (beats/min)[a]	75	35	24	109

Continuous variables are reported as median, IQR, minimum and maximum. Categorical variables are reported as numbers. BMI: body mass index; F: female; FAC: functional ambulation category; FSL: Fondazione Santa Lucia; HRmax: maximum heart rate; HRreserve: heart rate reserve; M: male; SU: Jessa Hospital campus Sint-Ursula.
[a]Data of 1 subject could not be calculated because resting heart rate was missing due to technical issues with heart rate belt (n = 11).

Results

Participant characteristics

Twelve participants (8 males) were enrolled in this trial (Table 1). Median age of the participants was 67 years (IQR = 12 years) and median time since stroke 80 days (IQR = 60 days). At the time of inclusion, seven subjects needed support of one person to help with balance and coordination (functional ambulation category 2), three subjects needed support of one person to help with weight carrying and balance (functional ambulation category 1), and 2 subjects could not walk or needed help from 2 or more persons (functional ambulation category 0). Four participants took β-blockers. All participants received physiotherapy (60–80 min/d) for 5 d/week. Eight participants also received occupational therapy (60 min/d) for 5 d/week.

Missing data

During conventional RATW, the heart rate data of one subject were discarded due to technical issues (minutes 1–20 missing) and one subject stopped due to fatigue (minutes 19–20 missing). During RATW with 60% robotic assistance, the data of one subject were missing due to technical issues with the respiratory gas analysis system (minutes 17–20 missing). Data of these minutes were not used in statistical analysis. The first two subjects that were included in this trial (two males) did not participate in the second and third trial. These subjects were part of a pilot phase to test the feasibility of the protocol. After this phase, the protocol had to be slightly adjusted. Initially, the effect of the level of robotic assistance was measured during a single session instead of two separate sessions. However, to prevent that fatigue would impact the results, the levels of robotic assistance were tested on separate days.

Physiological responses and RPE during conventional RATW

During conventional RATW, median robotic assistance decreased from 75% (IQR = 12.5%) to 60% (IQR = 12.5%); median BWS

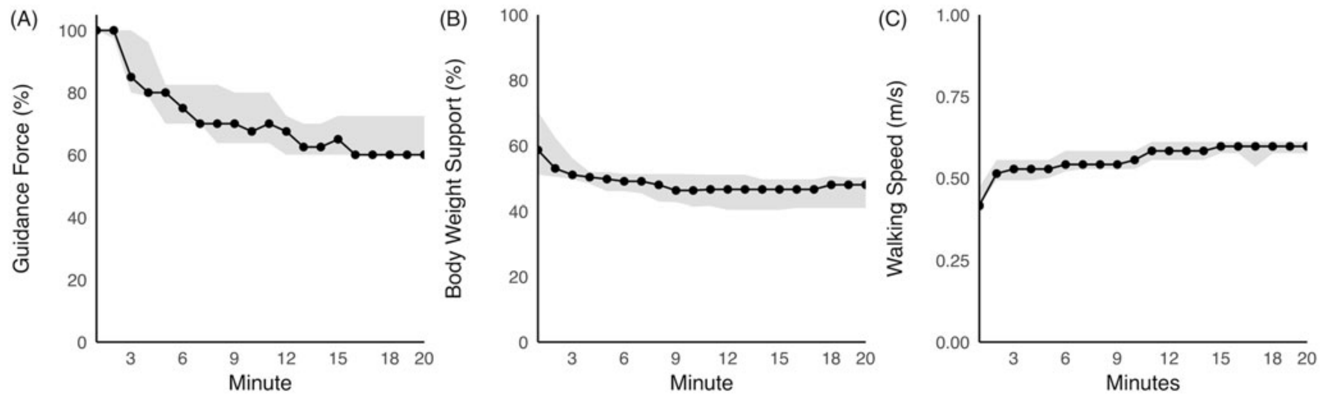

Figure 1. Changes in training parameters during 20-min conventional robot-assisted treadmill walking ($n = 12$). Plotted are median (solid line) and interquartile range (grey band) for (A) robotic assistance, (B) body weight support and (C) walking speed.

decreased from 49% (IQR = 5.9%) to 48% (IQR = 9.6%); and median walking speed increased from 0.54 m/s (IQR = 0.06 m/s) to 0.60 m/s (IQR = 0.04 m/s; Figure 1).

Net physiological measures did not significantly change between minutes 6, 12, and 18 ($p > 0.05$). Only net RPE significantly increased between minutes 6 and 12 ($Z = -2.840$, $p = 0.005$) and between minutes 6 and 18 ($Z = -2.692$, $p = 0.007$; Figure 2 and Table 2).

Comparison with aerobic training recommendations

Throughout conventional RATW, mean percentage of predicted maximum heart rate did not significantly differ from the minimum threshold for aerobic exercise (respectively, $p = 0.182$, $p = 0.110$, and $p = 0.155$ at minutes 6, 12, and 18). Mean percentage of predicted heart rate reserve however was significantly below the minimum threshold at minute 6 and 18 (respectively, $p = 0.004$ and $p = 0.004$), but not at minute 12 ($p = 0.050$). At minute 6, mean gross RPE was significantly below the minimum threshold ($p = 0.011$); at minutes 12 and 18, mean gross RPE did not significantly differ from the minimum threshold (respectively, $p = 0.329$ and $p = 0.959$; Table 2 and Figure 3).

Looking at the results of each subject individually, 8 subjects (73%) reached the minimum percentage of predicted maximum heart rate throughout the session and 1 subject (9%) reached the minimum percentage of predicted heart rate reserve. Five subjects (42%) reached the minimum RPE at minute 12, and two more subjects (58%) reached the minimum RPE at minute 18.

Effect of changing robotic assistance

Net physiological responses and net RPE did not differ significantly between RATW with 60% and 100% robotic assistance, except for net oxygen consumption ($Z = -2.090$, $p = 0.037$), net oxygen cost ($Z = -2.090$, $p = 0.037$), and net respiratory exchange ratio ($Z = -1.988$, $p = 0.047$) at minute 6 (Table 2 and Figure 4).

Discussion

In this study, we assessed to which extent RATW stresses the cardiorespiratory system in non-ambulatory subacute stroke survivors and whether it complies with aerobic exercise recommendations for stroke survivors. In contrast to our expectations, the stress on the cardiorespiratory system of these patients seems low. Participants perceived conventional RATW as "very light" at the beginning to "light" at the end. Median oxygen consumption ranged between 1.8 and 2.1 times the resting values and median heart rate increased only 8–10 beats/min compared to rest. However, it is important to note that 36% of the participants included in the analysis took beta-blocking medication, which could be a reason for the limited heart rate increase.

In our trial, the average heart rate during RATW (86 ± 13 beats/min, Supplementary Appendix S1) was lower than reported during manual wheelchair propulsion (98 ± 8 beats/min) in early subacute stroke survivors (4.0 ± 2.2 weeks post-stroke; Brunnstrom's Motor recovery stage II-IV) [23]. However, most participants in our trial were in a later stage of rehabilitation, which may explain lower rates. Also the average level of oxygen consumption (5.8 ± 1.6 ml/kg/min) was lower than the amount reported for unloaded cycling in acute stroke survivors with various levels of hemiparesis (up to 7.8 ± 0.4 ml/kg/min), but again these participants were earlier after the stroke event [24]. Nevertheless, the level of oxygen consumption was comparable to the amount reported for manual wheelchair propulsion in chronic stroke survivors (5.8 ± 2.6 ml/kg/min) [25].

Generally, the exercise intensity of conventional RATW was at the lower bound or below the minimum thresholds for aerobic exercise post-stroke. Especially, the mean percentage of heart rate reserve was substantially below the exercise guidelines (medians = 11–14%). These percentages were similar to those of Stoller and colleagues who reported an average of 14% (SD 2%) [5]. Though RATW seems a low-intensity exercise, there are likely subsets of stroke survivors for whom it is challenging. One subject in our sample reached heart rates between 105 and 144 beats/min (67–92% of predicted maximal heart rate) and perceived the exercise as "somewhat hard" to "very hard". The subject even reached oxygen consumption rates up to 10.0 ml/kg/min. Hence, heart rate monitoring during RATW could be useful to identify those patients for whom it is challenging.

One reason for this low exercise intensity could be the high level of robotic assistance (≥60%), and especially BWS (around 50%). Up to now, the highest oxygen demands during RATW have been achieved by lowering the level of BWS to 30% in combination with 60% robotic assistance and 0.55 m/s (8.09 ± 2.23 ml/kg/min) [14]. Unfortunately, the severity of hemiparesis of our participants prevented further changes in training parameters without negatively affecting the gait pattern, generating discomfort or causing the exoskeleton to block for safety. Stoller and colleagues [5] encountered the same problem. The low motor function of their participants prevented further decreases in BWS [5]. Hence, it seems that the level of assistance that non-

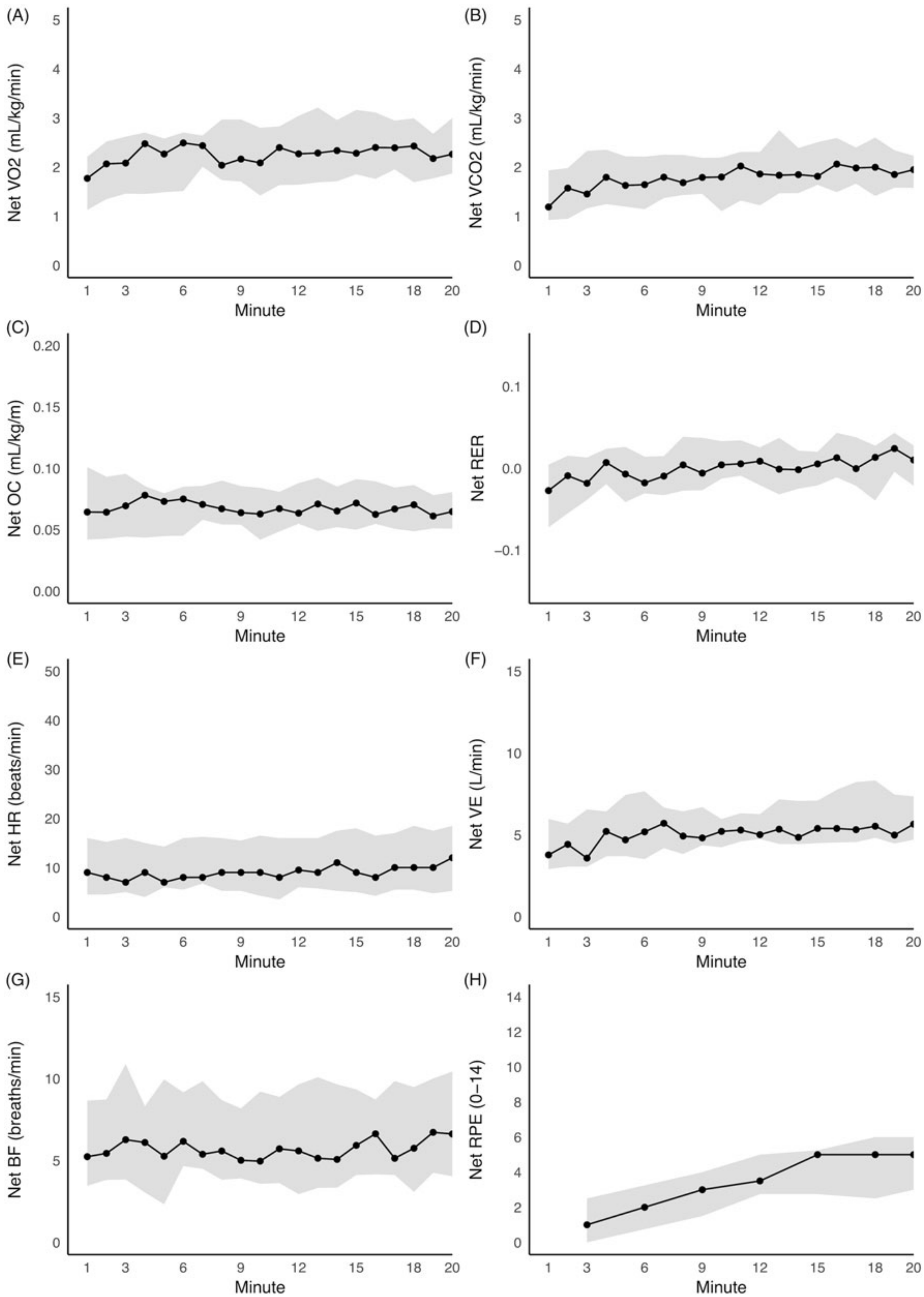

Figure 2. Changes in net physiological responses and net perceived exertion during 20-min conventional robot-assisted treadmill walking. Plotted are median (solid line) and interquartile range (grey band) for (A) net oxygen consumption (net VO2, $n = 12$), (B) net carbon dioxide production (net CO2, $n = 12$), (C) net oxygen cost (net OC, $n = 12$), (D) net respiratory exchange ratio (net RER, $n = 12$), (E) net heart rate (net HR, $n = 11$), (F) net minute ventilation (net VE, $n = 12$), (G) net breathing frequency (net BF, $n = 12$), and (H) net rating of perceived exertion (net RPE, $n = 12$). Net values were obtained by subtracting resting values (median of minute 5) from gross values during walking.

ambulatory stroke survivors require at their highest tolerable walking speed is too high to sufficiently stress the cardiorespiratory system during RATW.

Hence, future studies should investigate how we can reach higher exercise intensities to train the cardiorespiratory system of non-ambulatory stroke survivors. One alternative to increase the

Table 2. Descriptive statistics of the net physiological responses and net perceived exertion during conventional robot-assisted treadmill walking, robot-assisted treadmill walking with 60% robotic assistance and robot-assisted treadmill walking with 100% robotic assistance at minutes 6, 12, and 18.

	Conventional RATW (n = 12)			RATW with 100% robotic assistance (n = 10)			RATW with 60% robotic assistance (n = 10)		
Outcome	Minute 6 Median (IQR)	Minute 12 Median (IQR)	Minute 18 Median (IQR)	Minute 6 Median (IQR)	Minute 12 Median (IQR)	Minute 18 Median (IQR)	Minute 6 Median (IQR)	Minute 12 Median (IQR)	Minute 18[b] Median (IQR)
Gross VO_2 (mL/kg/min)	5.66 (1.19)	5.39 (1.96)	5.57 (1.67)	5.48 (1.25)	5.32 (1.63)	5.55 (1.35)	5.43 (1.75)	5.51 (1.62)	5.31 (1.65)
Net VO_2 (mL/kg/min)	2.49 (1.35)	2.27 (1.86)	2.43 (1.88)	2.71 (0.99)	2.71 (1.11)	2.88 (1.09)	1.96 (1.07)	2.33 (1.38)	2.35 (1.49)
Gross VCO_2 (mL/kg/min)	4.46 (1.57)	4.45 (1.63)	4.68 (2.29)	4.26 (1.00)	4.40 (1.49)	4.50 (1.32)	4.42 (1.52)	4.37 (1.60)	4.27 (1.43)
Net VCO_2 (mL/kg/min)	1.64 (1.24)	1.86 (1.31)	2.00 (1.86)	2.12 (0.70)	2.21 (0.94)	2.35 (1.04)	1.63 (0.88)	1.72 (1.24)	1.97 (1.35)
Gross OC (mL/kg/m)	0.17 (0.06)	0.15 (0.08)	0.16 (0.08)	0.15 (0.03)	0.15 (0.04)	0.15 (0.03)	0.13 (0.05)	0.14 (0.04)	0.14 (0.05)
Net OC (mL/kg/m)	0.07 (0.05)	0.06 (0.04)	0.07 (0.06)	0.07 (0.03)	0.07 (0.03)	0.07 (0.03)	0.05 (0.03)	0.06 (0.04)	0.06 (0.04)
Gross RER (no unit)	0.82 (0.05)	0.84 (0.05)	0.83 (0.06)	0.82 (0.06)	0.83 (0.04)	0.84 (0.05)	0.81 (0.04)	0.81 (0.07)	0.83 (0.04)
Net RER (no unit)	−0.02 (0.06)	0.01 (0.07)	0.01 (0.07)	−0.01 (0.04)	0.01 (0.02)	0.00 (0.03)	0.02 (0.07)	0.00 (0.05)	0.02 (0.05)
Gross HR (beats/min[a]	83 (19)	87 (19)	85 (20)	85 (17)	83 (15)	83 (16)	82 (11)	84 (10)	82 (15)
Net HR (beats/min)[a]	8 (16)	10 (14)	10 (17)	9 (9)	9 (9)	10 (8)	6 (4)	7 (6)	8 (6)
Gross VE (L/min)	16.0 (5.13)	16.2 (5.97)	15.7 (7.13)	15.7 (5.10)	15.3 (4.02)	16.3 (5.00)	14.3 (3.39)	14.1 (3.97)	14.7 (5.27)
Net VE (L/min)	5.18 (4.72)	5.01 (2.21)	5.52 (3.84)	6.67 (2.13)	7.09 (2.58)	7.31 (3.35)	5.46 (1.87)	5.53 (2.21)	6.99 (3.62)
Gross BF (breaths/min)	25 (8)	24 (10)	24 (9)	24 (7)	23 (7)	25 (6)	25 (7)	25 (7)	24 (8)
Net BF (breaths/min)	6 (6)	6 (7)	6 (8)	7 (3)	7 (4)	7 (4)	7 (4)	6 (3)	6 (4)
Gross RPE (6–20)	8.5 (3)	10 (3)	12 (4)	8.0 (2.0)	8.5 (3.0)	8.5 (4.0)	8.0 (3.0)	8.5 (3.0)	10.0 (3.0)
Net RPE (0–14)	2 (4)	3.5 (3)	5 (4)	2.0 (1.0)	2.5 (2.0)	2.5 (3.0)	2.0 (3.0)	2.0 (2.0)	3.5 (3.0)
Percentage HR_{max} (%)[a]	59.0 (16.1)	59.8 (13.7)	60.1 (14.4)	–	–	–	–	–	–
Percentage HRR (%)[a]	11.0 (18.2)	12.4 (17.0)	14.2 (21.2)	–	–	–	–	–	–

BF: breathing frequency; HR: heart rate; HR_{max}: predicted maximum heart rate; HRR: heart rate reserve; IQR: interquartile range; RER: respiratory exchange ratio; RPE: rating of perceived exertion; VCO_2: carbon dioxide production; VE: minute ventilation; VO_2: oxygen consumption. Net values were obtained by subtracting resting values (median of minute 5) from gross values.
[a]Data of 1 subject missing due to technical issues with heart rate belt (n = 11).
[b]Data of 1 subject of minutes 17–20 missing due to technical issues with respiratory gas analysis system (n = 9).

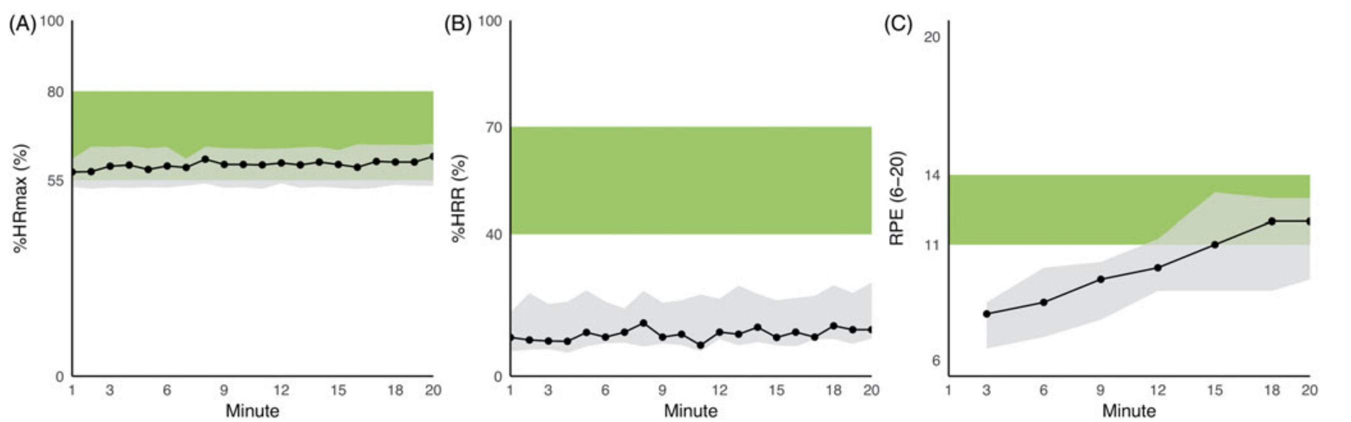

Figure 3. Comparison of the exercise intensity during 20-min conventional robot-assisted treadmill walking with aerobic training recommendations. Plotted are median (solid line) and interquartile range (grey band) and aerobic training zones (green horizontal band) for (A) percentage of predicted maximum heart rate (%HRmax, n = 11), (B) percentage of predicted heart rate reserve (%HRR, n = 11) and (C) gross rating of perceived exertion (RPE, n = 12).

exercise intensity may be the use of overground exoskeletons, which are not combined with an overhead BWS system, so users have to bear their full weight during walking. Another alternative, which would be a more low-cost solution, may be the use of modified recumbent steppers or bikes. Unfortunately, to date, little to nothing is known about the exercise intensity of these types of exercises, and especially about the differences between these types of exercises. So, it is still unclear which type of exercise induces the highest physiological stress.

Though the exercise intensity of RATW is probably low for most patients, it may still result in significantly greater improvements in cardiorespiratory fitness compared to usual care alone (or cycling training). Chang and colleagues found a larger increase in peak oxygen consumption after 2-week RATW training than after conventional physiotherapy alone (2.3 versus 1.3 ml/kg/min increase) [26]. Whereas, in non-ambulatory stroke survivors, cycling training showed no added value over a control intervention (mean difference = 1.84 ml/kg/min, 95%CI 1.06–4.73, I^2=73) [27]. A randomized controlled trial is needed to compare the effect RATW training with the effect of cycling training and usual care alone on cardiorespiratory fitness and walking function in subacute non-ambulatory stroke survivors.

Last, changing robotic assistance seems to have no significant impact on exercise intensity. We found no significant differences in physiological responses nor RPE between fully assisted walking and walking with 60% robotic assistance when BWS (44%±7%) and walking speed (0.61 ± 0.03 m/s) were individually adjusted. This result was in line with the few available studies on the effects of robotic assistance on post-stroke physiological responses that overall did not find relevant differences [11,14]. Lee and colleagues however did observe that at 0.50 m/s, lowering the robotic assistance significantly lowered the level of oxygen consumption, but the effect was small [11]. Van Kammen and colleagues [28], who studied muscle activity during RATW in

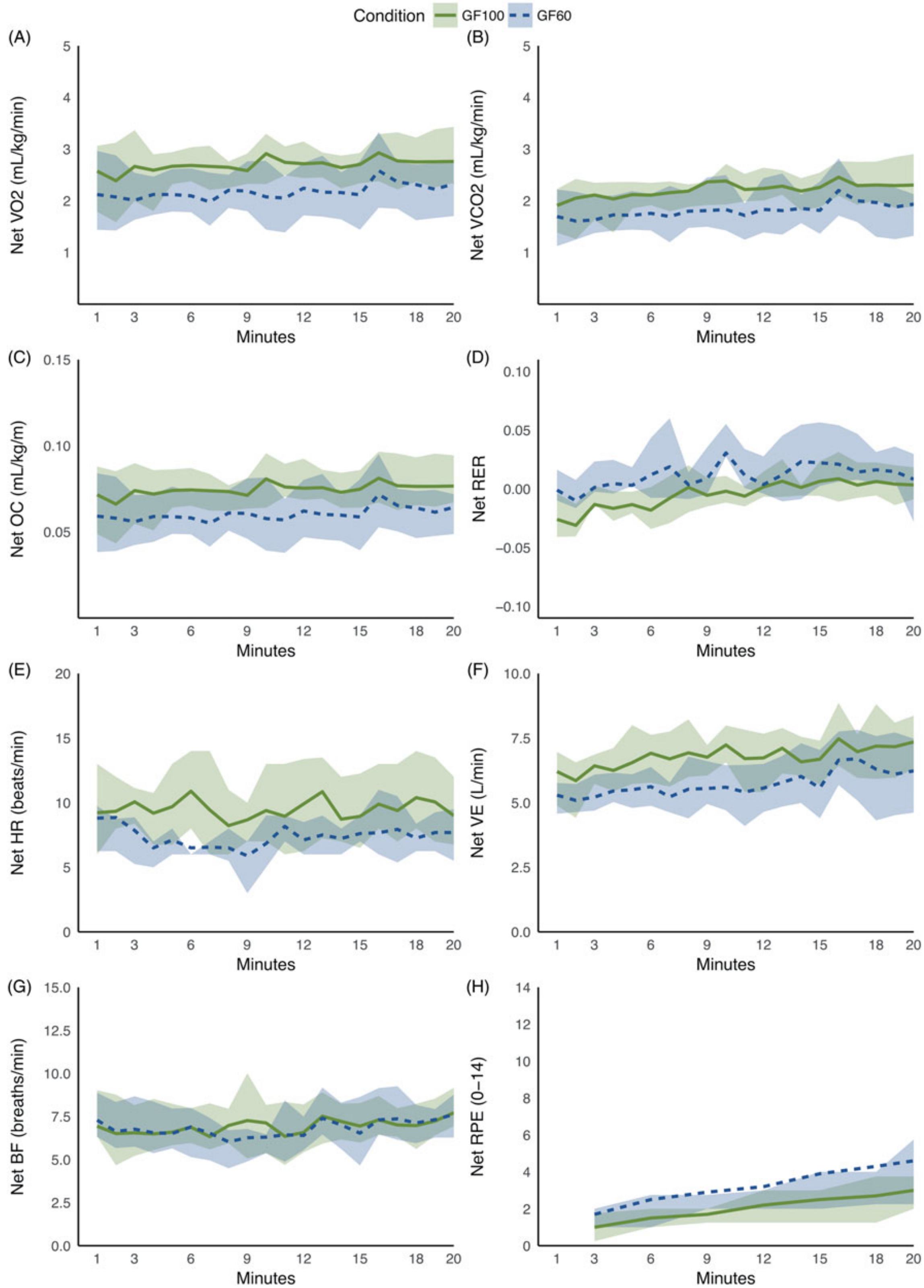

Figure 4. Changes in net physiological responses and net perceived exertion during 20-min robot-assisted treadmill walking with 100% and 60% robotic assistance ($n = 10$). Plotted are median (solid line = 100% robotic assistance; dashed line = 60% robotic assistance) and interquartile range (colored bands) for (A) net oxygen consumption (net VO2), (B) net carbon dioxide production (net CO2), (C) net respiratory exchange ratio (net RER), (D) net oxygen cost (net OC), (E) net heart rate (net HR), (F) net minute ventilation (net VE), (G) net breathing frequency (net BF) and (H) net rating of perceived exertion (net RPE). Net values were obtained by subtracting resting values (median of minute 5) from gross values during walking.

able-bodied subjects, reported that at high walking speed (0.78 m/s), muscle activation levels of muscles associated with stability and propulsion (Erector Spinae, Gluteus Medius, Biceps Femoris and Medial Gastrocnemius) only marginally differed between fully assisted (100%) and unassisted walking (0%) [28]. This may explain why we do not find relevant differences in oxygen consumption between RATW with 60% and 100% robotic assistance.

Study limitations

This study has two main limitations, i.e., small sample size and absence of incremental exercise tests. First, although we recruited patients for almost 2 years, we were unable to recruit an adequate number of eligible patients. For statistical analysis, 28 subjects would have been needed. Especially, the number of patients within the first month after stroke was scarce (median time since stroke: 80 d). One reason for this may be late referral to the rehabilitation wards where participants were recruited (median time between stroke and admission: 21 d). Future studies should investigate whether this type of exercise is also feasible in the first month post-stroke. Unfortunately, other reasons for low recruitment numbers are unclear as reasons for exclusion and screening numbers were not systematically recorded. To identify the difficulties with patient recruitment, future studies should keep those records. Second, because percentage of heart rate reserve and percentage of predicted heart rate were based on predictions rather than incremental exercise test results, we must interpret these results carefully. These predictions may have over- or underestimated participants' maximum heart rate, and therefore also the percentage of maximum heart rate and heart rate reserve.

Conclusion

In this study, cardiorespiratory responses and RPE were low during conventional RATW in non-ambulatory subacute stroke survivors. Our findings suggest that the level of assistance that non-ambulatory stroke survivors require at their highest tolerable walking speed is too high to sufficiently challenge the cardiorespiratory system during conventional RATW. Lowering the level of robotic assistance did not significantly change the exercise intensity. Future studies should examine if other types of exoskeletons, such as overground exoskeletons, induce higher cardiorespiratory stress and could be used as an alternative for walking aerobic exercise in severely impaired stroke survivors.

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