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Pierre-Yves de Müllenheim, Laurent Rouvière, Mathieu Emily, Ségolène Chaudru, Adrien Kaladji, et al.. Should I stay or should I go now? Recovery time effect on walking capacity in symptomatic peripheral artery disease. *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, 2021, 131 (1), pp.207-219. 10.1152/jappphysiol.00441.2020 . hal-03246582

HAL Id: hal-03246582

<https://hal.science/hal-03246582v1>

Submitted on 15 Jun 2021

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“Should I stay or should I go now?”

Recovery time effect on walking capacity in symptomatic peripheral artery disease

Short title: Recovery time and walking capacity in PAD

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Acknowledgements

This work was promoted and partially funded by the University Hospital of Rennes (CORECT 2013). This work was also partially funded by ENS Rennes. S. Chaudru received a PhD scholarship from the Bretagne region (Bourse ARED). P.-Y. de Müllenheim received a PhD scholarship from the ENS Cachan-Antenne de Bretagne (CDSN).

26 A.L.F., G.M., and P.-Y.d.M. conceived and designed the study; P.-Y.d.M., SC, A.L.F., and
27 G.M. performed the experiments; L.R., M.E., P.-Y.d.M., and A.L.F. analyzed the data; P.-
28 Y.d.M. and A.L.F. interpreted the results of the experiments; P.-Y.d.M. prepared the figures;
29 P.-Y.d.M. and A.L.F. drafted the manuscript; P.-Y.d.M., L.R., M.E., S.C., G.M., A.K. and
30 A.L.F. edited and revised the manuscript; P.-Y.d.M., L.R., M.E., S.C., G.M., A.K. and A.L.F.
31 approved the final version of the manuscript.

32

33 **Conflict of interest**

34 The authors declare no conflict of interest.

35

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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.

107 **METHODS**

108 **Study design**

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

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

121

122 **Inclusion visit**

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

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

134

135 **Experimental conditions**

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

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

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

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

163 (ii) *TW-CONS*. The rationale here was to assess the potential effect of RT on walking
164 capacity through a series of consecutive walking bouts, thereby moving toward what
165 was previously observed during outdoor walking in PAD (31). Thus, during one
166 single session, participants performed seven consecutive treadmill walking bouts (3.2
167 km/h, 12% grade) up to maximal claudication pain, interspersed by six RTs (between
168 0.5 and 8.5 min; or SSRT).

169 (iii) *OW-CONS*. The rationale here was close to that explained for TW-CONS except
170 that here, we aimed to reproduce the walking pattern of people with PAD under
171 “natural” outdoor walking conditions, as encountered while walking during daily life
172 (31) or during outdoor walking sessions of a home-based walking program (16). Thus,
173 during a single session, participants performed seven consecutive outdoor (athletic
174 track; 0% grade) walking bouts up to maximal claudication pain, interspersed by six
175 RTs (between 0.5 and 4.5 min; or SSRT). Consistent with previous observation (23),
176 RTs were intentionally shorter than those for TW-ISO and TW-CONS. Participants
177 were asked to walk at their usual walking speed and to stop walking only due to
178 maximal claudication pain. The outdoor walking session was supervised by two
179 investigators who walked approximately 10 meters behind the participant and
180 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.

185

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,

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

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

217

218 **Data analysis**

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

221 *Walking capacity outcomes.* For each treadmill walking bout, we computed the pain-free
222 walking times (PFWTs) and the maximal walking times (MWTs). From each outdoor
223 walking bout, the PFWT was the duration measured by the investigators, using the
224 chronometer, from the start of the walking bout to the moment where the participant
225 indicated the occurrence of pain using the watch provided for this purpose (7). The MWT
226 was the duration of the maximal walking bout detected using the GPS as previously reported
227 (7, 29).

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

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

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

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

244

245 **Statistical analysis**

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

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

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

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

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

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

294 For each treadmill condition, the time needed to reach a pain level of “0”, SSRT, and IRT
295 were compared using a Friedman test. If significant, pairwise comparisons were performed
296 using two-sided Wilcoxon signed rank tests with P value adjustment (Bonferroni correction).

297 For the TW-ISO and TW-CONS conditions, the values used for the time needed to reach a
298 pain level of “0” were the participant averages of the times measured during the
299 corresponding conditions (this time was not measured during the OW-CONS condition). In
300 the OW-CONS condition, SSRT and IRT were compared using a two-sided Wilcoxon signed
301 rank test.

302 For each RT in each condition and based on participants in whom there was a plausible
303 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.

313 **RESULTS**

314 Twenty-three participants with PAD were initially included in the study, but two were
315 excluded before the end of the study. One participant was excluded due to a need for medical
316 treatment modification, and another participant stopped participating to undergo a surgical
317 intervention. Thus, data from 21 participants were analyzed in the present study. The
318 participants' characteristics are shown in Table 2. Participants were mainly older,
319 overweight, Caucasian men with a resting ABI indicating a mild-to-moderate PAD severity
320 (0.67 ± 0.17). All participants were limited by exertional lower-limb symptoms during the
321 Gardner-Skinner test at the inclusion visit.

322

323 *Effect of RT on walking capacity*

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

332 Linear mixed models testing the effect of RT on the MWT_n/MWT_1 ratio at the group level
333 are shown in Table 3. Regardless of the model tested and the experimental conditions, the RT
334 significantly predicted the MWT_n/MWT_1 ratio ($P < 0.001$). Although the explained variance
335 remained quite low (R^2 between 0.19 and 0.45), a greater R^2 was obtained using the
336 logarithm of the RT as the explanatory variable. Furthermore, neither the cumulated time
337 (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 –

363 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
364 min), indicating full recovery in terms of ischemia. This time needed for full recovery of
365 ischemia was close to that needed for restoring 100% of the MWT (Figure 3).

366

367 *SSRT and IRT*

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

372 Figure 3 also displays how SSRT and IRT matched the restoration of both MWT and
373 ischemia (DROP values) during the treadmill conditions. As shown, the median SSRT
374 matched the time period during which DROP values were the lowest and the response was
375 blunted (i.e., maximal ischemia), allowing only a restoration of MWT below 80% in both the
376 TW-ISO and TW-CONS conditions. The median IRT matched the time from which DROP
377 values started to increase (i.e., ischemia decrease), allowing a restoration of MWT to >90%
378 in TW-ISO and between 78% and 86% in TW-CONS. Finally, when expressing the RTs
379 tested in terms of work-to-rest ratios, it was observed that a median work-to-rest ratio $\geq 1:1$
380 did not enable the participants with PAD to start to recover from ischemia (Figure 3), while
381 MWT started to be restored. As shown in Figure 3, the median SSRT was above this
382 threshold of a work-to-rest ratio of 1:1. Conversely, a median work-to-rest ratio of $\leq 1:2$
383 seemed to be necessary to enable the participants to fully recover from ischemia and restore
384 ~100% of their MWT. In terms of the work-to-rest ratio, the median IRT was between 1:1
385 and 1:2 and corresponded to an ischemia that started to decrease and to a restoration of MWT
386 to nearly 90% in TW-ISO and nearly 80% in TW-CONS.

387 **DISCUSSION**

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

396

397 *Effect of RT on ischemia recovery and walking capacity restoration*

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

412 occluded than during a normally perfused condition, the peak force restoration rate during
413 recovery was rapid, starting as early as 0.5 min of recovery and ending by 5 min of recovery
414 (43). Although phosphocreatine recovery from exercise is impaired in people with PAD
415 compared to healthy subjects (28), the initial recovery of walking capacity under ischemia
416 could be at least partially explained by a rapid (although incomplete) resynthesis of high-
417 energy phosphate stores of the anaerobic fibers that support the energy demands of the
418 ischemic musculature while walking is resumed (21, 43). However, it should be considered
419 that the pattern of TcPO₂ changes during recovery is delayed with respect to that of other
420 hemodynamic variables related to ischemia, i.e. systolic ankle pressure or ankle-to-brachial
421 index (18, 21). Consequently, it cannot be excluded that ischemia at the muscle level started
422 to resolve sooner than the TcPO₂ at the skin level. Of note, the blunting response of ischemia
423 during the first few minutes of recovery has been reported in other studies in which TcPO₂
424 measurements were made during a single maximal walking bout followed by a single
425 recovery period (5, 18-20, 35).

426

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

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

448

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

450 Although most of the participants with PAD exhibited a logarithmic effect of RT on walking
451 capacity, few patients had a linear profile (n = 1 to 3 depending on the walking condition).
452 This effect may have been logarithmic if longer RTs had been tested in those participants
453 with a linear profile. However, this approach would have increased the session duration and
454 the number of walking bouts to be performed, particularly for the TW-CONS and OW-CONS
455 conditions, and the accumulated fatigue could have exerted a major confounding effect on
456 walking capacity (31). The different profiles reported here seem consistent with the inter-
457 individual variability in the time course of recovery from ischemia, as previously reported
458 (48). The linear profile implies that some people with PAD need >10 min to recover from
459 ischemia after a maximal walking bout, independently of lower-limb symptom dissipation,
460 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

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

487

488

489 *Study limitations*

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

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

502

503 *Future directions*

504 “*Should I stay or should I go now?*” That is a core question that people with PAD may ask
505 themselves when they stop walking due to ischemic lower-limb pain and rest for a while
506 before resuming walking. The same question can be asked by clinicians when controlling the
507 RT during a rehabilitation session since the available recommendations are limited (4, 6, 17,
508 22, 52). The present study is only the first step, and complementary studies are needed before
509 a full response to this question can be provided. However, the present study provides

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

512 i) A median work-to-rest ratio $\geq 1:1$ implied the resumption of walking with a
513 substantial level of ischemia and did not allow the restoration of MWT by more
514 than 80% at the group level.

515 ii) A median work-to-rest ratio $\leq 1:2$ seemed to be necessary to allow full recovery
516 from ischemia and the restoration of $\sim 100\%$ MWT at the group level.

517 iii) The IRT, which is a new concept in terms of RT that we introduced here, was
518 associated with a median work-to-rest ratio between 1:1 and 1:2, which allowed
519 the symptomatic lower-limb muscle to start to recover from ischemia and the
520 participants with PAD to restore the MWT to 80-90%.

521 iv) The median SSRT, as well as the median time needed to reach a pain level of “0”
522 (which was similar to the SSRT), corresponded to median work-to-rest ratios of
523 $>1:1$, meaning that participants with PAD spontaneously resumed walking
524 following a RT that was clearly insufficient in terms of recovery from ischemia,
525 which precluded the restoration of MWT above 80%.

526 During rehabilitation programs, pain dissipation is currently used as the main criterion to
527 define the between-walking-bouts recovery duration (6, 26, 52). Our results confirm the well-
528 known dissociation between ischemia dissipation and symptom relief during recovery (13,
529 14), but the results show for the first time the detrimental effect of spontaneously resuming
530 walking on subsequent walking capacity after a walking stop induced by ischemic pain. Thus,
531 if the clinician aims to maximize walking restoration with full ischemia recovery after each
532 walking bout, it appears that the use of the SSRT or time to pain “0” is likely to be
533 inappropriate. However, clinicians often aim to maximize the time spent walking during each
534 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

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

561

562 **CONCLUSION**

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

571

572 **REFERENCES**

- 573 1. **Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C,**
574 **Fowkes FG, Hiatt WR, Jonsson B, Lacroix P, Marin B, McDermott MM, Norgren L,**
575 **Pande RL, Preux PM, Stoffers HE, Treat-Jacobson D, on behalf of the American Heart**
576 **Association Council on Peripheral Vascular Disease, Council on Epidemiology**
577 **Prevention, Council on Clinical Cardiology, Council on Cardiovascular Nursing,**
578 **Council on Cardiovascular Radiology Intervention, and Council on Cardiovascular**
579 **Surgery Anesthesia.** Measurement and interpretation of the ankle-brachial index: a scientific
580 statement from the American Heart Association. *Circulation* 126: 2890-2909, 2012.
- 581 2. **Abraham P, Picquet J, Vielle B, Sigaud-Roussel D, Paisant-Thouveny F, Enon**
582 **B, and Saumet JL.** Transcutaneous oxygen pressure measurements on the buttocks during
583 exercise to detect proximal arterial ischemia: comparison with arteriography. *Circulation*
584 107: 1896-1900, 2003.
- 585 3. **American College of Sports Medicine.** *ACSM's Guidelines for Exercise Testing and*
586 *Prescription.* Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2014.
- 587 4. **Askew CD, Parmenter B, Leicht AS, Walker PJ, and Golledge J.** Exercise &
588 Sports Science Australia (ESSA) position statement on exercise prescription for patients with
589 peripheral arterial disease and intermittent claudication. *J Sci Med Sport* 17: 623-629, 2014.
- 590 5. **Bouye P, Picquet J, Jaquinandi V, Enon B, Leftheriotis G, Saumet JL, and**
591 **Abraham P.** Reproducibility of proximal and distal transcutaneous oxygen pressure
592 measurements during exercise in stage 2 arterial claudication. *Int Angiol* 23: 114-121, 2004.
- 593 6. **Bulmer AC, and Coombes JS.** Optimising exercise training in peripheral arterial
594 disease. *Sports Med* 34: 983-1003, 2004.
- 595 7. **Chaudru S, Jehannin P, de Müllenheim PY, Klein H, Jaquinandi V, Mahé G,**
596 **and Le Faucheur A.** Using wearable monitors to assess daily walking limitations induced by

- 597 ischemic pain in peripheral artery disease. *Scandinavian journal of medicine & science in*
598 *sports* 29: 1813-1826, 2019.
- 599 8. **Creager MA, Belkin M, Bluth EI, Casey DE, Jr., Chaturvedi S, Dake MD, Fleg**
600 **JL, Hirsch AT, Jaff MR, Kern JA, Malenka DJ, Martin ET, Mohler ER, 3rd, Murphy**
601 **T, Olin JW, Regensteiner JG, Rosenwasser RH, Sheehan P, Stewart KJ, Treat-**
602 **Jacobson D, Upchurch GR, Jr., White CJ, and Ziffer JA.** 2012
603 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS Key data elements and definitions for
604 peripheral atherosclerotic vascular disease: a report of the American College of Cardiology
605 Foundation/American Heart Association Task Force on clinical data standards (Writing
606 committee to develop clinical data standards for peripheral atherosclerotic vascular disease).
607 *J Am Coll Cardiol* 59: 294-357, 2012.
- 608 9. **Criqui MH, Denenberg JO, Bird CE, Fronck A, Klauber MR, and Langer RD.**
609 The correlation between symptoms and non-invasive test results in patients referred for
610 peripheral arterial disease testing. *Vasc Med* 1: 65-71, 1996.
- 611 10. **Delagarde H, Ouadraougo N, Grall S, Macchi L, Roy PM, Abraham P, and**
612 **Prunier F.** Remote ischaemic preconditioning in intermittent claudication. *Arch Cardiovasc*
613 *Dis* 108: 472-479, 2015.
- 614 11. **Edwards AT, Blann AD, Suarez-Mendez VJ, Lardi AM, and McCollum CN.**
615 Systemic responses in patients with intermittent claudication after treadmill exercise. *Br J*
616 *Surg* 81: 1738-1741, 1994.
- 617 12. **Faisal A, Dyson KS, and Hughson RL.** Prolonged ischaemia impairs muscle blood
618 flow and oxygen uptake dynamics during subsequent heavy exercise. *J Physiol* 588: 3785-
619 3797, 2010.
- 620 13. **Fouasson-Chailloux A, Abraham P, Colas-Ribas C, Feuilloy M, Vielle B, and**
621 **Henni S.** Simultaneous pain intensity rating and quantification of ischemia throughout

- 622 exercise and recovery in proximal versus distal arterial claudication. *Vasc Med* 22: 490-497,
623 2017.
- 624 14. **Gardner AW.** Dissipation of claudication pain after walking: implications for
625 endurance training. *Med Sci Sports Exerc* 25: 904-910, 1993.
- 626 15. **Gardner AW, Montgomery PS, and Afaq A.** Exercise performance in patients with
627 peripheral arterial disease who have different types of exertional leg pain. *J Vasc Surg* 46:
628 79-86, 2007.
- 629 16. **Gardner AW, Parker DE, Montgomery PS, Scott KJ, and Blevins SM.** Efficacy
630 of quantified home-based exercise and supervised exercise in patients with intermittent
631 claudication: a randomized controlled trial. *Circulation* 123: 491-498, 2011.
- 632 17. **Gardner AW, and Poehlman ET.** Exercise rehabilitation programs for the treatment
633 of claudication pain. A meta-analysis. *JAMA* 274: 975-980, 1995.
- 634 18. **Gardner AW, Skinner JS, Cantwell BW, and Smith LK.** Progressive vs single-
635 stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 23: 402-408, 1991.
- 636 19. **Gardner AW, Skinner JS, and Smith LK.** Effects of handrail support on
637 claudication and hemodynamic responses to single-stage and progressive treadmill protocols
638 in peripheral vascular occlusive disease. *Am J Cardiol* 68: 99-105, 1991.
- 639 20. **Gardner AW, Skinner JS, Vaughan NR, Bryant CX, and Smith LK.** Comparison
640 of three progressive exercise protocols in peripheral vascular occlusive disease. *Angiology*
641 43: 661-671, 1992.
- 642 21. **Gardner AW, Skinner JS, Vaughan NR, Bryant CX, and Smith LK.** Comparison
643 of treadmill walking and stair climbing over a range of exercise intensities in peripheral
644 vascular occlusive disease. *Angiology* 44: 353-360, 1993.
- 645 22. **Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA,**
646 **Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra**

647 **S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH,**
648 **Stewart KJ, Treat-Jacobson D, and Walsh ME.** 2016 AHA/ACC Guideline on the
649 management of patients with lower extremity peripheral artery disease: a report of the
650 American College of Cardiology/American Heart Association Task Force on clinical practice
651 guidelines. *Journal of the American College of Cardiology* 69: e71-e126, 2017.

652 23. **Gernigon M, Le Faucheur A, Noury-Desvaux B, Mahe G, Abraham P, and Post-**
653 **GPS Study Coinvestigators Group.** Applicability of global positioning system for the
654 assessment of walking ability in patients with arterial claudication. *J Vasc Surg* 60: 973-981
655 e971, 2014.

656 24. **Hamburg NM, and Balady GJ.** Exercise rehabilitation in peripheral artery disease:
657 functional impact and mechanisms of benefits. *Circulation* 123: 87-97, 2011.

658 25. **Hiatt WR, Armstrong EJ, Larson CJ, and Brass EP.** Pathogenesis of the limb
659 manifestations and exercise limitations in peripheral artery disease. *Circ Res* 116: 1527-1539,
660 2015.

661 26. **Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL,**
662 **Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC,**
663 **Taylor LM, Jr., White CJ, White J, White RA, Antman EM, Smith SC, Jr., Adams CD,**
664 **Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R,**
665 **Ornato JP, Page RL, and Riegel B.** ACC/AHA 2005 Practice guidelines for the
666 management of patients with peripheral arterial disease (lower extremity, renal, mesenteric,
667 and abdominal aortic): a collaborative report from the American Association for Vascular
668 Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and
669 Interventions, Society for Vascular Medicine and Biology, Society of Interventional
670 Radiology, and the ACC/AHA Task Force on practice guidelines (writing committee to
671 develop guidelines for the management of patients with peripheral arterial disease): endorsed

672 by the American Association of Cardiovascular and Pulmonary Rehabilitation; National
673 Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society
674 Consensus; and Vascular Disease Foundation. *Circulation* 113: e463-654, 2006.

675 27. **Hogan MC, Richardson RS, and Kurdak SS.** Initial fall in skeletal muscle force
676 development during ischemia is related to oxygen availability. *J Appl Physiol* (1985) 77:
677 2380-2384, 1994.

678 28. **Kemp GJ, Roberts N, Bimson WE, Bakran A, Harris PL, Gilling-Smith GL,
679 Brennan J, Rankin A, and Frostick SP.** Mitochondrial function and oxygen supply in
680 normal and in chronically ischemic muscle: a combined ³¹P magnetic resonance
681 spectroscopy and near infrared spectroscopy study in vivo. *J Vasc Surg* 34: 1103-1110, 2001.

682 29. **Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, and Noury-
683 Desvaux B.** Measurement of walking distance and speed in patients with peripheral arterial
684 disease: a novel method using a global positioning system. *Circulation* 117: 897-904, 2008.

685 30. **Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, and Noury-
686 Desvaux B.** Study of human outdoor walking with a low-cost GPS and simple spreadsheet
687 analysis. *Med Sci Sports Exerc* 39: 1570-1578, 2007.

688 31. **Le Faucheur A, Noury-Desvaux B, Mahe G, Sauvaget T, Saumet JL, Leftheriotis
689 G, and Abraham P.** Variability and short-term determinants of walking capacity in patients
690 with intermittent claudication. *J Vasc Surg* 51: 886-892, 2010.

691 32. **Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, Caceres RD, and
692 Cooke JP.** Exercise capacity is the strongest predictor of mortality in patients with peripheral
693 arterial disease. *J Vasc Surg* 57: 728-733, 2013.

694 33. **Leplege A, Ecosse E, Verdier A, and Perneger TV.** The French SF-36 Health
695 Survey: translation, cultural adaptation and preliminary psychometric evaluation. *J Clin
696 Epidemiol* 51: 1013-1023, 1998.

- 697 34. **Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE,**
698 **and MacAllister RJ.** Remote ischemic preconditioning provides early and late protection
699 against endothelial ischemia-reperfusion injury in humans: role of the autonomic nervous
700 system. *J Am Coll Cardiol* 46: 450-456, 2005.
- 701 35. **Mahe G, Kalra M, Abraham P, Liedl DA, and Wennberg PW.** Application of
702 exercise transcutaneous oxygen pressure measurements for detection of proximal lower
703 extremity arterial disease: a case report. *Vasc Med* 20: 251-255, 2015.
- 704 36. **Manfredini F, Lamberti N, Guerzoni F, Napoli N, Gasbarro V, Zamboni P,**
705 **Mascoli F, Manfredini R, Basaglia N, Rodriguez-Borrego MA, and Lopez-Soto PJ.**
706 Rehabilitative exercise reduced the impact of peripheral artery disease on vascular outcomes
707 in elderly patients with claudication: a three-year single center retrospective study. *J Clin*
708 *Med* 8: 2019.
- 709 37. **McDermott MM, Liu K, Guralnik JM, Martin GJ, Criqui MH, and Greenland**
710 **P.** Measurement of walking endurance and walking velocity with questionnaire: validation of
711 the walking impairment questionnaire in men and women with peripheral arterial disease. *J*
712 *Vasc Surg* 28: 1072-1081, 1998.
- 713 38. **Mika P, Konik A, Januszek R, Petriczek T, Mika A, Nowobilski R, Nizankowski**
714 **R, and Szczeklik A.** Comparison of two treadmill training programs on walking ability and
715 endothelial function in intermittent claudication. *Int J Cardiol* 168: 838-842, 2013.
- 716 39. **Muggeo VMR.** Segmented: an R package to fit regression models with broken-line
717 relationships. *R News* 8: 20-25, 2008.
- 718 40. **Murrow JR, Brizendine JT, Djire B, Young H-J, Rathbun S, Nilsson KR, Jr.,**
719 **and McCully KK.** Near infrared spectroscopy-guided exercise training for claudication in
720 peripheral arterial disease. *European journal of preventive cardiology* 26: 471-480, 2019.

- 721 41. **Noury-Desvaux B, Abraham P, Mahe G, Sauvaget T, Leftheriotis G, and Le**
722 **Faucher A.** The accuracy of a simple, low-cost GPS data logger/receiver to study outdoor
723 human walking in view of health and clinical studies. *PLoS One* 6: e23027, 2011.
- 724 42. **Paradis S, Charles AL, Meyer A, Lejay A, Scholey JW, Chakfe N, Zoll J, and**
725 **Geny B.** Chronology of mitochondrial and cellular events during skeletal muscle ischemia-
726 reperfusion. *Am J Physiol Cell Physiol* 310: C968-982, 2016.
- 727 43. **Pitcher JB, and Miles TS.** Influence of muscle blood flow on fatigue during
728 intermittent human hand-grip exercise and recovery. *Clin Exp Pharmacol Physiol* 24: 471-
729 476, 1997.
- 730 44. **Poulin A, Guilcher A, Omarjee L, Jaquinandi V, Gandon Y, Mahe G, and**
731 **Stivalet O.** Validation of a software to perform exercise oximetry to diagnose arterial
732 stenosis of the lower limbs. *Atherosclerosis* 278: 325-327, 2018.
- 733 45. **R Core Team.** R: A language and environment for statistical computing. R
734 Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.
735 2019.
- 736 46. **Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott**
737 **MM, and Hirsch AT.** The impact of peripheral arterial disease on health-related quality of
738 life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for
739 Survival (PARTNERS) program. *Vasc Med* 13: 15-24, 2008.
- 740 47. **Saes GF, Zerati AE, Wolosker N, Ragazzo L, Rosoky RM, Ritti-Dias RM,**
741 **Cucato GG, Chehuen M, Farah BQ, and Puech-Leão P.** Remote ischemic preconditioning
742 in patients with intermittent claudication. *Clinics (Sao Paulo)* 68: 495-499, 2013.
- 743 48. **Schorr EN, Treat-Jacobson D, and Lindquist R.** The relationship between
744 peripheral artery disease symptomatology and ischemia. *Nurs Res* 66: 378-387, 2017.

- 745 49. **Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, and Rudan I.**
746 Global, regional, and national prevalence and risk factors for peripheral artery disease in
747 2015: an updated systematic review and analysis. *Lancet Glob Health* 7: e1020-e1030, 2019.
- 748 50. **Sorlie D, and Myhre K.** Lower leg blood flow in intermittent claudication. *Scand J*
749 *Clin Lab Invest* 38: 171-179, 1978.
- 750 51. **Stivalet O, Paisant A, Belabbas D, Omarjee L, Le Faucheur A, Landreau P,**
751 **Garlantezec R, Jaquinandi V, Liedl DA, Wennberg PW, and Mahe G.** Exercise testing
752 criteria to diagnose lower extremity peripheral artery disease assessed by computed-
753 tomography angiography. *PLoS One* 14: e0219082, 2019.
- 754 52. **Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui**
755 **MH, Gardner AW, Hiatt WR, Regensteiner JG, Rich K, on behalf of the American**
756 **Heart Association Council on Peripheral Vascular Disease, Council on Quality of Care**
757 **and Outcomes Research, and Council on Cardiovascular and Stroke Nursing.** Optimal
758 exercise programs for patients with peripheral artery disease: a scientific statement from the
759 American Heart Association. *Circulation* 139: e10-e33, 2019.
- 760 53. **Villemur B, Thoreau V, Guinot M, Gailledrat E, Evra V, Vermorel C, Foote A,**
761 **Carpentier P, Bosson JL, and Perennou D.** Short interval or continuous training programs
762 to improve walking distance for intermittent claudication: pilot study. *Ann Phys Rehabil Med*
763 63: 466-473, 2020.
- 764

765 **FIGURE LEGENDS**

766

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

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

772

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

776

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

779 *Note.* The figure displays the data related only to participants who exhibited a plausible
780 logarithmic or linear effect of recovery time (RT) on walking capacity ($P \leq 0.05$ for the slope).
781 TW-ISO = Isolated sequences of treadmill maximal walking bouts; TW-CONS =
782 Consecutive treadmill maximal walking bouts; OW-CONS = Consecutive outdoor maximal
783 walking bouts; SSRT = Self-selected RT; IRT = Individual RT; Walk_N = Walking time up to
784 maximal claudication pain performed after the RT tested; Walk₁ = First walking time up to
785 maximal claudication pain during the walking sequence; % $\dot{V}O_{2peak}$ = Percentage of peak
786 oxygen uptake; %HR_{peak} = Percentage of peak heart rate; DROP = Delta from resting
787 transcutaneous oxygen pressure; PFWT = Pain-free walking time; MWT = Maximal walking
788 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).

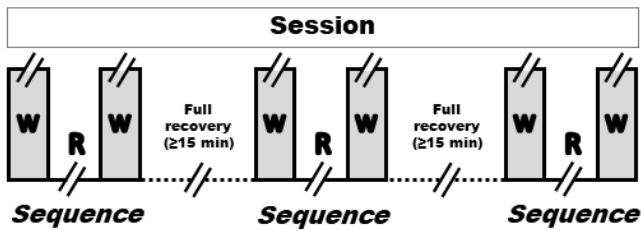
800 * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, compared with the previous RT.

CONDITIONS

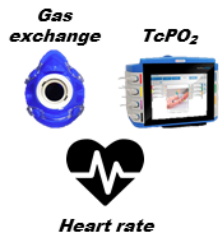
PROTOCOL

MEASURES

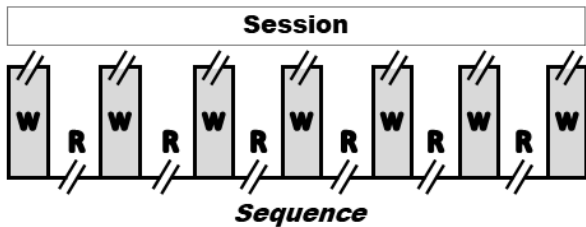
TW-ISO



- 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



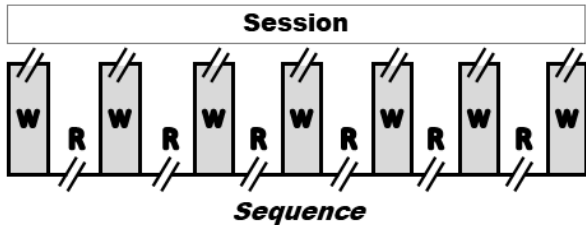
TW-CONS



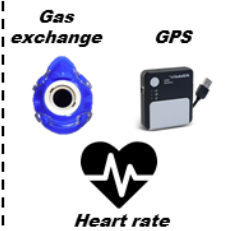
- Treadmill walking
- 1 sequence over one session
- R tested (min) → 0.5, 2.5, 4.5, 6.5, 8.5 + SSRT
- Walking intensity → 3.2 km/h; 12% grade
- Pain level → 4/4

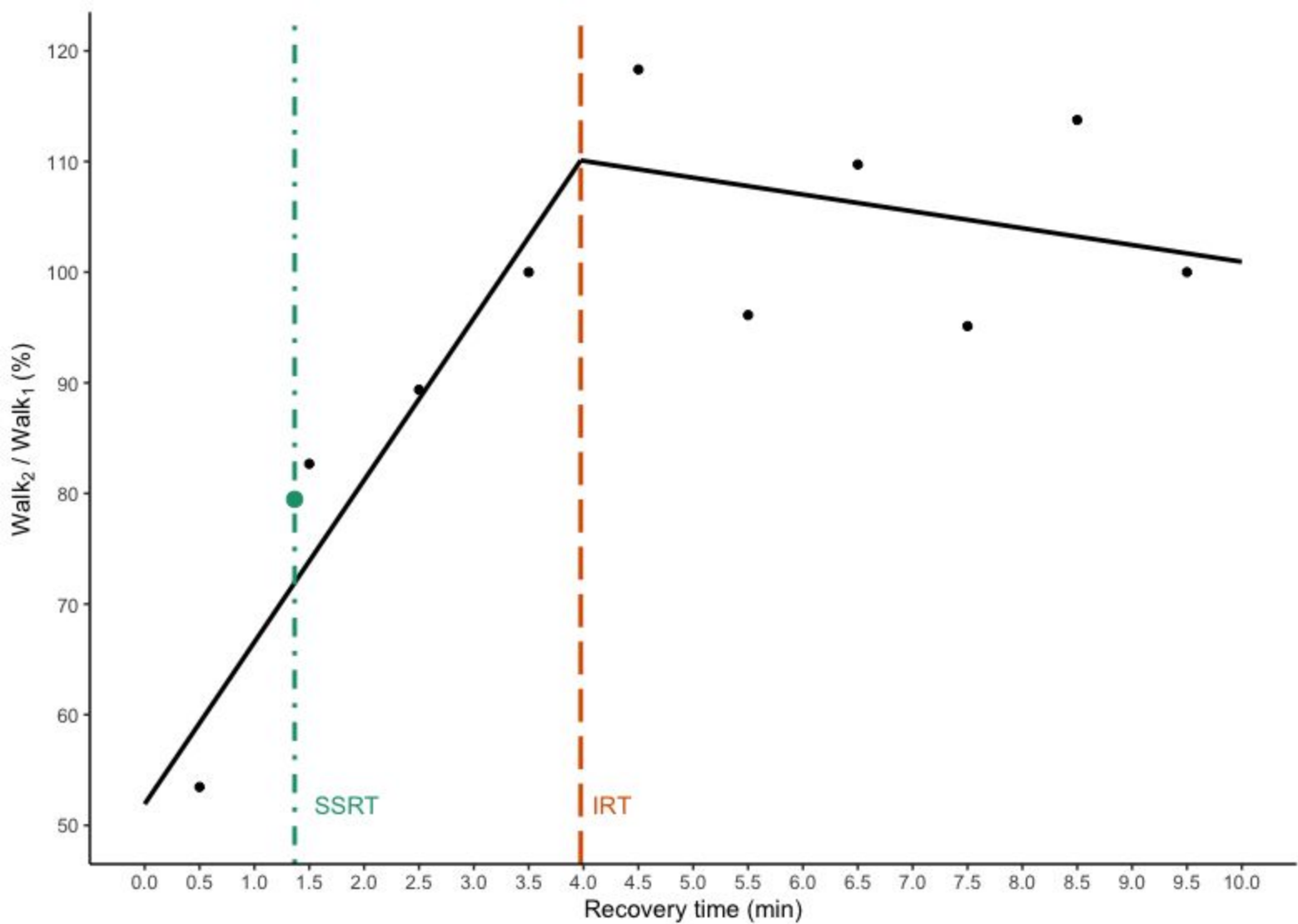


OW-CONS

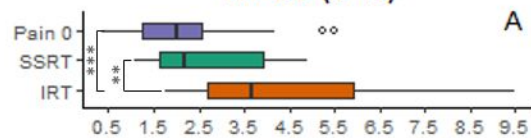


- Outdoor walking
- 1 sequence over one session
- R tested (min) → 0.5, 1.5, 2.5, 3.5, 4.5 + SSRT
- Walking intensity → usual pace; 0% grade
- Pain level → 4/4

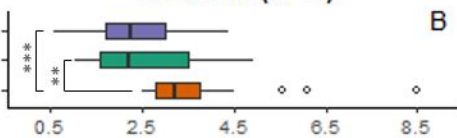




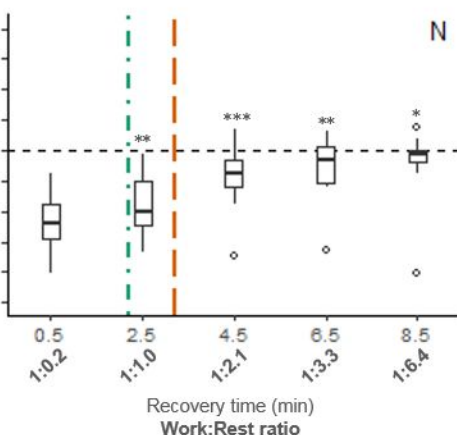
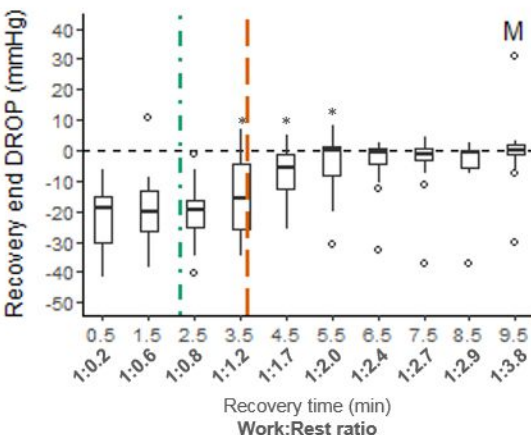
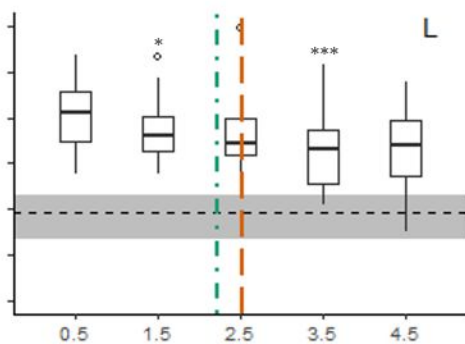
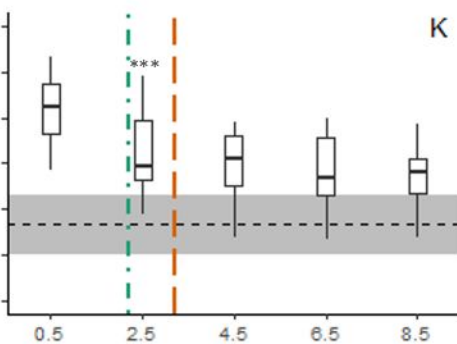
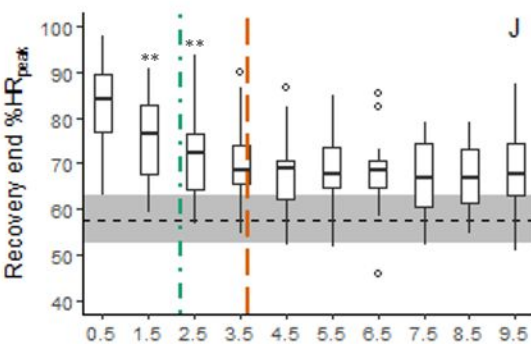
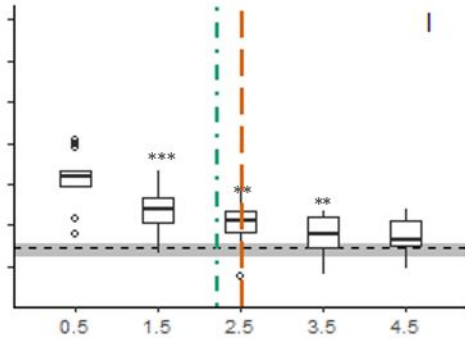
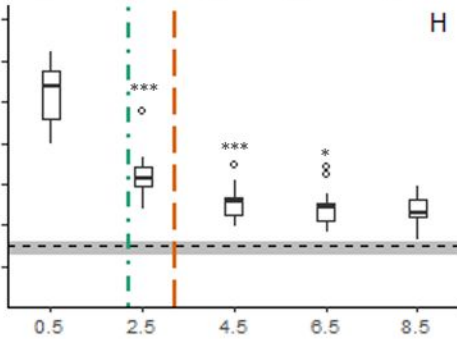
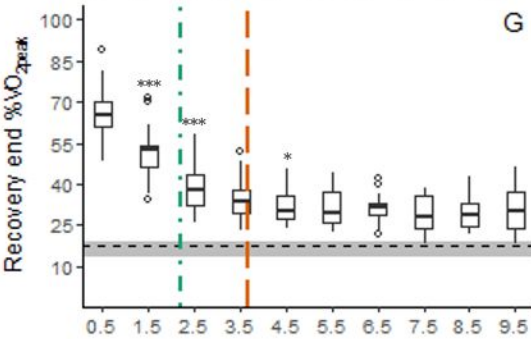
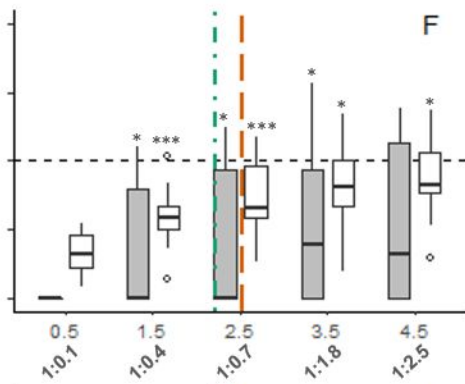
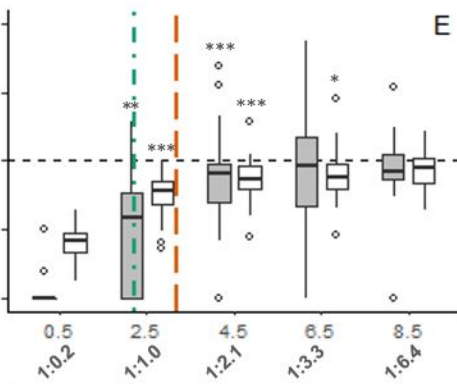
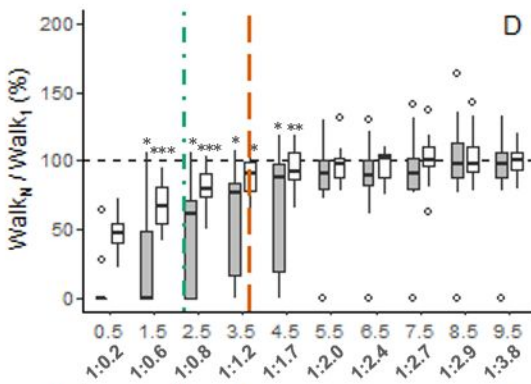
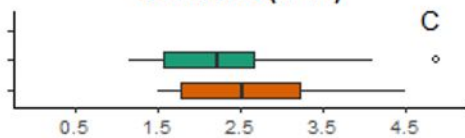
TW-ISO (n=18)



TW-CONS (n=17)

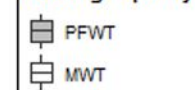


OW-CONS (n=14)



Recovery time (min)
Work:Rest ratio

Waking capacity



Recovery time



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

Inclusion criteria

- Age ≥ 18 years old
- Insured under the French social security system (according to French law)
- Presence of lower-extremity peripheral artery disease, defined by:
 - 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

- 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)
<hr/>	
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)
<hr/>	
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)
<hr/>	
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/MWT₁, 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	2.59·10 ⁻¹²	4.70·10 ⁻¹⁵	5.47·10 ⁻¹⁸	2.78·10 ⁻²⁹	2.15·10 ⁻¹³	1.11·10 ⁻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/MWT₁ x 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/MWT_1 , 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.