



Should I stay or should I go now? Recovery time effect on walking capacity in symptomatic peripheral artery disease

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1 **“Should I stay or should I go now?”**

2 **Recovery time effect on walking capacity in symptomatic peripheral artery disease**

4 **Short title:** Recovery time and walking capacity in PAD

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33 **Conflict of interest**

34 The authors declare no conflict of interest.

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40

41 **ABSTRACT**

42 **Objective:** To investigate the effect of recovery time on walking capacity (WC) throughout
43 repeated maximal walking bouts in symptomatic lower extremity peripheral artery disease
44 (PAD).

45 **Methods:** The effect of recovery time on WC (maximal walking time) was determined in 21
46 participants with PAD in three experimental conditions (recovery time from 0.5-9.5 min + a
47 self-selected recovery time [SSRT]): (i) 11 repeated sequences of two treadmill walking
48 bouts (TW-ISO); (ii) a single sequence of seven treadmill walking bouts (TW-CONS); (iii) a
49 single sequence of seven outdoor walking bouts (OW-CONS). Exercise transcutaneous
50 oxygen pressure changes were continuously recorded as an indirect measure of ischemia. An
51 individual recovery time (IRT) beyond which WC did not substantially increase was
52 determined in participants with a logarithmic fit.

53 **Results:** At the group level, mixed models showed a significant effect ($P<0.001$) of recovery
54 time on WC restoration. At the participant level, strong logarithmic relationships were found
55 (median significant $R^2\geq 0.78$). The median SSRT corresponded to a median work-to-rest ratio
56 $>1:1$ (i.e., a lower recovery time in view of the corresponding previous walking time) and
57 was related to unrecovered ischemia and a WC restoration level of $<80\%$. A median work-to-
58 rest ratio of $\leq 1:2$ allowed full recovery of ischemia and full restoration of WC. The IRT ratio
59 was between 1:1 and 1:2 and corresponded to the start of recovery from ischemia.

60 **Conclusion:** Recovery time affects the restoration level of WC during repeated maximal
61 walking bouts in symptomatic PAD. Meaningful variations in WC restoration were related to
62 specific levels of work-to-rest ratios.

63

64 **Key Words:** intermittent claudication, ischemia, walking, exercise, work-to-rest ratio,
65 exercise therapy.

66 **NEW & NOTEWORTHY**

67 This study demonstrated there is a significant and mostly logarithmic effect of recovery time
68 on walking capacity in people with symptomatic PAD. This study revealed that a median
69 work-to-rest ratio $>1:1$ leads to the resumption of walking with unrecovered ischemia and
70 precludes the restoration of full walking capacity, whereas a work-to-rest ratio $\leq 1:2$ allowed
71 walking capacity to fully be restored.

72 INTRODUCTION

73 Lower extremity peripheral artery disease (PAD) accounts for a considerable public health
74 burden, with more than 236 million people aged ≥ 25 years living with PAD worldwide (49).
75 Lower-limb pain during walking, caused by ischemia in active muscles (50), leads to an
76 impaired walking capacity (15), which decreases quality of life compared with that in people
77 without PAD (46) and independently predicts mortality (32). Supervised, or, when not
78 available, home-based or community-based walking programs are recommended as the first-
79 line therapy to improve functional status and quality of life and to reduce leg symptoms in
80 people with PAD (22).

81

82 The optimal exercise regimen for walking programs for people with PAD has been published
83 in several authoritative scientific reports (3, 4, 52). However, the current recommendations
84 fail to provide clear indications regarding the optimal work-to-rest ratio that should be
85 prescribed (6, 22, 52). This missing information is directly related to the fact that the
86 recovery pattern and the variation in walking performance throughout repeated walking bouts
87 limited by pain-related ischemia, either in treadmill or outdoor walking conditions, have
88 never been studied. Interestingly, from global positioning system (GPS) measurements, we
89 previously observed that the stop duration between two pain-limited walking bouts could be
90 inversely associated with the walking capacity of people with PAD during an outdoor
91 walking session including multiple walking bouts (31). While this previous study provided
92 some insights into the potential effect that recovery time (RT) may have on walking capacity,
93 to our knowledge, no studies have experimentally or systematically determined whether and
94 how RT predicts the walking capacity of people with PAD during repeated treadmill or
95 outdoor walking bouts.

96

97 Thus, the first aim of the present study was to determine the effect of RT on walking capacity
98 in people with symptomatic PAD throughout repeated walking bouts performed up to
99 maximal claudication pain, during both treadmill and outdoor walking conditions. Such an
100 approach is a preliminary and required step before implementing and testing future walking
101 training protocols that could be optimized based on different work-to-rest ratio strategies. We
102 hypothesized here that RT would predict the walking capacity through either a logarithmic or
103 a linear relationship (31). Furthermore, from these relationships, together with the study of
104 the time course of ischemia during recovery, a second aim was to explore the possibility of
105 identifying specific levels of work-to-rest ratios that would be associated with meaningful
106 variations in terms of walking capacity restoration.

METHODS

Study design

The CLASH protocol is a cross-sectional study that was approved by our local ethics committee (CPP OUEST V, Rennes, France) and registered with the American National Institutes of Health database under reference No. NCT02041169.

Participants were initially referred by their physician or angiologist to our Vascular Medicine Unit (University Hospital, Rennes, France) for a treadmill evaluation of walking capacity. After screening, they were invited to participate in the study if they fulfilled the inclusion criteria (Table 1). All included participants provided their written informed consent to participate. Then, within a ~1-month period, the included participants with PAD first underwent an inclusion visit followed by a 7-day free-living measurement of physical activity using wearable monitors (not reported here; see Chaudru et al. (7)). Thereafter, the participants were underwent testing in the three distinct experimental conditions described in Figure 1.

Inclusion visit

Physical characteristics, cardiovascular risk factors, comorbid conditions, claudication history and the list of current medications were obtained through the medical history and medical reports. Participants were asked to estimate the distance they could walk at the usual pace on a flat surface until lower-limb pain forced them to stop. Self-reported ambulatory walking impairment was also assessed using the walking impairment questionnaire (WIQ) (37). Quality of life was evaluated using the SF-36 questionnaire (33). Lower-limb symptoms were assessed and classified using the San Diego claudication questionnaire (9). The resting ankle brachial index (ABI) was measured using a handheld Doppler probe according to the recommendations of the American Heart Association (1). Then, participants with PAD

performed a Gardner-Skinner treadmill test (3.2 km/h, 0% grade with a 2% increase every 2 min) until maximal claudication pain.

Experimental conditions

Procedures. The effect of RT on walking capacity was investigated using three distinct experimental conditions (Figure 1): (i) isolated sequences of treadmill maximal walking bouts (TW-ISO); (ii) consecutive treadmill maximal walking bouts (TW-CONS); and (iii) consecutive outdoor maximal walking bouts (OW-CONS). Furthermore, to assess the outdoor walking capacity of the participants with PAD without controlling the effect of RT, participants performed another outdoor walking session on another day, as previously reported (29, 31).

For the three experimental conditions, the aim was to determine the effect of RT on walking capacity by manipulating the RT following an ischemia-limited walking bout and by measuring the walking time of the subsequent walking bout performed up to maximal claudication pain. The fixed RTs tested were <10 min, which was consistent with the definition of intermittent claudication (8) and previous observation during outdoor walking (23). In addition to fixed RTs, each experimental condition included a self-selected RT (SSRT) where each participant was asked to resume the walk once he/she felt it was possible, as he/she would have done in daily life. Furthermore, for all walking bouts in the three experimental conditions, we required participants to walk to maximal claudication to make the level of ischemia reached more comparable (at the maximal endpoint). The specific rationale and protocol for each condition are as follows:

(i) *TW-ISO.* To isolate, as much as possible, the potential effect of RT on treadmill walking capacity, participants performed 11 separated sequences of treadmill walking (Figure 1). A sequence included two walking bouts (3.2 km/h, 12% grade) until

maximal claudication pain, interspersed by a given RT (between 0.5 and 9.5 min; or SSRT). No more than three sequences were performed during a session, and they were separated by ≥ 15 min of recovery to retrieve baseline values of oxygen uptake ($\dot{V}O_2$) and transcutaneous oxygen pressure changes (TcPO₂). The 11 sequences were randomly spread over four sessions on four different days (3 sessions with 3 sequences and 1 session with 2 sequences).

(ii) *TW-CONS*. The rationale here was to assess the potential effect of RT on walking capacity through a series of consecutive walking bouts, thereby moving toward what was previously observed during outdoor walking in PAD (31). Thus, during one single session, participants performed seven consecutive treadmill walking bouts (3.2 km/h, 12% grade) up to maximal claudication pain, interspersed by six RTs (between 0.5 and 8.5 min; or SSRT).

(iii) *OW-CONS*. The rationale here was close to that explained for TW-CONS except that here, we aimed to reproduce the walking pattern of people with PAD under “natural” outdoor walking conditions, as encountered while walking during daily life (31) or during outdoor walking sessions of a home-based walking program (16). Thus, during a single session, participants performed seven consecutive outdoor (athletic track; 0% grade) walking bouts up to maximal claudication pain, interspersed by six RTs (between 0.5 and 4.5 min; or SSRT). Consistent with previous observation (23), RTs were intentionally shorter than those for TW-ISO and TW-CONS. Participants were asked to walk at their usual walking speed and to stop walking only due to maximal claudication pain. The outdoor walking session was supervised by two investigators who walked approximately 10 meters behind the participant and controlled the RTs.

181 *Randomization.* The order of the experimental conditions was randomized, with the two
182 outdoor walking sessions performed consecutively. All walking sessions were separated by at
183 least 48 hours. Within each experimental condition, the RTs were also randomized, and
184 participants were blinded to the RTs tested.

186 **Instrumentation & measurement**

187 *Treadmill walking.* Participants were blinded to the distance and time walked. Participants
188 were permitted to touch the handrail of the treadmill using their hands or fingers only to
189 maintain balance. Moreover, they were asked to orally indicate to the investigator the
190 claudication pain score they reached during both walking and recovery based on a 5-point
191 scale (0 = no pain; 1 = onset of pain; 2 = moderate pain; 3 = intense pain; 4 = maximal pain)
192 (3). The treadmill walking bouts were stopped when maximal claudication pain was reached.
193 During each recovery bout, the participants were asked about the localization of the lower-
194 limb pain.

195 *Cardiorespiratory variables.* Gas exchange and heart rate (HR) were measured during the
196 Gardner-Skinner treadmill test and all the experimental conditions. A metabolic cart
197 (MasterScreen CPX [MSCPX], Jaeger®, Germany) was used during treadmill walking, and a
198 portable metabolic system (K4b², Cosmed®, Italy) was used during outdoor walking. For
199 measuring HR, the MSCPX used a 12-lead electrocardiogram, while the K4b² used a Polar®
200 belt. The systems were calibrated according to the manufacturer's instructions before each
201 walking session.

202 *Exercise transcutaneous oxygen pressure (Exercise-TcPO₂).* Exercise-TcPO₂ was
203 continuously measured during the Gardner-Skinner treadmill test and the treadmill sessions.
204 Measurements were performed using five probes positioned on the chest, the two buttocks,

and the two calves, as previously described (35, 44). Exercise-TcPO₂ was used as an indirect measure of exercise-induced ischemia (2, 51).

Outdoor walking. For the two outdoor walking sessions, the participants were also equipped with a set of physical activity monitors (not reported here; see Chaudru et al. (7)), including a DG100 GPS receiver (GlobalSat®, Taiwan) (41), which was used to obtain walking times and distances, and a digital watch, which allowed the participant to indicate when pain occurred during walking (7). The walking times and distances were obtained from the walking bouts that were detected using the GPS speed signals along with a validated data processing methodology (30, 41). During the walking session, using a chronometer, the investigators reported the time when the participant pressed the marker button on the watch to indicate the occurrence of pain (the watch data were not used in the present study, see Chaudru et al. (7)).

Data analysis

Questionnaire outcomes. The responses to the WIQ and SF-36 questionnaires were recorded in a spreadsheet and were scored following the recommended procedures (9, 33, 37).

Walking capacity outcomes. For each treadmill walking bout, we computed the pain-free walking times (PFWTs) and the maximal walking times (MWTs). From each outdoor walking bout, the PFWT was the duration measured by the investigators, using the chronometer, from the start of the walking bout to the moment where the participant indicated the occurrence of pain using the watch provided for this purpose (7). The MWT was the duration of the maximal walking bout detected using the GPS as previously reported (7, 29).

Physiological outcomes. Oxygen uptake ($\dot{V}O_2$) and HR data were time-averaged to 5-s intervals. Data obtained during the experimental conditions are expressed as percentages of

peak $\dot{V}O_2$ ($\%\dot{V}O_{2peak}$) and HR ($\%HR_{peak}$). Since peak physiological variables can exhibit some variability, $\dot{V}O_{2peak}$ and HR_{peak} were the highest 15-s average values of $\dot{V}O_2$ and HR measured throughout the entire study protocol, respectively. We used an unpublished treadmill equation to make the $\dot{V}O_2$ data measured with the K4b² comparable with the MSCPX $\dot{V}O_2$ data. Indeed, our unpublished data showed that the K4b² overestimated $\dot{V}O_2$ compared with the MSCPX. The protocol and associated results, including the correction equation, are detailed in Supplemental Digital Content 1.

For the Exercise-TcPO₂ measurement, the delta values from the resting oxygen pressure (DROP) values (in mmHg) at each site were computed every 2.5 s as the changes in TcPO₂ from the 2-min resting mean value preceding the series of walking bouts minus the corresponding absolute change in TcPO₂ recorded at the chest (35, 44).

For all experimental conditions, end-walking and end-recovery physiological values were computed by averaging the last three-time intervals of the period. All these calculations were performed using Excel® (Microsoft®, Richmond, VA) spreadsheets.

Statistical analysis

All statistical analyses were performed using R software (45). The normality of continuous variables was assessed using the Shapiro-Wilk test. The mean and standard deviation (SD) were used when the data followed a normal distribution; otherwise, medians and 25th – 75th percentiles were used. The effects and differences tested during the statistical analysis were considered significant when $P \leq 0.05$.

Effect of RT on walking capacity. To test the hypothesis that RT would predict walking capacity, for each experimental condition, we first built linear mixed models at the group level, followed by models for each participant. In both cases, the response variable was the ratio of MWT performed after a given RT (MWT_n) divided by the first MWT of the sequence

(MWT₁), and the explanatory variable was either (i) the RT (x) or (ii) the logarithm of RT (ln(x)). The MWT_n/MWT₁ ratio was considered as the restoration level of the MWT of the participants. The use of a logarithm model was motivated by previous observation of the association of RT and walking capacity during outdoor walking sessions (31). At both the group and participant (individual) levels, data related to SSRT were not included in the models. In addition, for both the TW-CONS and OW-CONS conditions, we calculated the cumulated time of walking (from the beginning of the session) as an indirect estimate of fatigue (31). Then, at the group level, from the best model (using RT (x) or RT (ln(x))) obtained, we performed a step-by-step multivariate linear regression analysis with stepwise selection to determine whether the addition of the cumulated time could also be a predictor of the walking capacity. For OW-CONS, we also tested the potential effect of adding the walking speed in the multivariate analysis (31). Furthermore, at the individual level, the potential associations between walking capacity and each of these potential predictors were also investigated separately using correlation analyses. For this purpose, to take into account possible multicollinearity effects, significant associations between the cumulated time or walking speed (independent variables) and walking capacity were not considered if a correlation also existed between the independent variable tested and RT. R² coefficients for all models, root-mean-squared error (RMSE) for the mixed models, and standard error of estimate (SEE) for individual models were calculated to assess the goodness of fit and accuracy of the models.

Determination of an individual RT (IRT). For each experimental condition in participants who exhibited a plausible logarithmic effect of RT on MWT_n/MWT₁ (i.e., with $P \leq 0.05$ for the slope and $R^2_{\ln(x)} > R^2_x$), we investigated the presence of a possible *IRT* that could enable these participants to “maximize” their walking capacity after a symptom-limited walking bout. Conceptually, below the IRT, a small increase in RT should substantially increase the

MWT. Conversely, with an RT greater than the IRT, the MWT should increase much more slowly despite an important increase in RT. The IRT would be close to the breakpoint between the two lines of distinct slopes that fit the logarithmic curve related to the participant data. Thus, to determine the IRT for each experimental condition, we used the segmented linear regression model developed by Muggeo (39). This model assumes that the relationship between the response variable (i.e., MWT_n/MWT_1) and the explanatory variable (i.e., RT) is piecewise linear. In other words, we considered two linear models separated by a breakpoint, and the IRT corresponded to the estimator of this breakpoint. An example illustrating the procedure implemented to determine the IRT in one participant is shown in Figure 2.

Among the participants who exhibited a plausible linear effect of RT on MWT_n/MWT_1 (i.e., with $P \leq 0.05$ for the slope and $R^2_x > R^2_{\ln(x)}$), IRT was assigned to the participants with the highest RT tested in the considered experimental condition, assuming a possible underestimation of the IRT. The participants who did not exhibit a significant effect of RT on MWT_n/MWT_1 were not considered for the determination of IRT.

For each treadmill condition, the time needed to reach a pain level of “0”, SSRT, and IRT were compared using a Friedman test. If significant, pairwise comparisons were performed using two-sided Wilcoxon signed rank tests with P value adjustment (Bonferroni correction). For the TW-ISO and TW-CONS conditions, the values used for the time needed to reach a pain level of “0” were the participant averages of the times measured during the corresponding conditions (this time was not measured during the OW-CONS condition). In the OW-CONS condition, SSRT and IRT were compared using a two-sided Wilcoxon signed rank test.

For each RT in each condition and based on participants in whom there was a plausible logarithmic or linear effect of RT on walking capacity, we calculated the corresponding

304 median work-to-rest ratio. This ratio was first calculated by dividing the considered RT by
305 the previous MWT of the participant and then by taking the median of the participant ratios.
306 *Comparison of the restoration levels of walking capacity and physiological values between*
307 *the RTs tested.* For each experimental condition, we investigated the RTs for which the
308 $PFWT_n/PFWT_1$ and MWT_n/MWT_1 ratios, as well as the end-recovery $\% \dot{V}O_{2peak}$, $\%HR_{peak}$,
309 and ischemia levels, were likely to no longer change. For this purpose, pairwise comparisons
310 between two successive RTs were performed using a one-sided Wilcoxon signed rank test.
311 All calculations were performed using the participants who exhibited either a linear or
312 logarithmic effect of RT on walking capacity associated with a P value of ≤ 0.05 for the slope.

RESULTS

Twenty-three participants with PAD were initially included in the study, but two were excluded before the end of the study. One participant was excluded due to a need for medical treatment modification, and another participant stopped participating to undergo a surgical intervention. Thus, data from 21 participants were analyzed in the present study. The participants' characteristics are shown in Table 2. Participants were mainly older, overweight, Caucasian men with a resting ABI indicating a mild-to-moderate PAD severity (0.67 ± 0.17). All participants were limited by exertional lower-limb symptoms during the Gardner-Skinner test at the inclusion visit.

Effect of RT on walking capacity

A total of 742 walking bouts were performed ($n=462$ for TW-ISO; $n=146$ for TW-CONS; $n=134$ for OW-CONS). All 21 participants completed the 11 sequences of the TW-ISO condition. For the TW-CONS condition, one participant was unable to complete the last walking bout of the session (that would have followed the SSRT) because of fatigue. For the OW-CONS condition, one participant was not pain-limited (no RT tested), and three other participants did not perform their two last maximal walking bouts because the duration of the walking session would have exceeded the *a priori* fixed 1-h limit. The mean (\pm SD) of the session mean speed was 4.4 ± 0.4 km/h.

Linear mixed models testing the effect of RT on the MWT_n/MWT_1 ratio at the group level are shown in Table 3. Regardless of the model tested and the experimental conditions, the RT significantly predicted the MWT_n/MWT_1 ratio ($P<0.001$). Although the explained variance remained quite low (R^2 between 0.19 and 0.45), a greater R^2 was obtained using the logarithm of the RT as the explanatory variable. Furthermore, neither the cumulated time (TW-CONS & OW-CONS) nor the walking speed (OW-CONS) was found to be a predictor

338 of walking capacity ($P>0.05$). At the individual level (Table 4), the effect of RT on walking
 339 capacity (MWT_n/MWT_1) was significant in most participants ($\geq 70\%$) regardless of the
 340 condition tested, and this effect was logarithmic rather than linear in most cases ($n=16/21$,
 341 $16/21$ and $11/21$ for TW-ISO, TW-CONS and OW-CONS, respectively). For participants
 342 who exhibited a logarithmic effect, the median R^2 was high (0.80) in the TW-ISO condition
 343 to very high (>0.90) in the TW-CONS and OW-CONS conditions. For TW-CONS, a
 344 significant negative association ($P=0.011$) between walking capacity and cumulated time was
 345 found in only one participant who otherwise did not show an effect of RT.

346 The effect of RT on walking capacity in each of the three experimental conditions is
 347 illustrated in Figure 2. As shown, during TW-ISO, the MWT tended to be fully (100%)
 348 restored from 4.5 min of recovery (91.4% [86.7– 105.4]). During TW-CONS, the MWT
 349 tended to be fully restored from 6.5 min (88.2% [75.6 – 96.9]). We observed that during the
 350 outdoor walking condition, most of the participants (9/14) were unable to restore $\geq 80\%$ of
 351 their MWT after 4.5 min of recovery, whereas this was less often the case during treadmill
 352 walking conditions (3/18 for TW-ISO, 7/17 for TW-CONS). When observing the PFWT, the
 353 relationship between the percentage of the restored PFWT and the RT presented a sigmoidal
 354 shape, as several participants still had pain when they resumed walking after short RTs,
 355 particularly in the OW-CONS condition.

356 Figure 2 also shows how the physiological parameters were recovered at the end of each of
 357 the RTs tested. The main observation was that the percentages of peak $\dot{V}O_2$ and peak HR
 358 exponentially decreased as the RT increased. Interestingly, the recovery of DROP values
 359 followed a sigmoidal shape as a function of RT. Values were the lowest and the response was
 360 blunted until 2.5 min of recovery, whereas the MWT_n/MWT_1 ratio increased over the same
 361 period in both treadmill conditions ($P\leq 0.001$). Thereafter, DROP values increased with RT
 362 ≥ 3.5 min ($P<0.05$) and finally reached a plateau from 5.5 min in TW-ISO (-0.2 mmHg [-7.9 –

1.4]) and from 6.5 min in TW-CONS (-2.3 mmHg [-8.7 – 0.8], with a low increase up to 8.5 min), indicating full recovery in terms of ischemia. This time needed for full recovery of ischemia was close to that needed for restoring 100% of the MWT (Figure 3).

SSRT and IRT

For treadmill conditions, the SSRT was not significantly different from the time needed to reach a pain level of “0” ($P=1.000$), and both were lower than IRT ($P<0.001$), as illustrated in Figure 2. In contrast, for the outdoor condition, the SSRT and IRT were not significantly different ($P=0.391$).

Figure 3 also displays how SSRT and IRT matched the restoration of both MWT and ischemia (DROP values) during the treadmill conditions. As shown, the median SSRT matched the time period during which DROP values were the lowest and the response was blunted (i.e., maximal ischemia), allowing only a restoration of MWT below 80% in both the TW-ISO and TW-CONS conditions. The median IRT matched the time from which DROP values started to increase (i.e., ischemia decrease), allowing a restoration of MWT to >90% in TW-ISO and between 78% and 86% in TW-CONS. Finally, when expressing the RTs tested in terms of work-to-rest ratios, it was observed that a median work-to-rest ratio $\geq 1:1$ did not enable the participants with PAD to start to recover from ischemia (Figure 3), while MWT started to be restored. As shown in Figure 3, the median SSRT was above this threshold of a work-to-rest ratio of 1:1. Conversely, a median work-to-rest ratio of $\leq 1:2$ seemed to be necessary to enable the participants to fully recover from ischemia and restore ~100% of their MWT. In terms of the work-to-rest ratio, the median IRT was between 1:1 and 1:2 and corresponded to an ischemia that started to decrease and to a restoration of MWT to nearly 90% in TW-ISO and nearly 80% in TW-CONS.

DISCUSSION

To our knowledge, the present study is the first to experimentally investigate and demonstrate the effect of RT on walking capacity in people with PAD and to describe the association of RT with ischemic changes in the symptomatic lower limb. There were two main findings. First, by experimentally manipulating the RT, we showed that RT significantly predicts the walking capacity in people with PAD, highlighting two different profiles over the range of the RTs tested (<10 min): a logarithmic profile (for most participants) and a linear profile. The second main finding was the identification of specific levels of work-to-rest ratios that were associated with different levels of MWT restoration.

Effect of RT on ischemia recovery and walking capacity restoration

Most of the participants with PAD exhibited a logarithmic effect of RT on walking capacity and were unable to recover 100% of their walking capacity until ischemia was fully resolved. This finding is consistent with the fact that ischemia impairs force development and thus muscle performance via factor(s) related to blood flow and that are dependent or independent of O₂ delivery (27, 43). Furthermore, we found that the ischemia level at the end of the recovery was linked to the RT by a sigmoidal relationship due to a blunted response of ischemia for short RTs. This result suggests that a minimal time of recovery is needed at the symptomatic lower extremity (muscle) level for the initiation of recovery from ischemia. Nonetheless, the fact that the walking capacity started to recover at 40-50%, even after 0.5 min of recovery while the end-recovery ischemia response was blunted for up to 2.5 min during recovery, suggests that the restoration of walking capacity seems independent of underlying ischemia, at least during the first 2 to 3 min of recovery. This result is consistent with that in a previous study that showed that although the peak forces of forearm muscles during an isometric hand-grip exercise declined more when blood flow was mechanically

occluded than during a normally perfused condition, the peak force restoration rate during recovery was rapid, starting as early as 0.5 min of recovery and ending by 5 min of recovery (43). Although phosphocreatine recovery from exercise is impaired in people with PAD compared to healthy subjects (28), the initial recovery of walking capacity under ischemia could be at least partially explained by a rapid (although incomplete) resynthesis of high-energy phosphate stores of the anaerobic fibers that support the energy demands of the ischemic musculature while walking is resumed (21, 43). However, it should be considered that the pattern of $TcPO_2$ changes during recovery is delayed with respect to that of other hemodynamic variables related to ischemia, i.e. systolic ankle pressure or ankle-to-brachial index (18, 21). Consequently, it cannot be excluded that ischemia at the muscle level started to resolve sooner than the $TcPO_2$ at the skin level. Of note, the blunting response of ischemia during the first few minutes of recovery has been reported in other studies in which $TcPO_2$ measurements were made during a single maximal walking bout followed by a single recovery period (5, 18-20, 35).

Our experimental conditions based on the isolated (TW-ISO) or consecutive (TW-CONS and OW-CONS) repetitions of walking bout(s) inducing ischemia, followed by recovery bouts of different durations, could be reflected by a very short-term and acute model of repeated ischemia-reperfusion cycles (42). The ischemia-reperfusion (I/R) process causes local and distant changes (I/R injury) due to a number of pathophysiological events that occur during the ischemic phase (i.e., the production of reactive oxygen species, inflammation and mitochondrial dysfunction) and that amplify damage in the previously ischemic tissues when blood flow recirculates during the reperfusion phase (42). In the long term, acute repetitions of this ischemia-reperfusion cycle impair the exercising skeletal muscle function, which further limits the walking capacity of people with PAD (25). The chronology of deleterious

events involved in I/R injuries have been mainly investigated using experimental models that included several hours of ischemia (42). An acute bout of treadmill walking has been shown to trigger an excessive inflammatory response and oxidative stress leading to endothelium damage, suggesting that short-term I/R injuries are exercise induced in people with PAD (11). However, it is unknown whether such deleterious events delay walking capacity restoration until a given recovery time is reached, as shown here; this topic should be studied further. Finally, remote ischemic preconditioning has been shown to protect against I/R injuries (34), but the results regarding its acute effect on walking capacity in people with PAD are inconsistent (10, 47). Our results showed there was no ischemic preconditioning effect during acute repeated walking bouts since the restoration of MWT was capped at approximately 100%, even with longer RTs.

Effect of RT on walking capacity restoration: inter-subjects and inter-conditions variability

Although most of the participants with PAD exhibited a logarithmic effect of RT on walking capacity, few patients had a linear profile ($n = 1$ to 3 depending on the walking condition). This effect may have been logarithmic if longer RTs had been tested in those participants with a linear profile. However, this approach would have increased the session duration and the number of walking bouts to be performed, particularly for the TW-CONS and OW-CONS conditions, and the accumulated fatigue could have exerted a major confounding effect on walking capacity (31). The different profiles reported here seem consistent with the inter-individual variability in the time course of recovery from ischemia, as previously reported (48). The linear profile implies that some people with PAD need >10 min to recover from ischemia after a maximal walking bout, independently of lower-limb symptom dissipation, supporting the mismatch between time to symptom relief and resolution of ischemia (14, 48).

461 An important result was that the effect of RT on walking capacity was observed in three
462 different experimental conditions. However, there were some different results between the
463 tested experimental conditions. First, the RT needed to reach full restoration of walking
464 capacity and full recovery of ischemia was longer for TW-CONS than for TW-ISO. This can
465 be explained by the consecutive nature of the walking bouts performed: the time needed to
466 recover from a given walking bout limited by ischemia could be extended due to the
467 accumulation of previous walking bout(s), inducing slower adaptation of muscle blood flow
468 (12) and/or slower phosphocreatine recovery (28). Interestingly, assuming that cumulated
469 time is an acceptable tool for estimating fatigue, there was no negative association between
470 the cumulated time and walking capacity for all but one participant. This result suggests that
471 RT was the more predominant and powerful predictor of walking capacity during TW-
472 CONS. From a practical point of view, this is an important finding in view of defining a
473 feasible procedure to determine the effect of RT on walking capacity, as well as possibly
474 determining the IRT at the individual level. Second, compared with during TW-CONS,
475 during OW-CONS, participants with PAD were unable to restore their MWT to the same
476 extent. This was an unexpected observation. Indeed, because the intensity of outdoor walking
477 for people with PAD is lower outdoors than it is on the treadmill (29, 31), we could expect a
478 lower level of ischemia at the end of each outdoor walking bout (14), thereby allowing faster
479 restoration of walking capacity. Participants with PAD actually walked longer during OW-
480 CONS due to a lower walking intensity compared with that under TW conditions, which
481 required some participants to stop the session before testing all RTs to avoid an excessive
482 walking session duration. The low level of restoration was likely to be explained by the
483 longer walking duration that led to a marked level of ischemia and that would also have
484 required more than 5 min of recovery. We previously reported that the cumulative time could

also account for walking capacity changes during an outdoor walking session (31). This was not the case in the present study, as this was not the case for walking speed.

Study limitations

For a few participants (3 for TW-ISO, 4 for TW-CONS, 7 for OW-CONS), no significant effect of RT on walking capacity was found ($P>0.05$). Visually, the effect was observable, but the issue was statistical due to the presence of outlier(s), and a limited number of points (RTs) were available to build individual models. Furthermore, the absence of an effect would have meant an absence of the underlying physiological phenomenon for these participants, which should have been consistent across the three experimental conditions; this was not the case.

Furthermore, the absence of a physiological measurement of ischemia during OW-CONS made it difficult to ascertain whether the changes in walking capacity were due to ischemia or to other fatigue-related mechanisms (31). Portable TcPO₂ devices for ambulatory measures in the field are not available, but near-infrared spectroscopy may be used for such measurements (40).

Future directions

“Should I stay or should I go now?” That is a core question that people with PAD may ask themselves when they stop walking due to ischemic lower-limb pain and rest for a while before resuming walking. The same question can be asked by clinicians when controlling the RT during a rehabilitation session since the available recommendations are limited (4, 6, 17, 22, 52). The present study is only the first step, and complementary studies are needed before a full response to this question can be provided. However, the present study provides

benchmarks for clinicians or physical therapists on how to manage RT, which can be summarized as follows:

- i) A median work-to-rest ratio $\geq 1:1$ implied the resumption of walking with a substantial level of ischemia and did not allow the restoration of MWT by more than 80% at the group level.
- ii) A median work-to-rest ratio $\leq 1:2$ seemed to be necessary to allow full recovery from ischemia and the restoration of $\sim 100\%$ MWT at the group level.
- iii) The IRT, which is a new concept in terms of RT that we introduced here, was associated with a median work-to-rest ratio between 1:1 and 1:2, which allowed the symptomatic lower-limb muscle to start to recover from ischemia and the participants with PAD to restore the MWT to 80-90%.
- iv) The median SSRT, as well as the median time needed to reach a pain level of “0” (which was similar to the SSRT), corresponded to median work-to-rest ratios of $>1:1$, meaning that participants with PAD spontaneously resumed walking following a RT that was clearly insufficient in terms of recovery from ischemia, which precluded the restoration of MWT above 80%.

During rehabilitation programs, pain dissipation is currently used as the main criterion to define the between-walking-bouts recovery duration (6, 26, 52). Our results confirm the well-known dissociation between ischemia dissipation and symptom relief during recovery (13, 14), but the results show for the first time the detrimental effect of spontaneously resuming walking on subsequent walking capacity after a walking stop induced by ischemic pain. Thus, if the clinician aims to maximize walking restoration with full ischemia recovery after each walking bout, it appears that the use of the SSRT or time to pain “0” is likely to be inappropriate. However, clinicians often aim to maximize the time spent walking during each session, and the ideal RT for such a purpose remains a core issue. Additional future studies

535 are required to compare the use of the SSRT, IRT, or time to reach full walking capacity
536 recovery for maximizing the time spent walking within different session durations. An
537 important point also to consider is that our results regarding the relationship between RT and
538 walking capacity were obtained from walking bouts performed up to maximal claudication
539 pain, whereas in the majority of supervised exercise treadmill programs, patients are
540 instructed to walk to moderate or near-maximal level of claudication (24, 52). Although they
541 are experimentally challenging to conduct, studies on the relationship between different
542 work-to-rest ratios and walking capacity restoration according to various pain endpoints
543 should be conducted to identify optimal and maybe new walking training regimens, while
544 minimizing the acute adverse responses of exercise up to maximal claudication pain (e.g.,
545 inflammation, denervation), even if these adverse effects are overtaken by the benefits of
546 chronic exercise (24). Finally, besides the current recommendations on what is considered the
547 “optimal” exercise regimen (6, 52), our results may not be applicable in other context of
548 walking programs and that have proven to be efficient, e.g. programs with fixed work:rest
549 ratios and fixed walking speeds (36), those based on interval training with active recovery
550 (53) or those based on pain-free treadmill training (38).

551 In addition to rehabilitation programs, different strategies of recovery that vary by daily life
552 contexts could be of interest for people with PAD and could be studied in the future. Based
553 on our results, future studies should address whether the SSRT, the IRT or the time for full
554 recovery helps people with PAD manage pain according to specific contexts. Regardless,
555 managing RT from walking-induced ischemia during daily life could be facilitated through
556 the use of wearable monitors (7).

557 Future studies are also needed to determine the reliability of IRT. Finally, we are aware of no
558 study on the impact of walking duration on ischemia independently of the effect of walking

intensity and are likewise unaware of any previous implementation of ambulatory ischemia measurements during outdoor walking.

CONCLUSION

This study highlighted the significant and mostly logarithmic effect of RT on walking capacity in people with symptomatic PAD. Moreover, this study revealed that (i) self-selection of RT or the time to reach pain “0” corresponding to a median work-to-rest ratio higher than 1:1 leads to the resumption of walking with unrecovered ischemia and precludes restoration of full walking capacity; and (ii) it is possible to determine an individualized RT allowing the initiation of recovery from ischemia and better restoration of the walking capacity, while a work-to-rest ratio of $\leq 1:2$ should be preferred to fully restore the walking capacity.

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764

FIGURE LEGENDS

Figure 1. Schematic view of the experimental conditions tested in the protocol

Note. TW-ISO = Isolated sequences of treadmill maximal walking bouts; TW-CONS = Consecutive treadmill maximal walking bouts; OW-CONS = Consecutive outdoor maximal walking bouts; W = Walk; R = Recovery; SSRT = Self-selected recovery time; TcPO₂ = Transcutaneous oxygen pressure; GPS = Global Positioning System.

Figure 2. Illustration of the procedure to determine the individual recovery time (IRT) in one patient following the TW-ISO condition. The Self-selected recovery time (SSRT) is also displayed.

Figure 3. Effect of the recovery time on the restoration of walking capacity and end-recovery physiological variables

Note. The figure displays the data related only to participants who exhibited a plausible logarithmic or linear effect of recovery time (RT) on walking capacity ($P \leq 0.05$ for the slope). TW-ISO = Isolated sequences of treadmill maximal walking bouts; TW-CONS = Consecutive treadmill maximal walking bouts; OW-CONS = Consecutive outdoor maximal walking bouts; SSRT = Self-selected RT; IRT = Individual RT; Walk_N = Walking time up to maximal claudication pain performed after the RT tested; Walk₁ = First walking time up to maximal claudication pain during the walking sequence; % $\dot{V}O_{2peak}$ = Percentage of peak oxygen uptake; %HR_{peak} = Percentage of peak heart rate; DROP = Delta from resting transcutaneous oxygen pressure; PFWT = Pain-free walking time; MWT = Maximal walking time.

789 The left, middle, and right panels are related to the TW-ISO, TW-CONS, and OW-CONS
790 conditions, respectively. For panels G to L, dashed lines and gray bands represent the
791 medians of the participants' resting values and their respective interquartile ranges for the
792 physiological parameters considered. Resting $\dot{V}O_2$ and HR values were determined as the
793 lowest mean values of $\dot{V}O_2$ and HR obtained among all the 2-min resting periods (treadmill
794 and outdoor sessions included) of the protocol, respectively.

795 For TW-ISO, one datum was missing for PFWT and DROP, respectively, for the RTs of 6.5
796 and 3.5 min. For TW-CONS, one datum was missing for PFWT for the RT of 0.5 min. For
797 OW-CONS, one datum was missing for PFWT for each of the tested RTs. Data were missing
798 due to either no communication of pain onset by the participant (for PFWT) or device
799 malfunction (for DROP).

800 $*P \leq 0.05$, $**P \leq 0.01$, $***P \leq 0.001$, compared with the previous RT.

CONDITIONS

TW-ISO



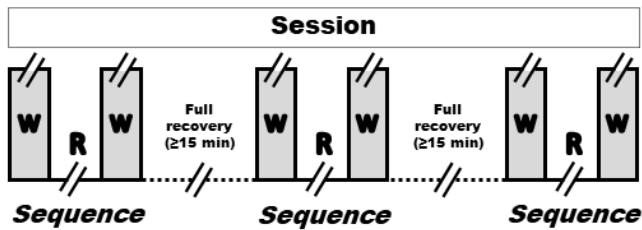
TW-CONS



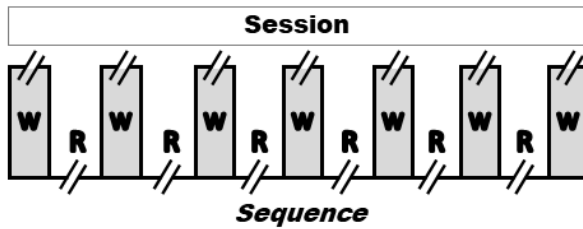
OW-CONS



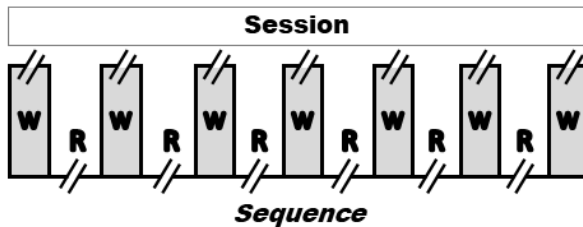
PROTOCOL



- Treadmill walking
- 11 sequences tested separately over four sessions (3x3 + 1x2)
- R tested (min) → 0.5; 1.5; 2.5; 3.5; 4.5; 5.5; 6.5; 7.5; 8.5; 9.5 + SSRT
- Walking intensity → 3.2 km/h; 12% grade
- Pain level → 4/4

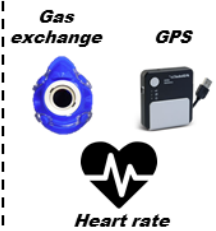
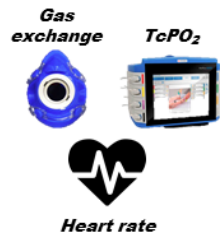


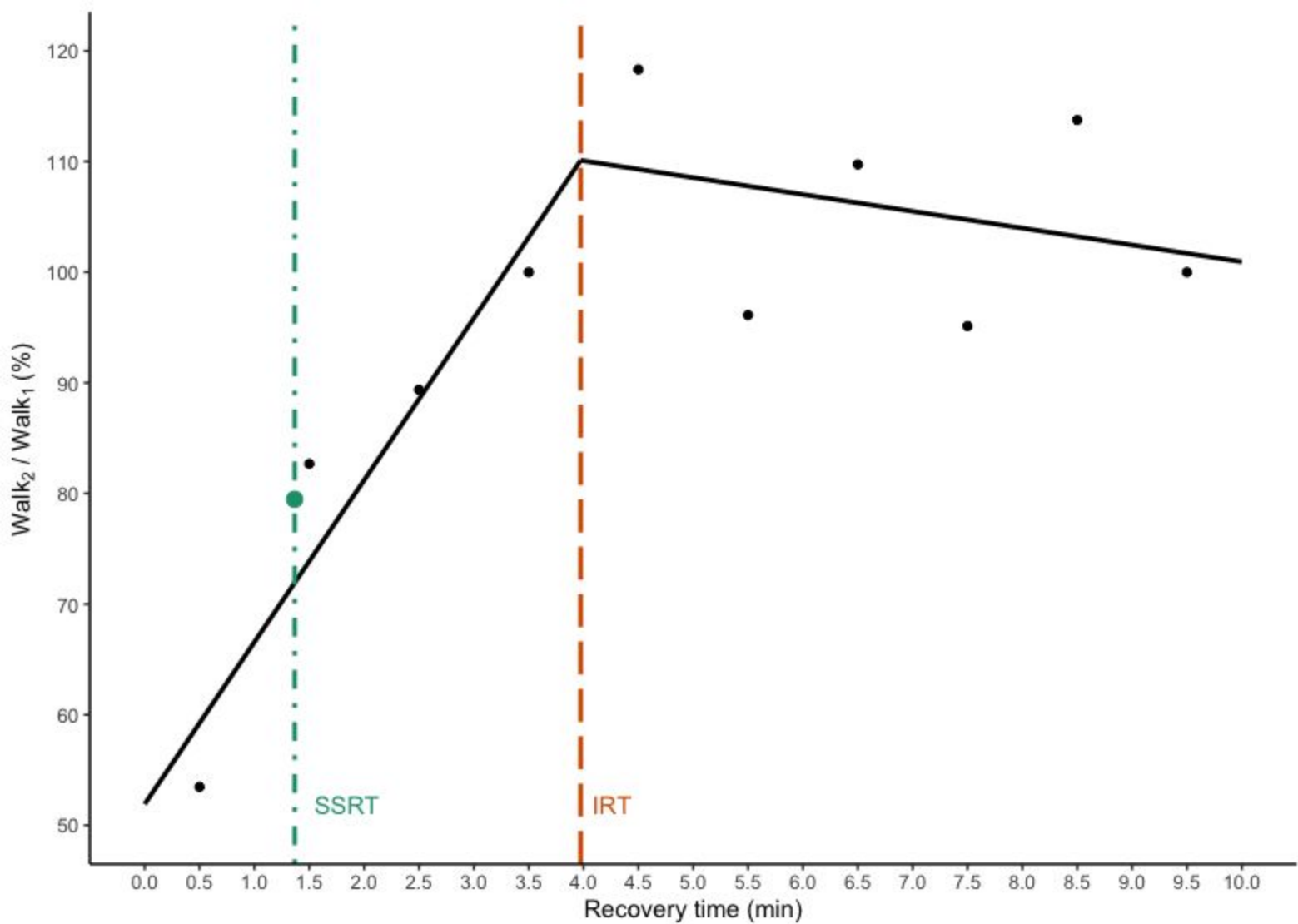
- Treadmill walking
- 1 sequence over one session
- R tested (min) → 0.5, 2.5, 4.5, 6.5, 8.5 + SSRT
- Walking intensity → 3.2 km/h; 12% grade
- Pain level → 4/4



- Outdoor walking
- 1 sequence over one session
- R tested (min) → 0.5, 1.5, 2.5, 3.5, 4.5 + SSRT
- Walking intensity → usual pace; 0% grade
- Pain level → 4/4

MEASURES

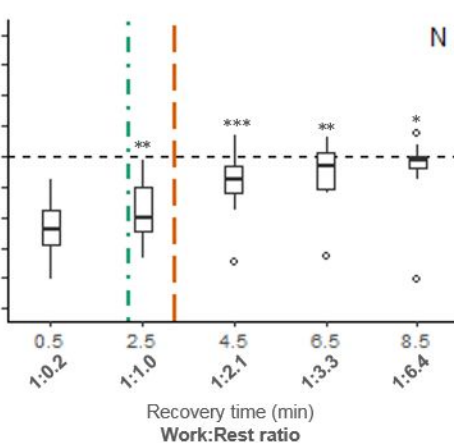
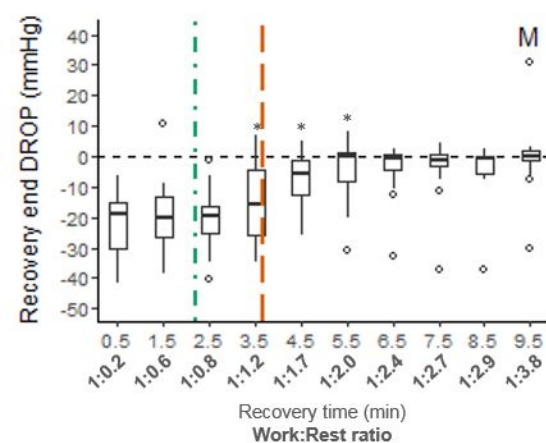
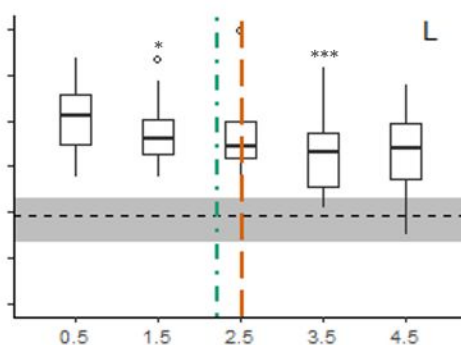
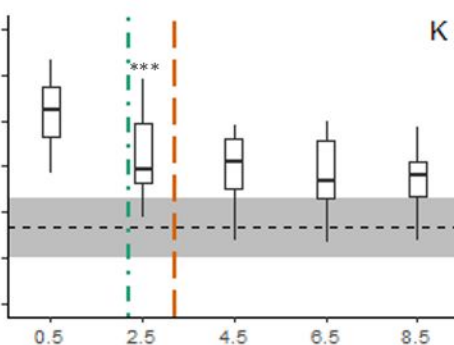
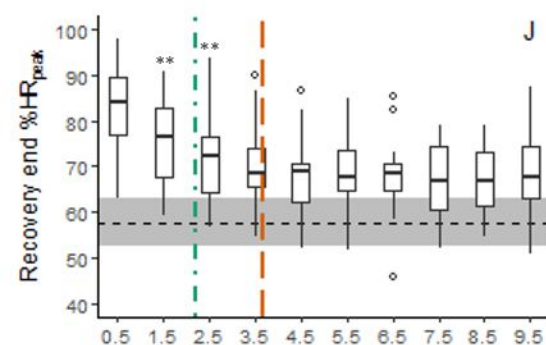
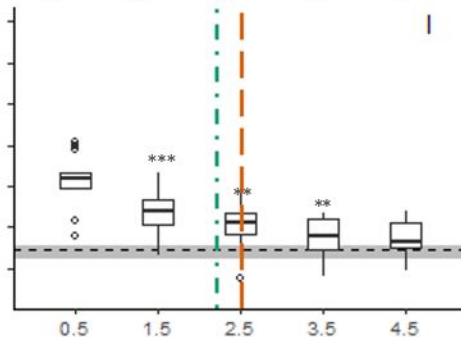
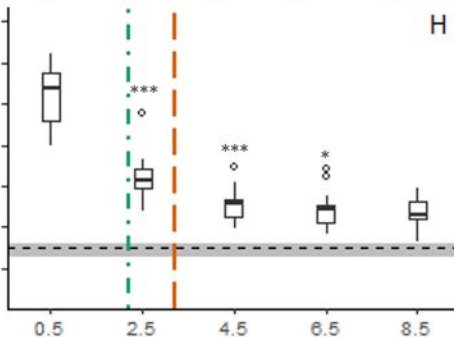
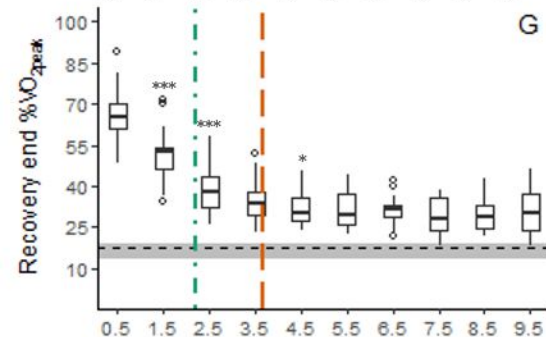
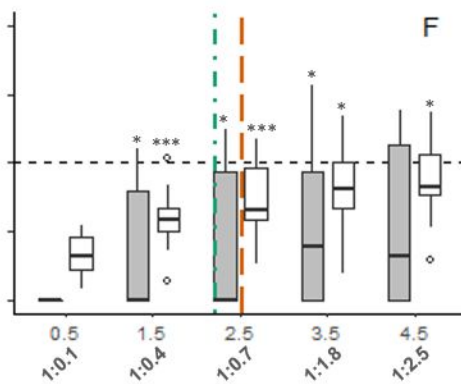
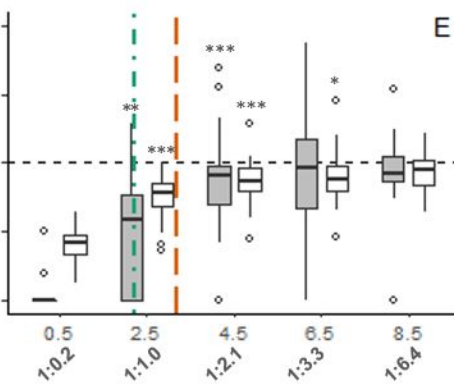
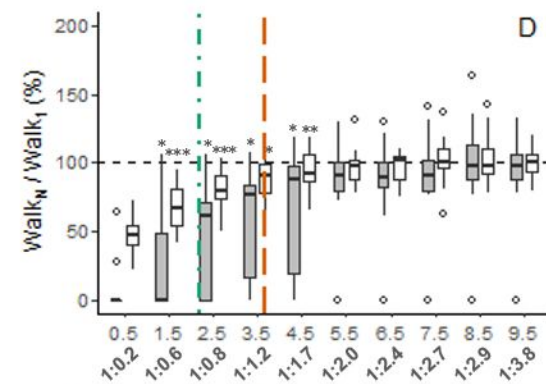
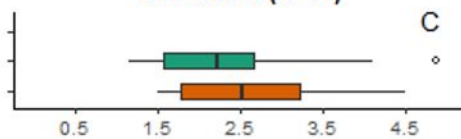
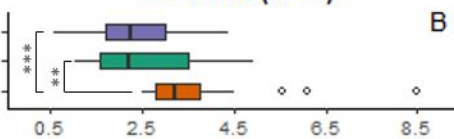
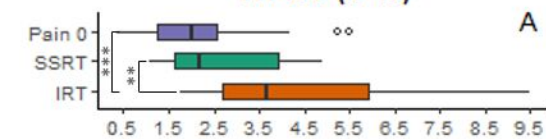




TW-ISO (n=18)

TW-CONS (n=17)

OW-CONS (n=14)



Recovery time (min)
Work:Rest ratio

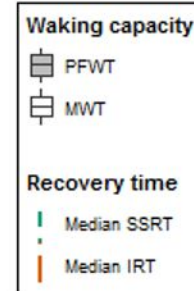


Table 1. Inclusion and non-inclusion criteria of the CLASH study

Inclusion criteria
<ul style="list-style-type: none">• Age ≥ 18 years old• Insured under the French social security system (according to French law)• Presence of lower-extremity peripheral artery disease, defined by:<ul style="list-style-type: none">○ A resting ankle-brachial index (ABI) ≤ 0.90○ OR if resting ABI > 0.90 and < 1.00, a decrease in recovery ankle systolic pressure or in recovery ABI from treadmill exercise greater than 30% or 20%, respectively (AHA recommendations(1)).○ OR if resting ABI > 1.40, a toe pressure index ≤ 0.70• Maximal walking distance on treadmill (3.2 km/h, 10% grade) < 500 m[†]• Complaint of exertional lower limb pain that can sometimes begin at rest, causing the participant to stop walking, and is relieved or lessened within 10 minutes of rest (confirmed during treadmill testing)[‡]
Non-inclusion criteria
<ul style="list-style-type: none">• Exercise limitation due to symptoms not related to an arterial insufficiency in the lower limbs (e.g., dyspnea, angina pectoris)• Contraindication for walking (abdominal aortic aneurysm > 4 cm)• Myocardial infarction and/or stroke in the last 3 months• Critical limb ischemia, amputation• Pregnant women• Adult subject to legal protection (guardianship or tutelage measure) and persons deprived from their liberty (according to French law).• People living more than 50 km from the university hospital• People unable to understand the instructions of the study

[†]As assessed during the medical appointment.

[‡]According to our inclusion criteria, PAD participants with leg symptoms that fell within the following leg symptom categories could be included in the study:

- i) Intermittent claudication. People with PAD who experience exertional leg pain that does not begin at rest and that forces them to stop walking and that relieves or lessens within 10 minutes of rest;
- ii) Leg pain on exertion and rest. In this category, people with PAD experience exertional lower limb pain during walking, but this pain can sometimes begin at rest when they are standing still or sitting. As noted by Criqui et al. (10), this category of people with PAD with “pain at rest” should not be confused with those who experience “resting pain”, which usually refers to people with such severe advanced PAD that ischemic pain is present even at rest. Subjects with ischemic rest pain were not included in the study.

Table 2. Characteristics of PAD participants

General	
Age, y	60 ± 10
Height, m	1.69 ± 0.08
Weight, kg	77 ± 15
Body mass index, kg·m ⁻²	27 ± 4
Waist circumference, cm	101 ± 11
Women, n (%)	3 (14)
Caucasian, n (%)	21 (100)
Former smokers, n (%)	11 (52)
Current smokers, n (%)	10 (48)
Comorbid conditions	
History of diabetes mellitus, n (%)	5 (24)
History of hypertension, n (%)	13 (62)
History of heart failure, n (%)	3 (14)
History of myocardial infarction/stable angina, n (%)	3 (14)
History of stroke, n (%)	1 (5)
History of cancer, n (%)	1 (5)
History of chronic obstructive pulmonary disease, n (%)	6 (29)
PAD condition	
Ankle-brachial index	0.67 ± 0.17
Leg symptoms [†] , n (%)	
Intermittent claudication	16 (76)
Leg pain on exertion and rest	4 (19)
Atypical claudication	1 (5)

Previous lower-extremity revascularization	7 (33)
Medications	
Anti-diabetics, n (%)	5 (24)
Antihypertensive drugs, n (%)	12 (57)
Antiplatelet agents or Anticoagulants, n (%)	19 (90)
Cholesterol-lowering drug, n (%)	19 (90)
β -blockers, n (%)	4 (19)
Vasodilators, n (%)	3 (14)
Walking capacity	
WIQ scores [‡]	
WIQ distance score, %	23 (14 – 40)
WIQ speed score, %	25 (17 – 33)
WIQ stairs score, %	63 (25 – 75)
WIQ total score, %	37 (21 – 49)
Maximal walking distance	
MWD _{SR} , m [§]	133 (100 – 250)
MWD _{GARDNER} , m	265 (171 – 364)
MWD _{6WT} , m	384 (339 – 433)
MWD _{GPS} , m	430 (298 – 529)
Peak physiological responses[¶]	
Peak $\dot{V}O_2$, mL·min ⁻¹ ·kg ⁻¹	16.03 ± 2.22
Peak HR, bpm	108 ± 18

For the purpose of the CLASH study, a six-minute walking test was also performed according to previous recommendations (4). This test was performed at the beginning of the TW-ISO session and included only two sequences. Sufficient recovery time (>30 min) was allowed following the six-minute walking test. Although normally distributed, the 6-min total walking distance is shown using the median and interquartile range to allow easier comparisons with the other walking capacity outcomes. PAD = peripheral artery disease; WIQ = walking impairment questionnaire; MWD_{SR} = self-reported maximal walking distance; MWD_{GARDNER} = maximal walking distance measured during the Gardner-Skinner treadmill test; MWD_{6WT} = total walking distance measured during the 6-min walking test; MWD_{GPS} = highest maximal walking distance measured using the Global Positioning System during the outdoor walking session; HR = heart rate; $\dot{V}O_2$ = oxygen uptake.

[†]Leg symptoms reported using the San Diego claudication questionnaire; see Table 1 for definition. [‡]WIQ scores range between 0 and 100%, with 100% indicating no impairment.

[§]Data were available for 18 participants because 3 participants could not estimate their maximal walking distance. [¶]Data correspond to the Gardner-Skinner treadmill test.

Table 3. Summary of the group-based (mixed) models tested for the effect of recovery time on walking capacity (MWT_n/MWT_1 , in %)

	TW-ISO (n=21)		TW-CONS (n=21)		OW-CONS (n=20)*	
	x	ln(x)	x	ln(x)	x	ln(x)
R^2	0.19	0.23	0.34	0.45	0.22	0.24
p-value	$2.59 \cdot 10^{-12}$	$4.70 \cdot 10^{-15}$	$5.47 \cdot 10^{-18}$	$2.78 \cdot 10^{-29}$	$2.15 \cdot 10^{-13}$	$1.11 \cdot 10^{-15}$
RMSE	24.51	24.08	21.27	19.50	35.56	35.09

x and ln(x) are the explanatory variables that have been used in the mixed models, x being the recovery time. TW-ISO = isolated sequences of maximal treadmill walking bouts; TW-CONS = single sequence of consecutive maximal treadmill walking bouts; OW-CONS = single sequence of consecutive maximal outdoor walking bouts; n = number of participants used for the models; RMSE = root-mean-squared error (in %: $MWT_n/MWT_1 \times 100$).

*Data for only 20 participants were available for the models related to the CONS-OW condition, as one participant did not stop in that condition. Moreover, in the OW-CONS condition, two recovery times were not tested in three participants. These times were 1.5 min and 3.5 min for two participants and 2.5 min and the SSRT (not included in the analysis) for the third participant.

Table 4. Summary of the participant-based (individual) models for the effect of recovery time on walking capacity (MWT_n/MWT₁, in %)

	TW-ISO		TW-CONS		OW-CONS	
	$R^2_x > R^2_{\ln(x)}$	$R^2_{\ln(x)} > R^2_x$	$R^2_x > R^2_{\ln(x)}$	$R^2_{\ln(x)} > R^2_x$	$R^2_x > R^2_{\ln(x)}$	$R^2_{\ln(x)} > R^2_x$
n (%)	2 (10)	16 (76)	1 (5)	16 (76)	3 (15)	11 (55)
R^2 , median	0.58	0.80	0.93	0.93	0.96	0.94
(IQR)	(0.54 – 0.62)	(0.70 – 0.87)	(n.a.)	(0.88 – 0.97)	(0.96 – 0.97)	(0.88 – 0.96)
SEE, median	10.60	7.39	6.09	4.34	3.40	4.88
(IQR)	(8.37 – 12.83)	(6.61 – 10.79)	(n.a.)	(3.60 – 5.93)	(2.86 – 4.01)	(4.27 – 6.11)

R^2_x and $R^2_{\ln(x)}$ are the R^2 coefficients related to models that respectively used either x or $\ln(x)$ as the explanatory variable, x being the recovery time. Statistics are shown only for the participants who exhibited a significant and plausible linear ($R^2_x > R^2_{\ln(x)}$) or logarithmic ($R^2_{\ln(x)} > R^2_x$) effect of recovery on walking capacity. TW-ISO = isolated sequences of maximal treadmill walking bouts; TW-CONS = single sequence of consecutive maximal treadmill walking bouts; OW-CONS = single sequence of consecutive maximal outdoor walking bouts; IQR = interquartile range; SEE = standard error of estimate; n.a. = not appropriate.