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1 **Relationship between the severity of exercise-induced ischemia and the prevalence of**
2 **exercise-induced symptoms at the calves during treadmill testing with transcutaneous**
3 **oximetry.**

4

5 Jeanne HERSANT^{1,§}, Pierre RAMONDOU^{1,§}, Jean PICQUET^{2,3}, Mathieu FEUILLOY⁴,
6 Pierre ABRAHAM^{2,5}, Samir HENNI^{1,2}.

7

8 1 Vascular Medicine, University Hospital, Angers, France pierre.ramondou@chu-angers.fr;
9 Jeanne.hersant@chu-angers.fr; Samir.henni@chu-angers.fr; Piabraham@chu-angers.fr

10 2 MitoVasc Institute UMR CNRS 6015/INSERM 1083, Faculty of Medicine, Angers
11 University, France.

12 3 Thoracic and Vascular Surgery, University Hospital, Angers, France. Jepicquet@chu-
13 anders.fr

14 4 School of Electronics (ESEO), Angers, France. Mathieu.feuilloy@eseo.fr

15 5 Sports Medicine, University Hospital Center, Angers, France

16

17 *Corresponding author:

18 Prof. Pierre ABRAHAM, Centre Hospitalier Universitaire, 4 rue Larrey

19 49 933 Angers Cedex 9; Tel.: 02 41 35 36 89 Fax: 02 41 35 50 42

20 ORCID: 0000 0001 7053 2801 Email: piabraham@chu-angers.fr

21

22 § P Ramondou and J Hersant share first authorship

23

24 Research paper.

25 Short title: Pain and Ischemia Relationship in Claudication

26

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28

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30 **WHAT THIS STUDY ADDS:**

31 Correlations between exercise-induced symptoms with hemodynamic parameters of LEAD
32 are fair at best. The present study shows a biphasic relationship between the prevalence of
33 symptoms (exercise-induced calf pain) and the severity of calf ischemia as assessed by the
34 minimal decrease from rest of oxygen pressure (DROPM) obtained by exercise oximetry. We
35 report a linear increase from DROPM= 0 (with origin being approximately 30% symptom
36 prevalence and a slope showing a 1.4 % increase in symptom prevalence for each 1 mmHg
37 decrease in DROPMin), until a plateau is reached for the more severe ischemic limbs
38 (symptom prevalence being ~70% at the plateau).

39

40 **ABSTRACT:**

41 Objectives: We hypothesized that we would find a linear relationship between the severity of
42 calf exercise-induced ischemia and the prevalence of calf claudication on a treadmill until a
43 plateau is reached. We also expected that no pain would be present in the absence of ischemia
44 and all severe ischemic calves would be symptomatic.

45 Design: Retrospective analysis of a cross-sectional acquired database recording.

46 Materials: Transcutaneous oxygen pressure (TcpO₂) on chest and on each calf was used to
47 evaluate calf ischemia during treadmill tests with simultaneous recording of calf pain in 7884
48 subjects (15,768 calves).

49 Methods: We calculated the minimal value of calf changes from rest minus chest changes
50 from rest (DROPM). Regression analyses were used to determine the correlation between the
51 proportion of exercise-induced symptoms present in calves and each unit of DROPM values.
52 We repeated the analysis after objective determination of the cut-off point between the linear
53 increase and the plateau.

54 Results: We found a linear relationship between the degree of ischemia and the proportion of
55 symptomatic calves for DROPM values ranging from 0 mmHg to -28 mmHg (Proportion = -
56 $0.014 \cdot \text{DROPM} + 0.32$, $r = 0.961$, $p < .001$). For DROPM values lower than -28 mmHg (severe
57 ischemia), on average 1/3 of limbs remained asymptomatic. The biphasic relationship
58 between DROPM to prevalence of symptoms persists after exclusion of patients with diabetes
59 mellitus, exercise-induced hypoxemia and no evidence of lower extremity arterial disease
60 (LEAD).

61 Conclusions: The relationship between exercise-induced pain and ischemia is biphasic with a
62 linear increase in the proportion of symptomatic limbs with ischemia severity, until a plateau
63 is reached for the more severe ischemic limbs. The presence of exercise-related calf
64 symptoms should not automatically be reported as indicating the presence of LEAD; and the
65 absence of exercise-induced symptoms is not proof that ischemia does not occur during
66 exercise.

67

68 **KEYWORDS**

69 Lower extremity artery disease; Intermittent claudication; Calf pain; Exercise oximetry;
70 Symptoms; Ischemia
71

72 INTRODUCTION

73 Lower limb pain while walking is a frequent symptom in elderly patients. Vascular type
74 claudication is defined as lower limb pain or discomfort that is absent at rest, induced by
75 exercise and disappears within 10 minutes when exercise is stopped ¹. A better knowledge of
76 the relationship of symptoms to ischemia is required to explain why 4% of patients do not
77 show improvement after revascularization ² or why patients may clinically improve without
78 apparent hemodynamic improvements (i.e. absence of ABI increase) during rehabilitation
79 programs ³.

80 Pain in arterial claudication is assumed to result from the stimulation of nociceptors by tissue
81 acidosis induced by the lactate accumulation. Lactate accumulates because of the disparity
82 between the oxygen demand of exercising muscle and the oxygen delivery to the active
83 muscle via blood flow. Therefore, one potential way to evaluate the severity of ischemia is to
84 estimate the difference between the oxygen demand of the exercising muscle and the impaired
85 oxygen delivery resulting from lower extremity arterial disease (LEAD). Transcutaneous
86 oxygen pressure (T_{cp}O₂) recordings allow the monitoring of lower limb regional blood flow
87 impairment (RBF_I) throughout exercise and recovery in both calves simultaneously ⁴⁻⁶. The
88 calculation of the lowest value of the “decrease from rest of oxygen pressure” (DROPM)
89 index provides measurable evidence for this oxygen deficit: the lower the DROPM value, the
90 more severe the RBF_I ⁴.

91 We hypothesized that in patients referred for treadmill testing for suspected, or follow-up of,
92 vascular type claudication, we would find a biphasic relationship between DROPM values and
93 the prevalence of exercise-related symptoms. The first part of the biphasic relationship would
94 be a linear increase until a plateau is reached. In theory, no symptoms would be found in the
95 absence of ischemia (in which case the regression line starts from zero). For the second part of
96 the biphasic response all severely ischemic limbs should be symptomatic, and a plateau
97 should be observed with 100% symptomatic limbs when DROPM values are low enough.

98 METHODS

99 **Study population, inclusion criteria and ethical approval:**

100 Since 1999, we have used exercise-T_{cp}O₂ as routine among all patients referred to our
101 laboratory for the diagnosis or follow-up of exercise-induced claudication of suspected
102 arterial origin ⁴⁻⁷. As routine, all subjects had to fill in a questionnaire about their age, sex,

103 ongoing treatment, presence or absence of diabetes mellitus based on either medical history
104 of, or ongoing treatment for, diabetes mellitus. Height and weight were recorded to calculate
105 body mass index (BMI: kg/m²), as well as ankle-to-brachial index (ABI). The presence of
106 LEAD was based on either ABI<0.90 or a report for ultrasound or angiography confirming
107 the presence of “significant stenoses”.

108 As routine, patients were systematically informed that their record and the medical database
109 as a whole would be used for research purposes and were informed of their right to object to
110 such use, but that according to French law, the analysis of routine practice does not require
111 written individual consent. The database was ethically approved and was fully declared to
112 national authorities. The present analysis of the recording and database received local ethics
113 committee approval under reference 2020/42 and conforms to the Declaration of Helsinki. It
114 was registered on the American National Institutes of Health database clinicaltrial.gov under
115 reference NCT04376099. For the present work, we analysed all adult patients (age > 18 years
116 old) referred for exercise TcpO₂ since the database was initiated. Exclusion criteria were the
117 absence of TcpO₂ results (test not performed for technical reasons, contra-indication to the
118 test, missing results, leg amputation) or a lack of information on exercise-related symptoms.

119 **Exercise tests and symptom description:**

120 For patients who were able to walk 10 m in less than 15 sec we proposed a standard treadmill
121 procedure, consisting of a transition phase of 1 minute from a flat gradient and 0 km/h to 3.2
122 km/h and a 10% slope, while for the other patients, the maximum speed was limited to 2
123 km/h. Before 2007, in the absence of limiting symptoms, the test was stopped at 20 minutes,
124 whereas since 2007 after 15 minutes the speed and gradient were increased by increments of 1
125 minute until exhaustion or limiting symptoms occurred, as previously described⁸. Throughout
126 the walking period, patients were asked to report symptoms in one or both calves. We
127 recorded maximum walking time (MWT) as the time at which the treadmill was stopped as
128 well as exercise-related lower limb symptoms at calf level on each side.

129 **TcpO₂ measurements:**

130 We used three 44.5 °C heated sensors (E5250 Radiometer, DK) either connected to a
131 TCM400 Radiometer device (Radiometer; Copenhagen, Denmark) or PF5010 device
132 (Perimed; Stockholm, Sweden), with double calibration to air. Probes were positioned on the
133 lower third external aspect of each calf and at chest level (in the upper part of the back,). A

134 detailed description of the technique is provided as supplementary material. At chest level, the
135 normal response is an increase of TcpO₂ from rest^{9, 10}. Then exercise-induced systemic
136 hypoxemia was arbitrarily defined as a decrease in chest TcpO₂ from resting values of 10
137 mmHg or more in order to account for spontaneous baseline changes. We calculated the
138 decrease from rest of oxygen pressure (DROP) by subtracting chest changes from rest from
139 calf changes from rest^{11, 12}. The lowest DROP value observed during a test is denoted
140 DROPm. The DROPm is considered indicative of the severity of RBF1.

141 **Statistical analysis:**

142 TcpO₂ values were recorded without decimals in the database. Results are reported as number
143 of observation (Nb) with percentage (%) of the observations within the considered group,
144 mean, +/- standard deviation (SD) or *median [25° - 75° centiles]*, according to distribution
145 normality. Statistical analyses were performed using SPSS (IBM SPSS statistics V15.0;
146 Chicago, USA). Distribution normality was tested using Kolmogorov-Smirnov tests.
147 Comparison between groups was performed using an unpaired T-test for numerical data and
148 Chi-square test for categories. For each DROPm value, we calculated the proportion of
149 symptomatic limbs (exercise-induced calf pain under the probe). These proportions are
150 reported with 95% confidence intervals. In order to objectively detect the degree of severity
151 above which the correlation between DROPm values and the proportion of symptomatic
152 limbs (exercise-induced calf pain) would result in a plateau, we progressively increased the
153 range of values involved in the regression line calculation. Due to the inverse relationship
154 between DROPm values and the proportion of symptomatic limbs, we hypothesized that the
155 coefficient of correlation would decrease toward minus 1 with the increase in range of
156 included values, as long as linearity was respected. Thereafter, it would increase while
157 additional values from the plateau are included in the calculation. Thereby, the DROPm that
158 resulted in the best coefficient of correlation was used as a cut-off point to separate the linear
159 part of the relationship from the plateau in the expected biphasic response. Then, linear
160 regression analyses of the data were performed for the whole range of data as well as
161 separately for DROPm values down to, and below this cut-off point, and we calculated the
162 origin and slope of the two regression lines. Coefficients of correlation were expected to be
163 negative values (higher proportions of symptomatic calves for lower DROPm values). For all
164 statistical tests, a 2-tailed probability level of $p < .05$ was used to indicate statistical
165 significance. Non-significant results are reported as NS.

166

167 **RESULTS**

168 Of the 8551 records available in the database on July 8, 2021, we identified 7884 records for
169 which information on calf symptoms and measurements of calf TcpO₂ were available for both
170 sides as shown in Figure 1. Characteristics of the patients are presented in Table 1.

171 Typical examples of TcpO₂ recordings are presented in Figure 2. It is interesting to note that
172 despite widely different starting values, changes on the two chest probes of both patients are
173 almost similar in pattern and in amplitude on the right and left side. This underscores the
174 importance of the DROP calculation in eliminating the unpredictable transcutaneous gradient
175 in oxygen.

176 Figure 3 presents the results for the 15,768 calves. As shown on the upper panel, the DROPm
177 values did not follow a Gaussian distribution which is important because the number of
178 observations directly influences the confidence intervals observed for the proportion of
179 symptomatic limbs for each DROPm value, as will be reported below. The optimal cut-off
180 point between the increase and plateau phases of the DROPm to the proportion of
181 symptomatic calves relationship was found to be -28 mmHg (fig. 3 middle panel). As shown
182 in the lower panel of figure 3, we found a linear relationship between the degree of ischemia
183 and the proportion of symptomatic calves for DROPm values ranging from 0 mmHg to -28
184 mmHg ($r = 0.961$, $p < .001$). The slope and origin of the regression line suggested a 1.4%
185 increase in the proportion of symptomatic calves for each 1 mmHg decrease in DROPm value
186 and that 32% limbs were symptomatic for a theoretical zero DROPm value. For DROPm
187 values lower than -28 mmHg (severe ischemia), the slope is almost flat (results are
188 independent from the severity of ischemia), with an average of approximately 30% of calves
189 remaining asymptomatic. Note that, for the whole range of DROPm values the coefficient of
190 correlation for the relationship between the proportions of symptomatic calves and each of the
191 DROPm values was only $r = 0.183$ ($p = 0.072$).

192

193 **DISCUSSION**

194 The study allowed us to confirm our hypothesis of a biphasic relationship between the
195 DROPm index and the proportion of symptomatic limbs. Notably, approximately 30% of

196 limbs were symptomatic for a zero DROPm value (absence of measurable exercise-induced
197 RBFi) and approximately 30% of limbs remained asymptomatic for DROPm values lower
198 than -28 mmHg.

199 There have been multiple attempts to correlate quality of life or symptoms to hemodynamic
200 parameters of LEAD severity¹³⁻¹⁷. The relationship between the Walking Impairment
201 Questionnaire (WIQ) Score and various indices of LEAD severity (ankle-brachial index, time
202 to maximal claudication, 6-minute walked distance) ranged from 0.16 to 0.45 in 80 patients
203 with claudication¹³. In 555 patients with intermittent claudication, Feinglass et al. found a
204 weak coefficient of correlation between ABI and the WIQ distance score ($r = 0.18$, $p < .001$)
205¹⁷. Last, in 150 subjects, U Müller-Bühl et al.¹⁸ found a weak correlation ($r = 0.20$, $p < .01$)
206 between ABI and maximal walking distance.

207 Since a non-linear relationship exists for ABI and vascular risk¹⁹, recent studies have reported
208 other indices of hemodynamic results. For example, contrast-enhanced ultrasound showed a
209 much better correlation with the Rutherford classification than ABI^{20,21}. Gardner et al. also
210 showed that the minimum calf muscle oxygen saturation (log-transformed) is associated with
211 maximal walking time ($r = 0.56$; $p < .001$)²². Many factors such as arterial stiffness or
212 myopathia may participate to these non-linear relationships between vascular indices and their
213 clinical correlates^{23,24}. The coefficient of correlation for the linear regression analysis that we
214 had for the whole range of DROPm values ($r = 0.569$) is close to previous publications and
215 underlines the interest of analysing the data in two different phases (which result in a very
216 high coefficient from 0 to -28 mmHg, consistent with our initial hypothesis).

217 It is worth noting that we previously showed that among patients complaining of isolated calf
218 pain, a perfect concordance with symptoms on a treadmill and underlying ischemia (calf pain
219 only and calf ischemia only) was observed in only 19.5% of the cases²⁵. Although we did not
220 expect that our observation would result in a simplistic linear 0 to 100% prevalence of
221 symptoms with the decrease in DROPm values, the proportion of symptomatic limbs without
222 associated ischemia and that of asymptomatic limbs despite severe ischemia (both being close
223 to 30%) were higher than we presumed. Multiple reasons could contribute to these high rates.
224 Obviously, a lack of sensitivity (false negative results) of TcpO2 cannot be excluded (e.g.
225 patients stopping their test for cardiac or osteo-articular reasons before ischemia occurred).
226 We previously showed that, in many cases, these apparently false-negative tests found
227 explanations and that the normal TcpO2 indicated that the origin of symptoms was probably

228 not vascular despite the presence of LEAD as expanded upon below ²⁵. Although we
229 accounted for exercise-induced symptoms only, it is likely that many of these symptoms
230 observed in the absence of ischemia are of non-vascular origin (e.g. osteo-articular, statin-
231 induced myalgia, lumbar spinal stenosis, etc.). Lastly, it should be kept in mind that DROPm
232 is calculated as the decrease in limb TcpO₂ during exercise from which an eventual decrease
233 in chest (systemic) TcpO₂ is subtracted ⁹. Exercise-induced systemic hypoxemia may
234 therefore mask the eventual peripheral limb hypoxia, while oxygen delivery in the limb will
235 be impaired, possibly resulting in anaerobic lactate accumulation and pain. Nevertheless, the
236 relationship between DROPm and the proportion of symptomatic limbs remained unchanged
237 after exclusion of patients with an exercise-induced decrease in chest TcPO₂ of more than 10
238 mmHg (see supplementary data). Another possibility is that the sensor was not positioned at
239 the optimal location, specifically in patients complaining of proximal and distal symptoms.
240 The present study focused on calf symptoms only and results for TcpO₂ at the buttock level
241 were not taken into consideration despite the fact that we previously reported that isolated calf
242 pain was relatively frequent (pseudo-sciatica) in patients with isolated buttock ischemia ²⁶.

243 The absence of symptoms in almost 30% of severely ischemic limbs can also have various
244 origins. A lack of specificity (false-positive results) of TcpO₂ is one possible explanation.
245 Another possible explanation is that another more painful localisation occurred in the patient,
246 who did not report the calf as a less painful location. The presence of a neuropathy,
247 specifically in cases of diabetes mellitus or the use of pain killers or decreased sensitivity to
248 pain (as a possible mechanism of training), is another possible explanation for these
249 asymptomatic but severely ischemic limbs. Nevertheless, the results seem to remain
250 unchanged after diabetic patients have been excluded.

251 With regard to limitations of the present study, first of all, it might be legitimate to suggest
252 that there was a bias in recruitment because we should have focused on patients with
253 confirmed LEAD only. Since it was previously shown that 13% of patients with claudication
254 have a normal ABI at rest ²⁷, we believe that recruiting patients regardless of resting ABI was
255 meaningful. Furthermore, the results are almost unchanged when only patients with abnormal
256 resting ABI (ABI < 0.90 or > 1.30) are studied. Second, no study of the influence of walking
257 duration was undertaken, but most tests were brought to a halt on request of the patient. The
258 heterogeneity of protocols (slow procedure in slow walkers) could also be considered a
259 limitation. It affected only 7.7 % of all patients. Furthermore, we previously reported that
260 DROPm was unaffected by the protocol used ²⁸. Third, no sex-specific analysis was

261 performed, but for reasons we have not been able to explain, our patients were predominantly
262 males, and a female-specific analysis would result in too few cases per group. Forth, diabetes
263 mellitus was based on the self-reported presence of, or treatment for, diabetes while no
264 recording of the objective presence of neuropathy was carried out. Almost all patients were
265 outpatients and we often do not have direct access to their medical files. Fifth, some patients
266 had multiple tests over the study period. Due to our database construction, identification of
267 such patients in the present study was impossible, but we estimate that they represent less than
268 15% of all cases. Sixth, TcpO2 is a microvascular technique that can be influenced by acute
269 drug intake, smoking or caffeine absorption²⁹. Tests were performed in routine, and patients
270 had not been advised to stop usual medication or avoid drinking coffee or smoking cigarettes
271 before the tests were carried out. Seventh, in our routine practice we do not always have
272 access to the medical files of the patients and cannot report the presence or absence of
273 osteoarthritis, cardiac or renal dysfunction or previous revascularization. Similarly, due to our
274 retrospective design, although most of our patients taking cholesterol-lowering drug received
275 statins, our database does not differentiate statins from other cholesterol-lowering drugs. Last
276 of all, we do not report proximal ischemia and/or non-calf symptoms because during the
277 initial phase of exercise oximetry development in the laboratory, we did not have sufficient
278 probes to allow proximal recordings. The number of calves studied (> 15,000) is expected to
279 compensate for many of these limitations.

280 **CONCLUSION**

281 Our results confirm our hypothesis that the proportion of symptomatic limb increases linearly
282 with the severity of ischemia up to a plateau for the most severely ischemic calves.
283 Nevertheless, exercise-related limb symptoms should not automatically be reported as
284 indicating the presence of LEAD, with almost one third of calves with exercise-related
285 symptoms showing no exercise-induced calf ischemia. Furthermore, the absence of exercise-
286 induced symptoms is not proof that ischemia does not occur in patients during exercise, with
287 almost one third of legs with severe calf ischemia (DROPm < -28 mmHg) remaining
288 asymptomatic during treadmill tests. Future studies are required to determine whether
289 systematic analysis of the presence/absence of ischemia through exercise oximetry may allow
290 better decisions to be made regarding therapeutic interventions in patients with claudication
291 and/or LEAD and the effects of these to be better monitored.

292

293

294 **CONFLICTS OF INTEREST**

295 PA has benefited from the support of Radiometer, Perimed, Profusa and Medicap. None of
296 these companies had access to or interfered in the present project.

297

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299 The protocol was promoted (and then indirectly funded) by the University Hospital, Angers.

300

301 **AUTHOR CONTRIBUTIONS**

302 PA and SH conceived and designed the study. PR, JP, JH, PA and SH participated in the
303 recruitment of patients. MF, JH and PR participated in the data analysis and interpretation. PA
304 and SH prepared the manuscript draft, the other authors critically revised the manuscript. All
305 authors approved the final version of the manuscript.

306

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311

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393

394 **TABLES:**

395 Table 1: Characteristics of the patients and results for the exercise test. TcpO2 stands for
 396 transcutaneous oxygen pressure and DROP stands for decrease from rest of oxygen pressure.

	Total	No diabetes and no hypoxemia	Diabetes or hypoxemia	p
	N = 7884	N = 5180	N = 2704	
<i>Characteristics of the patients</i>				
Age - years	63.7 ± 11.3	62.8 ± 11.7	65.4 ± 10.2	.001
Male sex	6373 (80.8)	4113 (79.4)	2260 (83.6)	.001
Body weight - kg	76.9 ± 15.4	74.6 ± 14.6	81.6 ± 15.9	.001
Height - cm	169 ± 8	169 ± 8	169 ± 8	.215
LEAD based on either ...	6075 (77.1)	3968 (76.6)	2107 (77.9)	.194
... positive imaging	3606 (45.7)	2249 (43.4)	1357 (50.2)	.001
... ABI < 0.90 or > 1.30	5389 (68.4)	3541 (68.4)	1848 (68.3)	1
<i>Ongoing treatments</i>				
Anti-platelet agents	5984 (75.9)	3865 (74.6)	2219 (82.1)	.001
Anti-hypertensive drugs	4629 (58.7)	2787 (53.8)	1842 (68.1)	.001
Cholesterol-lowering drugs	4935 (62.6)	3026 (58.4)	1909 (70.6)	.001
Pain killers	1242(15.8)	825 (15.9)	417 (15.4)	.580
Beta blockers	2297 (29.1)	1326 (25.6)	971 (35.9)	.001
<i>Resting TcpO2 values</i>				
Chest - mmHg	66 ± 13	66 ± 13	66 ± 14	.854
Right calf - mmHg	71 ± 12	71 ± 12	69 ± 13	.001
Left calf - mmHg	71 ± 12	71 ± 12	69 ± 12	.001
<i>Treadmill test</i>				
Standard procedure	7318 (92.8)	4844 (93.5)	2474 (91.5)	.001
Maximal walking time – sec	326 [190 / 743]	342 [197 / 832]	300 [180 / 598]	.001
Maximal heart rate - beats/min	119 ± 22	120 ± 22	119 ± 22	.188
Left calf DROP min - mmHg	-15 [-26 / -8]	-14 [-26 / -8]	-14 [-25 / -8]	.190
Right calf DROP min - mmHg	-14 [-26 / -8]	-15 [-26 / -8]	-14 [-25 / -8]	.530
Lower limb symptoms on treadmill	6719 (85.2)	4437 (85.7)	2282 (84.4)	.141
Left calf pain	4195 (53.2)	2726 (52.6)	1469 (54.3)	.154
Right calf pain	4110 (52.1)	2705 (52.2)	1405 (52.0)	.183
Non-limb symptoms	1752 (22.2)	1077 (20.8)	675 (25.0)	.001

397 Data are presented as n (%) or mean ± standard deviation (SD) or median (interquartile range [IQR]).

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400 **LEGENDS FOR ILLUSTRATIONS:**

401 **Figure 1:** Flowchart of the study.

402

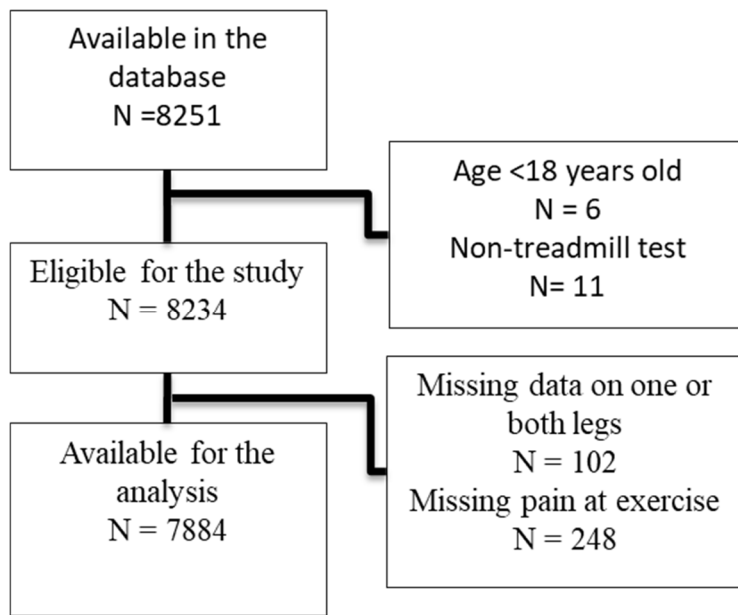
403 **Figure 2:** Typical examples of TcpO₂ recordings. Note that in these two patients two chest probes
404 were used, although only the right chest value was used to calculate the decrease from rest of oxygen
405 pressure (DROp) at the calves. Patient A is an 88-year-old female patient with ultrasound-detected
406 stenosis of both femoral arteries estimated at 50 - 60% and an ankle-to-brachial systolic pressure index
407 (ABI) of > 1.6 on both sides, who complains of bilateral calf pain while walking. As shown, the
408 walking duration (white arrow) was approximately 6 minutes and DROp values did not decrease at the
409 calves and DROpm was -1 mmHg on both calves. Nevertheless, chest values decreased significantly,
410 suggesting exercise-induced systemic hypoxemia as the cause (or the worsening cause of calf muscle
411 oxygen delivery/oxygen requirement disparity). Patient B is a 77-year-old male with bilateral stenoses
412 on ilio-femoral arteries. Right ABI was 0.41 and left ABI was 0.79. Walking (11 minutes) on treadmill
413 induced a unilateral right calf pain consistent with underlying severe DROp decrease throughout
414 exercise: DROpm was -14 mmHg on the left calf and -36 mmHg on the right calf, respectively.

415

416 **Figure 3:** Number of legs for each unit of DROpm value (upper panel) and analysis of the relationship
417 between minimal decrease from rest of oxygen pressure (DROpm) and the proportion of symptomatic
418 limbs (exercise-induced calf pain) on a limb-by-limb basis (lower panel) among the 15768 calves of
419 the 7884 studied subjects. Middle panel is the evolution of the coefficient of correlation between
420 DROpm and the proportion of symptomatic limbs with the increase in the number of DROpm
421 categories starting from zero. The lowest value of the coefficient (black point) was used to determine
422 the cutoff point that separates the linear relationship between DROpm values and the proportion of
423 symptomatic limbs shown in the lower panel. Note that the cutoff point was -28 mmHg. The
424 proportions are represented with 95% confidence intervals.

425

426 **Figure 1:**



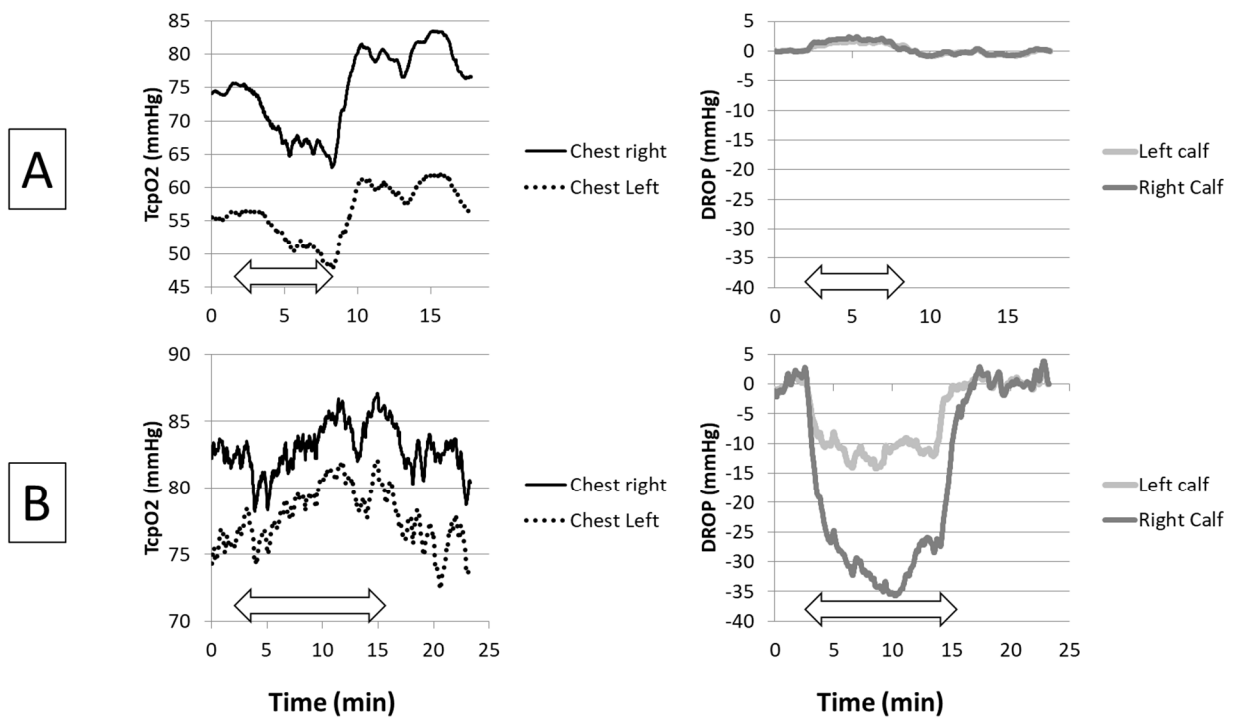
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430 **Figure 2:**

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