Ability of The Cardiorespiratory System to Adapt to Exercise is Impaired in Individuals With Severe Post-Stroke Fatigue

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Ability of the cardiorespiratory system to adapt to exercise is impaired in individuals with severe post-stroke fatigue

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Abstract

Physical deconditioning after stroke may induce post-stroke fatigue. However, research on this association is limited. Our primary objective was to investigate the associations of post-stroke fatigue with oxygen uptake ($\dot{V}O_2$) at peak exercise and the time constant of $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$) at the onset of exercise. The secondary objective was to examine the associations between fatigue and cardiorespiratory variables potentially affecting $\dot{V}O_2$ during exercise. Twenty-three inpatients from a subacute rehabilitation ward were enrolled in this study. The median (interquartile range) Fatigue Severity Scale (FSS) score as a measure of fatigue was 32 (27, 42) points. The FSS score was not associated with $\dot{V}O_2$ at peak exercise during a symptom-limited graded exercise test (rho = −0.264; p = 0.224), while it was significantly associated with $\tau\dot{V}O_2$ during a submaximal constant-load exercise test (rho = 0.530; p = 0.009). A higher FSS score was also significantly correlated with a longer time constant of cardiac output kinetics (rho = 0.476, p = 0.022). These results suggest that the ability of the cardiorespiratory system to adapt to exercise is impaired in individuals with severe post-stroke fatigue. Our findings can contribute to the development of an appropriate rehabilitation program for such individuals.

Introduction

Post-stroke fatigue can be defined as 'a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities' [1,2]. In addition, a case definition for post-stroke fatigue included a criterion for self-reported significant fatigue that interfered with daily activities [3,4]. A systematic review reported that the prevalence of post-stroke fatigue could range between 25% and 85% [2]. Post-stroke fatigue is associated with various factors, such as depressive symptoms and functional disability [1]. Furthermore, individuals with post-stroke fatigue are reported to have poor recovery of activities of daily living [5,6], a lower rate of returning to work [7], reduced health-related quality of life [8], and increased mortality [6,9]. The underlying pathophysiology of post-stroke fatigue is not completely understood, although probable factors include low excitability of the motor cortex and inflammatory responses [1]. In addition, there is insufficient evidence regarding the effectiveness of rehabilitative exercise programmes for improving post-stroke fatigue [1,10], although there is sufficient evidence that exercise training can improve fitness, balance, mobility, and activities of daily living in individuals with stroke [11].

Post-stroke fatigue has been suggested to be triggered by physical deconditioning, which may lead to the avoidance of physical activities and further deconditioning [12]. However, there is limited evidence on the association between post-stroke fatigue and

cardiorespiratory fitness [12]. Oxygen uptake ($\dot{V}O_2$) at peak exercise measured during a symptom-limited graded exercise test is widely accepted as an indicator of cardiorespiratory capacity in individuals with stroke [11,13,14]. $\dot{V}O_2$ at peak exercise in individuals with stroke is 26%–87% of that in healthy age- and sex-matched individuals [13]. However, a cross-sectional study in individuals with chronic stroke (4.1 ± 3.5 years post-stroke) reported that post-stroke fatigue was associated with depressive symptoms but not with $\dot{V}O_2$ at peak exercise [15].

The assessment of $\dot{V}O_2$ kinetics at the onset of submaximal exercise has also been shown to provide objective information on cardiorespiratory fitness in individuals with stroke [16,17]. Transient measurements of $\dot{V}O_2$ to a constant-load exercise at an intensity below the ventilatory threshold are classified into three phases. The time constant of $\dot{V}O_2$ in phase II ($\tau\dot{V}O_2$) has often been used to assess $\dot{V}O_2$ kinetics at the onset of exercise, which reflects the ability of the cardiorespiratory system to adapt from rest to a new steady-state during submaximal exercise [18]. A longer $\tau\dot{V}O_2$ is associated with poorer health status, ageing, and a sedentary lifestyle [18,19]. Tomczak et al. [16] reported that $\tau\dot{V}O_2$ was greater in individuals with stroke than in age-, sex-, and activity-matched healthy adults. $\tau\dot{V}O_2$ has been reported to be more sensitive than $\dot{V}O_2$ at peak exercise in assessing cardiorespiratory functional changes associated with training and inactive lifestyle [19-22]. Therefore, we hypothesised that the severity of post-stroke fatigue could be associated more strongly with $\tau\dot{V}O_2$ than $\dot{V}O_2$

75 at peak exercise.

76 Wu et al. [4] proposed a conceptual model of post-stroke fatigue that biological
77 factors may trigger fatigue present at an early stage after stroke (usually within the first 3
78 months after stroke), whereas fatigue present at a later stage after stroke (usually over 1 year
79 after stroke) may be more attribute to psychological and behavioural factors. However, the
80 association between post-stroke fatigue at the early stage after stroke and cardiorespiratory
81 fitness has not been reported. The primary objective of this study was to examine whether
82 more severe fatigue was associated with a longer $\tau\dot{V}O_2$ at the onset of exercise measured
83 during a submaximal constant-load exercise test rather than a lower $\dot{V}O_2$ at peak exercise
84 obtained during a symptom-limited graded exercise test in inpatients at a subacute
85 rehabilitation ward. In addition, impairments of respiratory and cardiac function to supply
86 oxygen and the inability of skeletal muscles to extract oxygen may limit the increase in $\dot{V}O_2$
87 during exercise in individuals with stroke [16,23,24]. Thus, our secondary objective was to
88 identify associations between post-stroke fatigue and cardiorespiratory variables potentially
89 affecting $\dot{V}O_2$ during exercise such as the oxygen uptake kinetics efficiency slope (OUES),
90 cardiac output (CO), and arterial-venous oxygen difference (AVO_2diff). Although there have
91 been no published studies regarding the cardiorespiratory mechanisms underlying the
92 impairments of $\tau\dot{V}O_2$ in individuals with stroke, ventilatory efficiency and muscle oxygen
93 extraction, measured by the OUES and AVO_2diff, respectively, are lower in individuals with

stroke than in healthy adults [25,26]. Therefore, we hypothesised that the impairment of these variables would also be associated with post-stroke fatigue. Elucidating cardiorespiratory factors associated with post-stroke fatigue could contribute to the development of an appropriate rehabilitation program for individuals with post-stroke fatigue.

Results

Participants

A flow chart of participants enrolled in the study is shown in Fig. 1. Thirty individuals with stroke provided informed consent. However, two participants refused to perform exercise tests. In addition, in five of 28 participants who performed the submaximal constant-load exercise test, cardiorespiratory data during the test could not be measured because of technical difficulties. Consequently, 23 participants were included in the analysis. Although all participants were recruited from a subacute rehabilitation ward, five participants were in the chronic phase of stroke recovery (≥3 months after stroke) [27]. Table 1 shows the characteristics of the participants.

Exercise testing

No significant adverse events occurred during or after these exercise tests. All participants had to stop the symptom-limited graded exercise test due to their inability to

maintain a cycling cadence of >40 rpm. Concerning each of the three criteria for reaching the maximal effort, 21 participants (91.3%) had an increase in $\dot{V}O_2$ <150 mL·min^{-1} for >1 min despite increased work rate, six (26.1%) achieved a respiratory exchange ratio >1.10, and 11 (47.8%) reached 85% of the age-predicted maximal heart rate. The ventilatory threshold was determined in all participants.

Regarding cardiorespiratory variables measured during the submaximal constant-load exercise test, the mean ± standard deviation (SD) coefficients of determination of the kinetics of $\dot{V}O_2$, CO, AVO_2diff, and minute ventilation ($\dot{V}E$) were 0.99 ± 0.01, 0.96 ± 0.02, 0.93 ± 0.03, and 0.98 ± 0.01, respectively. In addition, the mean ± SD ratio of the time constant of CO (τCO) to $\tau\dot{V}O_2$ was 1.19 ± 0.56. In 15 of 23 participants (65.2%), the ratio of τCO to $\tau\dot{V}O_2$ was >1.00.

Measurement values obtained during the symptom-limited graded and submaximal constant-load exercise tests are shown in Table 2.

Correlations between the Fatigue Severity Scale (FSS) score and cardiorespiratory variables measured during the symptom-limited graded and submaximal constant-load exercise tests (Table 2)

The median (interquartile range) FSS score was 32 (27, 42). The mean ± SD $\dot{V}O_2$ values at peak exercise and $\tau\dot{V}O_2$ at the onset of exercise were 18.0 ± 4.2 mL·kg^{-1}·min^{-1} and

38.6 ± 10.1 s, respectively.

The FSS score was not significantly correlated with $\dot{V}O_2$ at peak exercise (rho = −0.264, p = 0.224; Fig. 2a), while a higher FSS score was significantly correlated with a longer $\tau\dot{V}O_2$ (rho = 0.530, p = 0.009; Fig. 2b). Although the FSS score was not also associated with other cardiorespiratory variables at peak exercise and at the ventilatory threshold measured during the symptom-limited exercise test, a higher FSS score was significantly associated with a longer τCO (rho = 0.476, p = 0.022; Fig. 3) during the submaximal constant-load exercise test. Changes in $\dot{V}O_2$ and CO at the onset of exercise in representative participants with different fatigue levels (low and high) are shown in Supplementary Figs. S1 and S2, respectively, online.

Associations of participants' characteristics with the FSS score, $\tau\dot{V}O_2$, and τCO

No demographic and clinical variables were significantly associated with the FSS score (Table 1) and $\tau\dot{V}O_2$ and τCO (Table 3). These results indicate that there were no potentially confounding variables in the associations of the FSS score with $\tau\dot{V}O_2$ and τCO measured during the exercise tests.

Discussion

The primary objective of this study was to examine whether more severe fatigue was

associated with a longer $\tau\dot{V}O_2$ measured during a submaximal constant-load exercise test rather than a lower $\dot{V}O_2$ at peak exercise obtained during a symptom-limited graded exercise test in inpatients at a subacute rehabilitation ward. The results of post-stroke fatigue assessment in this study are in line with those of previous studies [28,29]. This study demonstrated that a higher FSS score was associated with a longer $\tau\dot{V}O_2$ at the onset of exercise; however, fatigue was not associated with $\dot{V}O_2$ at peak exercise. In addition, our secondary objective was to identify the associations between post-stroke fatigue and cardiorespiratory variables potentially affecting $\dot{V}O_2$ during exercise, such as the OUES, CO, and AVO_2diff. As a result, a higher FSS score was associated with a longer τCO at the onset of exercise. As we observed no demographic and clinical variables significantly correlated with the FSS score, $\tau\dot{V}O_2$, and τCO, this study indicated that the FSS score was associated with $\tau\dot{V}O_2$ and τCO independently of other participants' characteristics. Our findings suggest that the ability of the cardiorespiratory system to adapt to exercise is impaired in individuals with severe post-stroke fatigue.

Individuals with post-stroke fatigue lack the energy necessary to perform activities, are more easily tired by activity, experience unpredictable and unexplainable feelings of fatigue, and have increased stress sensitivity and increased need for longer sleep durations, naps, or rest [30]. Thus, it is plausible that post-stroke fatigue might be associated with decreased cardiorespiratory fitness and reduced physical activity [12,31]. A systematic review

reported that both post-stroke fatigue and reduced cardiorespiratory fitness were associated with low levels of physical activity in individuals with stroke [32]. However, no statistically significant correlation between the FSS score and $\dot{V}O_2$ at peak exercise has been shown in individuals with chronic stroke [15]. Therefore, based on the conceptual model of post-stroke fatigue that fatigue at the early stage after stroke may be attributed to biological factors [4], all participants in the present study were recruited from a subacute rehabilitation ward. However, our result regarding the association between the FSS score and $\dot{V}O_2$ at peak exercise is consistent with that in a previous study on chronic stroke [15]. To the best of our knowledge, this is the first study to investigate the association between post-stroke fatigue and $\tau\dot{V}O_2$ measured during the submaximal constant-load exercise test. We observed that the mean coefficient of determination of cardiorespiratory kinetics was >0.85, which indicates that the fitting procedures were acceptable [33]. The mean value of $\tau\dot{V}O_2$ in this study was similar to the value obtained in a previous study, which showed that individuals with stroke had a longer $\tau\dot{V}O_2$ than age-, sex-, and activity-matched healthy adults [16]. In healthy adults, the acceleration of $\tau\dot{V}O_2$ has been reported to occur in the early period of endurance training, and $\dot{V}O_2$ at peak exercise can subsequently increase [20,21]. Additionally, a previous study reported that $\tau\dot{V}O_2$ was shorter in the recreationally active group than in the inactive group; however, there was no significant difference in $\dot{V}O_2$ at peak exercise between the two groups [19]. These results of previous studies indicated that $\tau\dot{V}O_2$ was more sensitive than $\dot{V}O_2$ at

peak exercise in assessing cardiorespiratory functional changes, which may explain our results that a higher FSS score was significantly correlated with a longer $\tau\dot{V}O_2$ but not with $\dot{V}O_2$ at peak exercise.

We found that the mean ratio of τCO to $\tau\dot{V}O_2$ was >1.00, indicating that oxygen delivery was not in excess of the metabolic demand during exercise onset and that $\dot{V}O_2$ kinetics at exercise onset were limited by a delayed increase in CO [34]. These findings may explain the association between the FSS score and τCO observed in this study. Unfortunately, because there have been no published studies that measured τCO in individuals with stroke, it is unclear why participants with severe post-stroke fatigue showed a longer τCO. However, given that post-stroke fatigue is associated with low physical activity [32], an inactive lifestyle may lead to a longer τCO in individuals with severe fatigue. The prompt increase in CO at the onset of exercise is compatible with the notion of immediate vagal withdrawal. Capelli et al. [35] reported that the increase in CO at the onset of exercise became slower after than before prolonged bed rest in healthy adults because of the decreased vagal activity at rest and the elimination of vagal withdrawal during exercise. Individuals with stroke have been reported to show decreased vagal modulation [36,37]. In addition, reductions in cardiac mass and function, reduced plasma volume, and decreased venous return after prolonged bed rest [38-41] may also negatively affect the increase in CO during exercise onset. In the future, understanding the pathogenesis of a delayed increase in CO during exercise onset in

208 individuals with fatigue at the early stage after stroke can contribute to the development of an
209 appropriate rehabilitation program for these individuals.

210 Our findings suggest that individuals with severe post-stroke fatigue need to improve
211 $\tau\dot{V}O_2$ at the onset of exercise. Previous studies showed that aerobic exercise training was
212 effective in the improvement of $\tau\dot{V}O_2$ in older individuals [22,42,43]. In addition, a
213 randomised controlled trial reported that the combination of cognitive-behavioural therapy
214 and graded activity training was more effective than cognitive-behavioural therapy alone in
215 treating post-stroke fatigue [44]. Although post-stroke fatigue has a negative impact on the
216 recovery of activities of daily living [5,6], a systematic review reported that aerobic exercise
217 can improve the functional ability in individuals with stroke [11]. Furthermore, at the
218 subacute phase of stroke recovery, several articles demonstrate the effectiveness of exercise
219 in improving health outcomes after stroke including cardiovascular, functional, and mobility
220 outcomes [45,46]. Therefore, because fatigue is associated with low levels of daily activities
221 after stroke [32], rehabilitative exercise programmes may be beneficial in individuals with
222 post-stroke fatigue.

223 The use of exercise testing for the clinical assessment and exercise prescription is
224 limited in stroke rehabilitation settings [47,48], limiting the clinical applicability of our
225 findings. A lack of exercise equipment, time, space, and support staff have also been reported
226 as a barrier to exercise testing [47]. In addition, the cardiac, cognitive, functional, and

physical impairments in individuals with stroke may make it difficult to perform exercise testing safely [47]. More specific clinical guidelines for post-stroke exercise testing, educational training associated with exercise testing, and greater collaboration between stroke and cardiac rehabilitation teams can help implement exercise testing in stroke rehabilitation settings [47,48].

This study had some limitations. First, the sample size was relatively small, although it was determined based on a power analysis. The sum score of 36 or the average score of 4 was the cut-off value of the FSS score [2,49]. We could not examine whether the association between the FSS score and cardiorespiratory variables during exercise could differ between participants with and without post-stroke fatigue. In addition, although post-stroke fatigue has been reported to be associated with clinical variables, such as depressive symptoms and functional disability [1], these associations were not statistically significant. These results may be attributed to a relatively small sample size. Furthermore, we could not perform the subgroup analyses according to sex, the phase of stroke recovery, and the type of stroke of the participants. Being female has been reported to be associated with the presence of post-stroke fatigue and a longer $\tau\dot{V}O_2$ [1,50]. Changes in the brain after stroke may also affect post-stroke fatigue and cardiorespiratory control during exercise [1,51]. Even though our participants were recruited from a subacute rehabilitation ward, five participants were in the chronic phase of stroke recovery [27]. In addition, 12 participants with ischaemic stroke and 11 with

haemorrhagic stroke were included in this study. Functional recovery differs between individuals with ischaemic and haemorrhagic stroke. Stroke severity is higher in haemorrhagic stroke than in ischaemic stroke, while individuals with haemorrhagic stroke have been shown to have a higher therapeutic response to rehabilitation than those with ischaemic stroke [52,53]. This study demonstrated that sex, the time since stroke, and the type of stroke were not confounding variables in the associations of the FSS score with $\tau\dot{V}O_2$ and τCO. Nevertheless, further studies employing a stratified sampling method would increase the generalisability of our results.

Second, most participants were in the subacute phase of stroke recovery. Because fatigue present over 1 year after stroke may be more associated with psychological and behavioural factors than biological factors [4], the generalisation of our findings to individuals who are over 1 year after stroke should be made with caution. Third, many individuals with stroke (n = 424) were excluded from the study. Many of them were excluded due to being >80 years of age, a Mini-Mental State Examination score ≤24 points, and/or unstable medical conditions, as shown in Fig.1. This may limit the generalisability of our findings to individuals with these conditions. Finally, because this study used a cross-sectional observational design, the cardiorespiratory variables associated with temporal changes in post-stroke fatigue could not be examined. Thus, further longitudinal studies are needed to investigate the temporal association between post-stroke fatigue and

cardiorespiratory fitness variables.

In summary, a higher FSS score statistically significantly correlated with longer $\tau\dot{V}O_2$ at the onset of exercise measured during a submaximal constant-load exercise test, but not with $\dot{V}O_2$ at peak exercise obtained during a symptom-limited graded exercise test. In addition, a higher FSS score was associated with a longer τCO at the onset of exercise. These results suggest that the ability of the cardiorespiratory system to adapt to exercise is impaired in individuals with severe post-stroke fatigue. Collectively, our findings can contribute to the development of an appropriate rehabilitation program for individuals with post-stroke fatigue.

Methods

Study design

This study used a cross-sectional design. The study protocol was approved by the appropriate ethics committees of Tokyo Bay Rehabilitation Hospital (approval number, 172-2) and Shinshu University (approval number: 3813). All participants provided written informed consent before their enrolment in the study. The study was conducted according to the Declaration of Helsinki of 1964, as revised in 2013.

Participants

Participants were recruited from a subacute rehabilitation ward between November

2017 and March 2020. The inclusion criteria for the study were age 40–80 years, within 180 days of the initial stroke, ability to maintain a target cadence of 50 rpm during exercise, and a Mini-Mental State Examination score >24 [54]. Conversely, the exclusion criteria were limited range of motion and/or pain that could affect the exercise test; unstable medical conditions, such as unstable angina, uncontrolled hypertension, or tachycardia; the use of beta-blocker; and any comorbid neurological disorders. Demographic and clinical data, such as age and the type of stroke, were obtained from the patients' medical record.

Procedure

Data collection was completed within a week from the start of the procedure. On the first day, we assessed post-stroke fatigue, depressive symptoms, and functional outcomes. On the second day, participants performed a symptom-limited graded exercise test to determine the workload for their submaximal exercise test. On the third day, three repetitions of a submaximal constant-load exercise test were performed at 80% of the workload corresponding to the ventilatory threshold to assess the kinetics of cardiorespiratory variables [55].

Assessments of post-stroke fatigue, depressive symptoms, and functional outcomes

Post-stroke fatigue was assessed using the 9-item FSS [49], the most widely used

303 measure of post-stroke fatigue [2]. Each item was rated on a 7-point Likert scale that ranged
304 from 1 to 7 (1, strongly disagree; 7, strongly agree). The FSS score was calculated as the sum
305 of 9-item scores. A higher score indicated a large impact of fatigue on daily activities.
306 The 15-item Geriatric Depression Scale (GDS) [56] was used to assess depressive
307 symptoms. The presence of depressive symptoms was denoted by a GDS score ≥5 points.
308 The motor function and independency in performing daily activities were assessed as
309 functional outcomes. The total Stroke Impairment Assessment Set motor function score was
310 measured to assess motor impairments in the paretic upper and lower extremities [57]. The
311 Functional Independence Measure score was used to evaluate the degree of independence in
312 activities of daily living [58].
313
314 ***Exercise testing***
315 Participants were instructed to refrain from food consumption for 3 h, caffeine intake
316 for at least 6 h and vigorous physical activity for 24 h before the symptom-limited graded and
317 submaximal constant-load exercise tests [59]. These tests were performed on a recumbent
318 cycle ergometer (Strength Ergo 240; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan)
319 that could be precisely load-controlled (coefficient of variation, 5%) over a wide range of
320 pedalling resistance (0–400 W). Participants were instructed to maintain a target cadence of
321 50 rpm in all exercise phases [59]. Expired gas was measured on a breath-by-breath basis

during the exercise test using an expired gas analyser (Aerosonic AT-1100; ANIMA Corp., Tokyo, Japan). Before expired gas data collection, the analyser was calibrated using gas mixtures with accurately known concentrations of oxygen and carbon dioxide. CO was measured on a beat-by-beat basis using a noninvasive impedance cardiography device (Task Force Monitor model 3040i; CN Systems Medizintechnik GmbH., Graz, Austria), as previously described [60]. Three short band electrodes, one on the neck and two others below the thorax, were placed on participants. Stroke volume was calculated with the following equation:

$$\text{Stroke volume} = V_{th} \times \text{LVET} \times (dZ/dt)_{max}/Z_0$$

where V_{th} is the electrical participating thoracic volume, LVET is the left ventricular ejection time, $(dZ/dt)_{max}$ is the maximal rate of decrease in impedance for a given heartbeat, and Z_0 is the base impedance. CO was calculated as the product of stroke volume and heart rate. The impedance cardiography method is a valid and reliable method for measuring cardiac haemodynamics at rest and during exercise [60]. The measurement values of cardiorespiratory variables were interpolated to 1 s intervals, time-aligned, and averaged into 5 s bins to derive the AVO_2diff on a second-by-second basis [16,24], which was calculated as the ratio between $\dot{V}O_2$ and CO based on Fick's equation [61]:

$$\dot{V}O_2 = CO \times AVO_2\text{diff}.$$

All participants rested for 5 min before obtaining the measurements. The symptom-

limited graded exercise test started with a warm-up at 0 W for 3 min followed by a 10-W increment every minute [59]. The test was terminated if the participant showed signs of angina, dyspnoea, inability to maintain a cycling cadence of more than 40 rpm, hypertension (>250 mmHg systolic or >115 mmHg diastolic), or a drop in systolic blood pressure by >10 mmHg, despite the increase in workload [24]. To identify whether the maximal effort was reached during the exercise test, at least one of the following criteria had to be met: $\dot{V}O_2$ increased <150 $mL \cdot min^{-1}$ for >1 min despite increased work rate, respiratory exchange ratio >1.10, or heart rate achieved 85% of the age-predicted maximal heart rate calculated as 220 minus age [14]. $\dot{V}O_2$, CO, AVO_2diff, $\dot{V}E$, and respiratory exchange ratio at peak exercise were defined as the average value obtained during the last 30 s of the exercise test [59]. In addition, the OUES was determined by calculating the slope of the regression line between $\dot{V}O_2$ and the log transformation of $\dot{V}E$ during the whole exercise period using the following equation:

$$\dot{V}O_2 = a \log\dot{V}E + b$$

where the constant *a* is the OUES [62]. A low OUES represents a higher amount of ventilation required in response to a given oxygen uptake, which indicates ventilatory inefficiency during exercise.

The ventilatory threshold was determined using a combination of the following criteria: the point where the ventilatory equivalent of oxygen reaches its minimum or starts to

increase, without an increase in the ventilatory equivalent of carbon dioxide; the point at which the end-tidal oxygen fraction reaches a minimum or starts to increase, without a decline in the end-tidal carbon dioxide fraction; and the point of deflection of carbon dioxide output versus $\dot{V}O_2$ (the V-slope method), as previously described [24,63]. $\dot{V}O_2$, CO, AVO_2diff, $\dot{V}E$, and respiratory exchange ratio at the ventilatory threshold were obtained.

The submaximal constant-load exercise test started with resting on the cycle ergometer for 3 min, followed by performing exercise at 80% of the workload corresponding to the ventilatory threshold for 6 min [19,34]. The protocol was repeated three times, with a rest between each repetition. The kinetics of the $\dot{V}O_2$, CO, AVO_2diff, and $\dot{V}E$ data at the onset of exercise were obtained by averaging the three repeats. Additionally, before modelling, the first 20 s of data after the onset of the exercise was eliminated, as during this period, the increase in $\dot{V}O_2$ reflects merely an increase in the pulmonary blood flow rather than changes in tissue gas exchange [18]. To calculate the time constants of $\dot{V}O_2$, CO, AVO_2diff, and $\dot{V}E$ at the onset of exercise, a non-linear least squares regression procedure (GraphPad Prism version 7.00 for Windows; GraphPad Software, CA, USA) was applied to the onset phase, using the following formula:

$$Y(t) = Y_{baseline} + (Y_{steady\text{-}state} - Y_{baseline}) * (1 - \exp^{-(t - TD)/\tau})$$

where Y (t) represents $\dot{V}O_2$, CO, AVO_2diff, or $\dot{V}E$ at a given time (t); TD is the time delay; and τ is the time constant. $Y_{baseline}$ and $Y_{steady\text{-}state}$ were defined as the average values of Y

379 during the last minute of the resting period and exercise, respectively. Fit quality was
380 determined by the coefficient of determination. The fitting procedure was considered
381 acceptable if the coefficient of determination was >0.85 [33]. In addition, the ratio of τCO to
382 $\tau\dot{V}O_2$ >1.00 indicated a slow increase in CO relative to $\dot{V}O_2$ at the onset of exercise.
383
384 **Statistical analyses**
385 The sample size for correlational analysis was computed for 0.05 alpha, 0.80 power,
386 and 0.50 estimated effect size (large) [15] with G Power software version 3.1.9.2 (Heinrich
387 Heine University, Dusseldorf, Germany). Consequently, a minimum sample size of 26
388 participants was required. Assuming 10% of the participants could be excluded, we aimed to
389 recruit 30 participants.
390 The results are shown as medians (interquartile ranges) or means ± SDs. We
391 examined the associations between the FSS score and cardiorespiratory variables measured
392 during the exercise tests using the Spearman's rank correlation coefficient. To identify the
393 potentially confounding variables, we also determined the associations of participants'
394 characteristics with the FSS score and cardiorespiratory variables that significantly correlated
395 with the FSS score using the Pearson's product-moment correlation coefficient, the
396 Spearman's rank correlation coefficient, and the unpaired t-test based on variable types.
397 Statistical analyses were performed with R version 3.2.2 (R Foundation for Statistical

Computing, Vienna, Austria). Poisson (p) values <0.05 were considered statistically significant.

Data availability

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

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Author contributions

KO conceptualised and designed the study, carried out the data analysis and interpretation, and drafted the submitted article. YB, YS, JM, AM, YI, and HA designed the study, coordinated subject recruitment, and performed data collection. YO and KK designed the study, carried out the data analysis and interpretation, and revised the final version. KM conceptualised and designed the study, carried out the data analysis and interpretation, and revised the final version. All authors approved the final version.

Competing interests

The authors declare no competing interests.

610 **Figure legends**

611

612 **Figure 1.** Flow diagram of study participants. MMSE, Mini-Mental State Examination.

613

614 **Figure 2.** Correlations of the Fatigue Severity Scale score with (a) oxygen uptake at peak

615 exercise and (b) the time constant of oxygen uptake kinetics.

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617 **Figure 3.** Correlations of the Fatigue Severity Scale score and the time constant of cardiac

618 output kinetics.

Figures

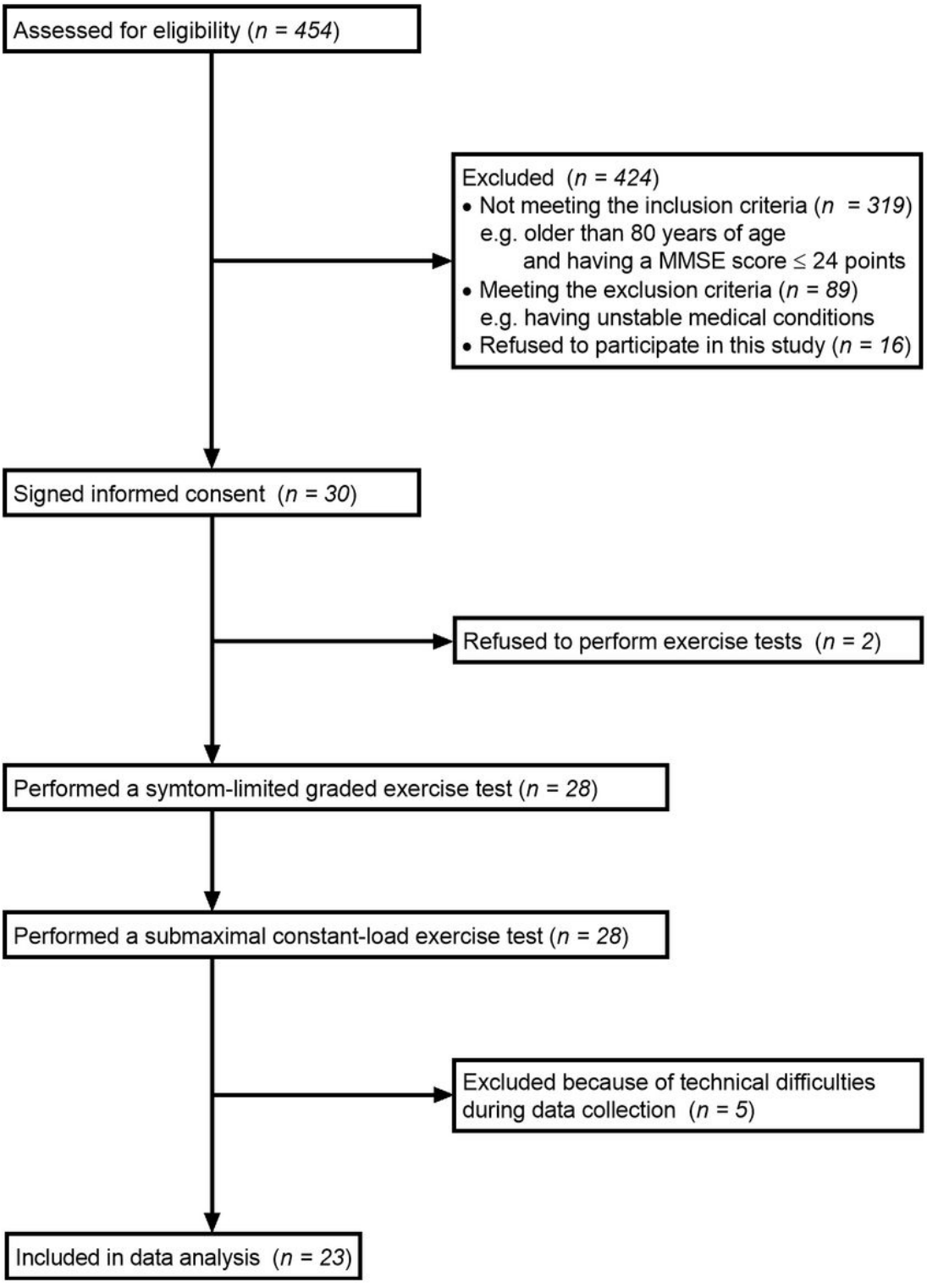

Figure 1

Flow diagram of study participants. MMSE, Mini-Mental State Examination.

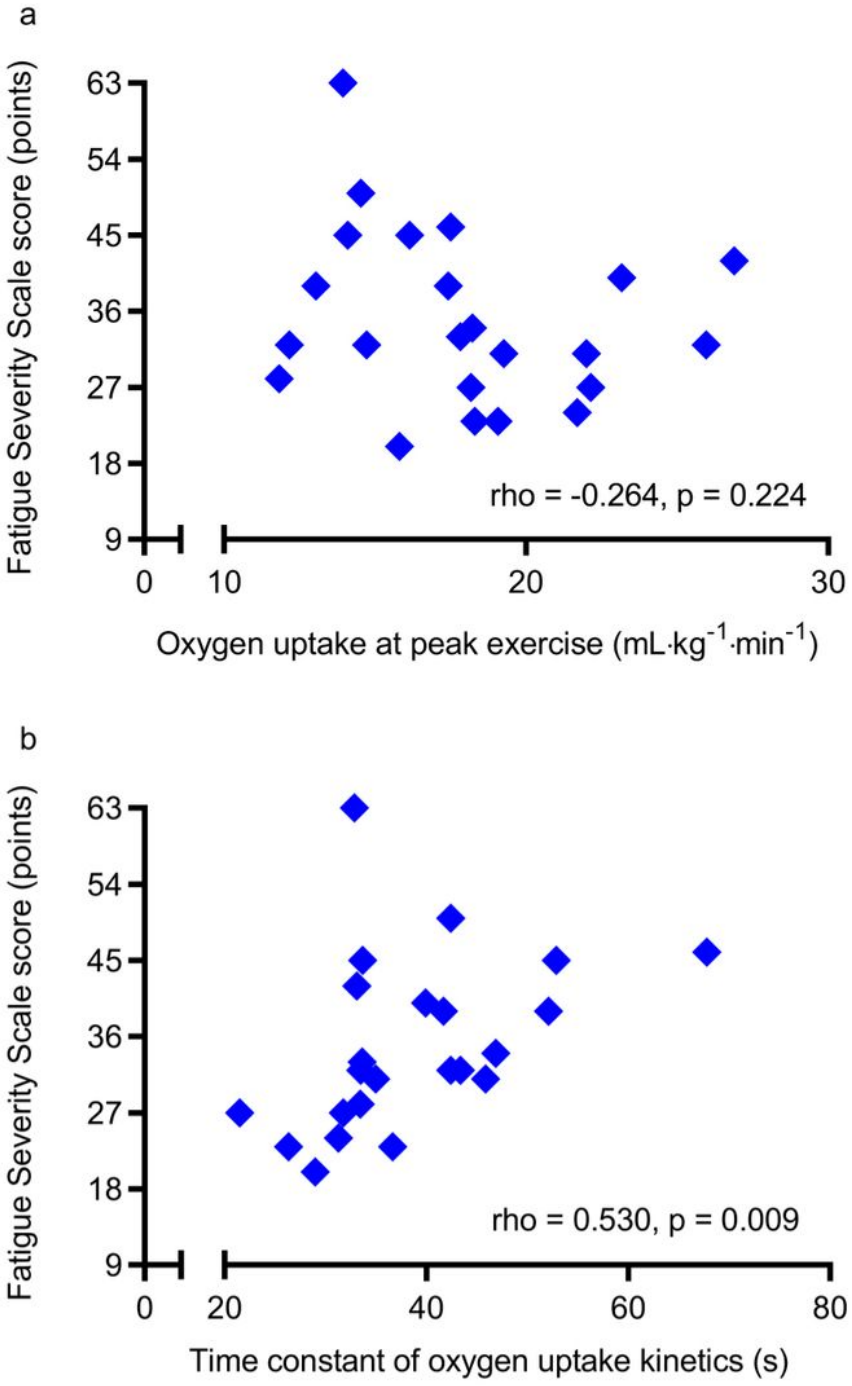

Figure 2

Correlations of the Fatigue Severity Scale score with (a) oxygen uptake at peak exercise and (b) the time constant of oxygen uptake kinetics.

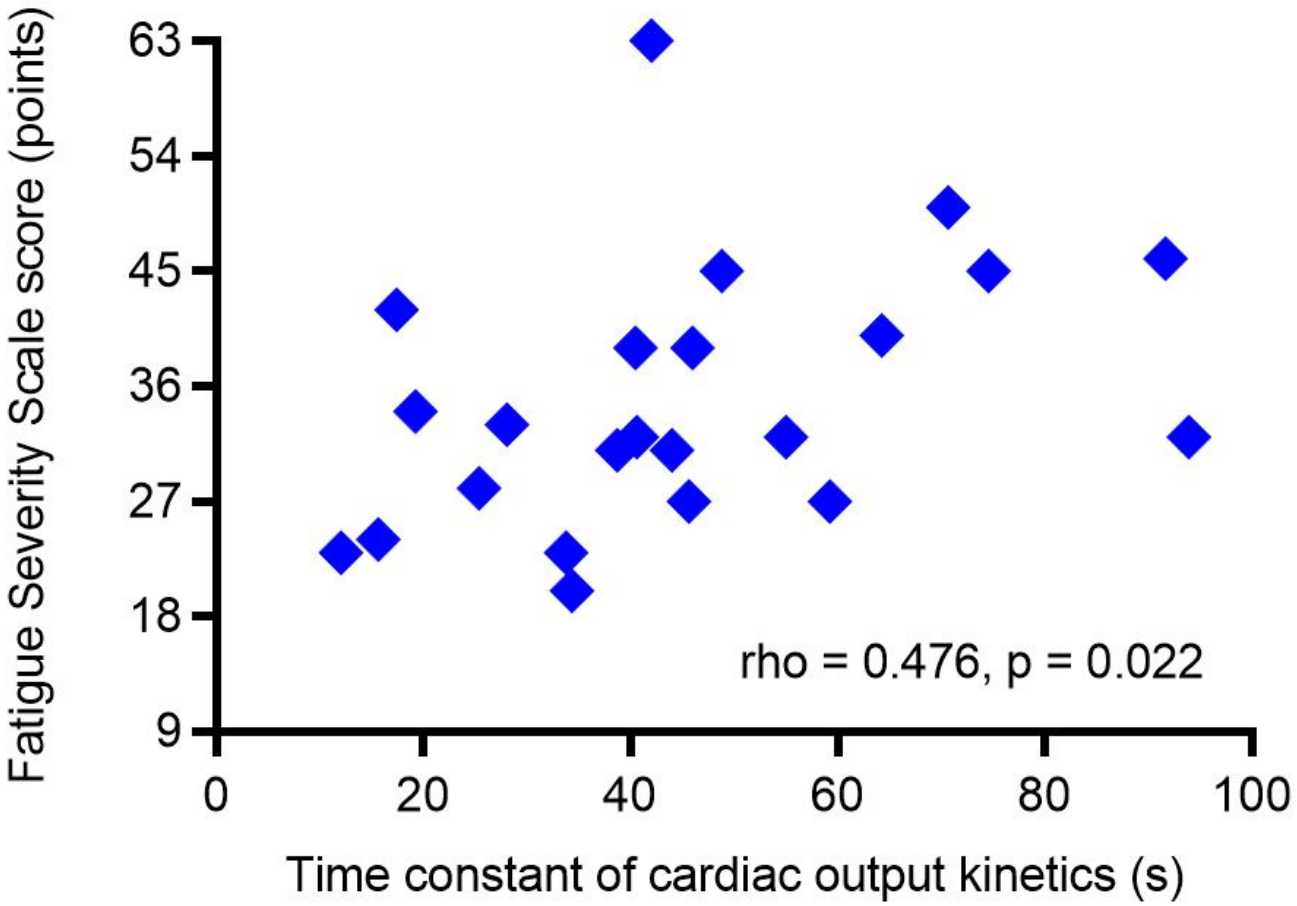

Figure 3

Correlations of the Fatigue Severity Scale score and the time constant of cardiac output kinetics.

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