



HAL
open science

The hidden side of calf claudication: Hemodynamic and clinical results of treadmill testing in 584 patients complaining of isolated exertional calf pain

Pierre Ramondou, Wendsendaté Yves Sempore, Céline Guilleron, Jeanne Hersant, Nafi Ouedraogo, Pierre Abraham, Samir Henni

► To cite this version:

Pierre Ramondou, Wendsendaté Yves Sempore, Céline Guilleron, Jeanne Hersant, Nafi Ouedraogo, et al.. The hidden side of calf claudication: Hemodynamic and clinical results of treadmill testing in 584 patients complaining of isolated exertional calf pain. *Atherosclerosis*, 2020, 314, pp.41 - 47. 10.1016/j.atherosclerosis.2020.10.891 . hal-03493540

HAL Id: hal-03493540

<https://hal.science/hal-03493540v1>

Submitted on 7 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **The hidden side of calf claudication: Hemodynamic and clinical results of treadmill testing in**
2 **584 patients complaining of isolated exertional calf pain.**

3

4 Pierre Ramondou^{a,b}, Wensendaté Yves Sempore^c, Céline Guilleron^{b,d}, Jeanne Hersant^a, Nafi
5 Ouedraogo^c, Pierre Abraham^{a,b,e*}, Samir Henni^{a,b}

6

7 ^aVascular Medicine, University Hospital Center, 4 rue Larrey, 49000 Angers, France.

8 ^bMitoVasc Institute UMR CNRS 6015 / INSERM 1083, Faculty of Medicine, Angers University, rue
9 Haute de Reculée, 49000 Angers, France.

10 ^cUniversité Nazi Boni, Bobo Dioulasso, Burkina Faso.

11 ^dUMR CNRS 6613 LAUM, Le Mans University, avenue Olivier Messiaen, 72000 Le Mans, France.

12 ^eService of Sports Medicine, University Hospital, 4 rue Larrey, 49000 Angers, France

13

14 *Corresponding author: Pierre Abraham

15 Centre Hospitalier Universitaire, 4 rue Larrey

16 49 933 Angers Cedex 9; Tél. 02 41 35 36 89 Fax : 02 41 35 50 42

17 PiAbraham@chu-angers.fr

18

19 KEYWORDS

20 Intermittent claudication; calf symptoms; exercise oximetry; ischemia; pain

21

22 ABSTRACT

23 *Background and aims.* Calf pain is the most frequent symptom of arterial claudication. We
24 hypothesized that patients with self-reported isolated calf claudication have frequent exertional non-
25 calf symptoms during objective laboratory testing, and that many would show not only distal, but also
26 proximal ischemia.

27 *Methods.* We retrospectively analyzed the patients referred since 2016 for exercise transcutaneous
28 oxygen pressure (Ex-tcpO₂). The Edinburgh Claudication Questionnaire (ECQ) was self-completed
29 before and during a treadmill test. For calf and non-calf (buttock and thigh) Ex-tcpO₂, a lowest
30 decrease of rest of oxygen pressure (DROP) < -15 mmHg was indicative of ischemia. We selected the
31 patients that reported calf claudication only and analyzed minimal DROP and per-test ECQ
32 observations.

33 *Results.* Exertional symptoms on a treadmill occurred in 526 (90.1 %) of the 584 patients analyzed
34 (65.6 ± 11.4 years old), with 391 (74.3 %) of these symptoms affecting only the calf. Isolated calf
35 ischemia with or without symptoms was found in only 139 (23.8 %) patients. Overall, among the 584
36 patients self-reporting isolated calf symptoms, a perfect concordance between symptoms on a
37 treadmill and Ex-tcpO₂ (i.e. calf symptoms associated to calf ischemia) was observed in only 114
38 (19.5%) cases.

39 *Conclusions.* Our study demonstrated that patients self-reporting exertional limb pain strictly limited
40 to the calf may also have non-calf claudication on a treadmill and frequently show not-only-calf
41 ischemia. These observations are important when planning reeducation or when studying the tissue
42 consequences of ischemia in patients with claudication.

43

44 INTRODUCTION

45 Lower extremity arterial disease (LEAD) is a frequent ailment in elderly patients and can impair
46 walking ability. Historically, claudication in LEAD was defined in 1962 by George Rose as a pain in
47 the calf, absent at rest, that disappears within 10 minutes when exercise is stopped [1]. It is now
48 recognized that symptoms (pain or discomfort) in arterial claudication may also involve non-calf
49 locations (i.e. thigh, buttock, or lower back) [2]. The higher prevalence of calf symptoms (CS) among
50 symptoms of arterial claudication is likely a result of the more distal location of the calf on the arterial
51 tree, therefore holding more severe ischemia and suffering more severe symptoms than proximal areas.
52 Consequently, patients report the symptomatic location while they neglect less painful areas. Another
53 possibility is that patients are not aware that claudication can be a non-calf symptom (NCS), since in
54 general public data sources, the calf is frequently presented as the sole location of pain in “intermittent
55 claudication”.

56 Exercise transcutaneous oxygen pressure (Ex-TcpO₂) can detect ischemia simultaneously on both
57 sides of the calf, but also non-calf (thigh and buttock) levels [3-7]. We hypothesized that a significant
58 number of patients with self-reported isolated CS have exercise-related NCS and/or non-calf (thigh or
59 buttock) ischemia (NCI) during objective laboratory testing. Similarly, we hypothesized that most
60 patients with isolated CS would show not only calf ischemia (CI), but also an associated NCI. We
61 tested these hypotheses by a retrospective analysis of the patients complaining of isolated unilateral or
62 bilateral CS when referred to our laboratory for a treadmill evaluation of lower limb claudication.
63 These hypotheses are of particular interest, since on the one hand, it is generally admitted that research
64 into the consequences of ischemia in patients with claudication and an abnormal ankle to brachial
65 index (ABI) should give further consideration to the calf muscles [8-11]; and on the other hand, it is
66 well known that a normal ABI does not exclude the vascular origin of calf claudication, but although
67 post exercise ABI is of interest, it cannot be used interchangeably with Ex-TcpO₂ for the diagnosis of
68 LEAD in patients with exertional symptoms and normal rest ABI [12].

69

70 PATIENTS AND METHODS

71 *Study population*

72 Upon arrival, all patients referred to the Vascular Medicine Department of the University Hospital
73 Center of Angers for exercise-induced claudication of suspected arterial origin had to fill a
74 questionnaire about their ongoing treatment, presence or absence of cardiovascular risk factors (active
75 smoking, diabetes, hypercholesterolemia, arterial hypertension), and to answer the Edinburgh
76 Claudication Questionnaire (ECQ) [2]. Age, gender, and clinical history (particularly lower limb
77 vascular surgery) were recorded, as well as height and weight, from which body mass index (kg/m²)
78 was calculated. Non-lower-limb artery diseases were classified as cerebrovascular disease, coronary
79 artery disease, or other non-lower-limb diseases (renal, upper-limb, mesenteric, etc.). When not
80 available in the recent patient file, ABI was measured for each leg as the ratio of systolic blood
81 pressure at ankle (from posterior tibial or dorsalis pedis arteries), divided by brachial systolic blood
82 pressure. The lowest ABI between the two legs was recorded for each patient. An ABI < 0.9 was
83 considered positive for the presence of stenosis on the arterial tree toward the ankle. Missing values or
84 non-compressible arteries were encoded negative.

85 *Encoding of self-reported symptoms*

86 The ECQ was encoded to unilateral or bilateral non-calf (buttock/thigh) symptoms (NCS) or calf
87 symptoms (CS) excluding knee, groin and foot pain from the analysis [2]. Only patients with typical
88 symptoms of a claudication from vascular origin were kept for the analysis. These typical symptoms
89 were an exertional limb pain that does not begin at rest, worsens when walking uphill or hurrying and
90 resolves within 10 minutes of rest.

91 *Exercise tests*

92 The standard walking test procedure consisted of 2 minutes at rest in standing position, followed by a
93 transmission phase of 1 minute, during which speed and slope of the treadmill were gradually
94 increased to 3.2 km/h and 10%, respectively. This load was maintained for a maximum of 15 minutes,

95 during which any symptom was recorded by the physician. The test was interrupted whenever the pain
96 forced the patient to stop walking. In the absence of limiting symptoms after 15 minutes, the speed and
97 slope were increased by ~ 0.3 km/h and ~ 0.6% every minute until exhaustion or apparition of limiting
98 symptoms, as previously described [13]. Before patients were admitted to the test room, their normal
99 walking speed was assessed by a simple recording of the time required to walk 10 meters in the
100 corridor. Patients able to walk 10 m in less than 15 seconds then underwent a standard treadmill
101 procedure at 3.2 km/h. For those patients for whom it took more than 15 sec to walk 10 m, the same
102 procedure was conducted at only 2 km/h. We recently demonstrated that treadmill test results are not
103 influenced by walking speed [14]. The maximum walking time (MWT) was recorded.

104 *TcpO₂ measurements*

105 For a number of years, we have been routinely using exercise transcutaneous oxygen pressure (Ex-
106 TcpO₂) measurements to monitor exercise-induced ischemia simultaneously on several locations of the
107 lower limb [3, 15-17]. Transcutaneous oximetry measurements were carried out using an 8-probe
108 PeriFlux 5040 module (Perimed, Stockholm, Sweden) driven by the AcqTcpO₂ program [18]. Probes
109 were tape-fixed to the patient's skin (1 thoracic, 2 buttock, 2 thigh, and 2 calf probes) 15 minutes
110 before the start of the walking test in order to stabilize basal pO₂ and to allow the PeriFlux system to
111 heat the probes to 44.5°C, which corresponds to the optimal temperature for TcpO₂ measurement.
112 Thereafter, TcpO₂ was continuously recorded over 2 minutes at rest, then throughout the
113 abovementioned walking test and for a minimum of 10 minutes during recovery. The AcqTcpO₂
114 program automatically calculates the minimum decrease from rest of oxygen pressure (DROP) as the
115 difference between the decrease from rest of TcpO₂ for each limb probe, minus the decrease from rest
116 of TcpO₂ at the chest probe [6]. DROP value is, by construction, smaller than or equal to zero. The
117 main advantage of this calculation is to overcome the main limitation of the technique which is related
118 to the unpredictable transcutaneous gradient affecting the absolute starting values of TcpO₂. The
119 pathological threshold of < -15 mmHg for the DROP index was validated against gold standard
120 arteriography at both the buttock and calf levels [6]. The same threshold was arbitrarily applied for the
121 thigh. Thus, calf ischemia (CI) was defined when DROP < -15 mmHg was calculated at the calf probe,

122 while non-calf ischemia (NCI) was characterized when $\text{DROP} < -15$ mmHg was calculated at buttock
123 or thigh probes [6]. We have previously demonstrated that one advantage of TcpO_2 is the detection of
124 exercise-induced hypoxemia as a worsening cause of lower limb impaired delivery [19]. For the
125 present study, a decrease of chest value in excess of 5 mmHg was considered indicative of exercise-
126 induced hypoxemia.

127 *Symptoms observed on the treadmill*

128 The physician performing the test encoded the presence or absence of unilateral or bilateral buttock or
129 thigh pain, further referred to as non-calf symptoms (NCS), and/or calf symptoms (CS) during the
130 walking period, excluding knee, groin and foot pain from the analysis. As for symptoms by history,
131 only vascular-type lower limb symptoms were kept for the analysis.

132 *Ethical approval*

133 All subjects were notified that their medical file could be used for research purposes and reminded of
134 the right to deny this use. Where the patient denied such use, this refusal was recorded in the database.
135 As a retrospective analysis of our routine practice, and according to the French law, individual written
136 informed consent prior to participation was not required. This study received local ethics committee
137 approval 2020-042, conforms to the Declaration of Helsinki and was registered to the American
138 National Institute of Health database clinicaltrials.gov under reference NCT04376099.

139 *Statistical analysis*

140 Statistical analyses were performed using SPSS (IBM SPSS statistics V15.0, Chicago, USA). Results
141 are reported as mean \pm SD, and proportions with 95% confidence intervals. Comparisons between
142 groups were performed by one-way ANOVA with Tukey's multiple comparisons test. For all
143 statistical tests, a 2-tailed probability level of $p < 0.05$ was used to indicate statistical significance.

144

145

146 RESULTS

147 As shown in Figure 1, 584 patients reported exercise-induced, vascular-type isolated unilateral (n =
148 294) or bilateral (n = 290) calf pain, resulting in 874 legs with CS-only, by history.

149 Characteristics of the included patients are reported in Table 1. Most patients were males (78.9 %) and
150 24.1% were active smokers. No difference appeared between the prevalence of right and left CS in
151 290 (49.7% [95% CI: 45.6–53.7]) of the patients reporting bilateral CS by history. Few differences
152 were observed according to the characteristics of symptoms and ischemia on the treadmill. Note that
153 patients that had no symptoms or ischemia on the treadmill, had higher ABI results than patients with
154 calf symptoms and calf ischemia.

155 Results of the exercise test are reported in Table 2. Interestingly, one third of the patients had a
156 decrease in chest TcpO₂ greater than 5 mmHg. Moreover, the proportion of patients with NCI
157 exceeded the proportion of patients self-reporting exercise-induced NCS.

158 Among 584 patients, only 114 (19.5% [95%CI: 16.3–22.7]) had an isolated self-reported CS
159 associated with an isolated CI on the treadmill, among which ABI was not < 0.90 in 16. As reported in
160 Tables 1 and 2, some significant differences were found between these patients and the remaining
161 groups. Logically, patients with an ABI < 0.90 were more likely to have isolated CS associated with
162 isolated CI than those with an ABI not < 0.90: 23.11 % vs. 10.0 %, respectively (Chi² test *p* value <
163 0.001). These patients with CI+CS were less likely to have had a lower limb revascularization than
164 those with CS associated with NCI (respectively 17.5 % and 36.8 %, Chi² test *p* value < 0.001). No
165 significant difference was found regarding MWT between the five groups of patients.

166 As shown in Figure 2, the treadmill test did not reproduce lower limb symptoms in 58 (9.9 % [95%
167 CI: 7.5–12.4]) patients. In these 58 patients, the walking test was stopped because of dyspnea, chest
168 pain, fatigue, or abnormal cardiac or pulmonary response. It should be noted that 13 out of the 31
169 patients with neither pain nor ischemia during the treadmill test had evidence of exercise-induced
170 hypoxemia, a putative worsening factor of lower limb ischemia. However, in these patients,
171 hypoxemia may have occulted a true ischemia at lower limb given the abovementioned DROP

172 calculation formula. Logically, only 31 of the 424 (7.3%) patients with ABI < 0.90 did not have
173 symptoms on the treadmill while the proportion was 16.9% in the other patients (Chi² test *p* value <
174 0.001).

175 Among the 526 patients with or without ABI < 0.90 and with lower limb pain during the treadmill test,
176 113 (21.5% [95% CI: 18.0–25.0]) did not have ischemia. In 32 of these patients, lower limb ischemia
177 may have been obscured by the observed exercise-induced hypoxemia. Among the 413 patients with
178 or without ABI < 0.90 that had ischemia on the treadmill, 299 reported a CS only. However, an
179 associated CI was confirmed in only approximately one third of them (n = 114; 38.1% [95% CI: 34.6–
180 41.7]). The remaining patients described either purely NCS (n = 10) or associated CS+NCS (n = 104).
181 Three out of ten patients with isolated NCS on a treadmill had isolated CI, suggesting a pain of non-
182 vascular origin. Likewise, among the 104 patients with both CS and NCS on treadmill, 9 had isolated
183 CI, suggesting that NCS was probably of non-vascular origin. Interestingly, ischemia was more severe
184 (lowest DROP value) at the calf than at the non-calf level in most (n = 47) of the 79 patients (59.5%;
185 CI 95% [48.7–70.3]) with CI and NCI associated with both CS and NCS.

186 The leg-by-leg analysis provided in Figure 2B further confirmed that only a limited number of legs
187 (19.9%, 95% CI [17.3–22.6]) symptomatic by history had both isolated CI and isolated CS on the
188 treadmill. Although this proportion of consistent results is higher when ABI < 0.90 than in a leg
189 without ABI < 0.90, it remains relatively low in the former group (25.0%) than in the latter group
190 (10.8 %); Chi² test *p* value < 0.0001. Overall, 19.3% (95% CI [16.3/22.8]) of the legs with ABI < 0.90
191 had neither NCI nor CI, while in legs that did not have ABI < 0.90, 41.1% (95%CI [35.6/46.5]) had CI
192 or NCI on the treadmill.

193

194 DISCUSSION

195 Classical “vascular-type” intermittent claudication is defined as exertional calf symptoms that do not
196 begin at rest, worsen when walking uphill or hurrying and resolve within 10 min of rest [20]. For
197 decades, the gold standard tool for the assessment of leg pain in patients with vascular-type

198 claudication was the World Health Organisation/Rose Questionnaire [2]. However, this questionnaire
199 defines claudication as a pain limited to the calf area while recent progresses (including the ECQ)
200 demonstrated lower limb vascular claudication can be extended to pain in non-calf (thigh, buttock)
201 locations.

202 To date, little is known about the concordance of symptoms by history, symptoms during exercise and
203 the location of exercise-induced ischemia. We demonstrated that only two third of the patients with
204 calf-only pain by history reported calf-only pain on treadmill. The measurement of Ex-TcpO₂ during
205 the treadmill test provided further evidence showing that less than a quarter of the patients with calf
206 claudication by history showed symptomatic or asymptomatic isolated calf (calves) ischemia on the
207 treadmill. Overall, only 19.5% of patients complaining of isolated calf pain had a purely distal
208 ischemia during the treadmill test.

209 In previous studies, the prevalence of NCS is highly variable. As an example, in 1487 outpatients with
210 no history of atherosclerotic disease, Manzano et al. showed that the number of patients with calf
211 claudication (n = 107; 7.2%) is similar to the number of patients with non-calf claudication (n = 86;
212 5.8%)[21]. The same proportions were observed when the analysis was restricted to the 393 patients
213 with LEAD (ABI < 0.9), with 70 (17.8%) patients with calf claudication and 52 (13.2%) with non-calf
214 claudication [21]. Similarly, in 163 patients with LEAD, the prevalence of Rose-type typical
215 intermittent claudication was 24.1% (n = 40) while exertional leg symptoms other than Rose-type
216 typical intermittent claudication were observed in 22.9% (n= 37) [20]. The same study in 105 patients
217 without LEAD identified 3.8% (n= 4) and 4.8% (n = 5) of typical and non-typical claudication,
218 respectively. Even if non-typical claudication as defined by Rose does not only correspond to non-calf
219 claudication, it seems that in this population, the prevalence of non-calf symptoms was close to that of
220 calf-only symptoms [20].

221 On the contrary, in 980 legs from 508 patients having completed the San Diego Claudication
222 Questionnaire, Criqui et al. classified symptoms as no pain, pain at rest, non-calf claudication, non-
223 Rose calf claudication, or Rose claudication and observed only 38 legs with non-calf (buttock or thigh)

224 claudication, whereas typical Rose-type claudication was by far more frequent (n = 258 legs) [22]. In
225 another analysis of the data from 3 epidemiological studies including 1465 legs with LEAD and 5813
226 without LEAD, the authors observed a large dominance of patients with calf (31.4%), over non-calf
227 (4.2%) claudication, in the presence of LEAD. In patients without LEAD, there was still twice the
228 number of cases of classic claudication (2.2%) than non-calf pain (1.1%) [23].

229 These discrepancies may arise from the different methods used for patient recruitment or evaluation of
230 pain across these studies. Indeed, the result of the ECQ could be drastically influenced by the
231 assistance of a physician [24]. For example, if no significant change was found at the thigh level, the
232 proportion of patients reporting buttock pain significantly decreases from 30.3 to 3.9% after
233 supervised interview ($p < 0.01$), while right and left calf pain increased from 39.5 and 32.9% to 55.3
234 and 55.3%, respectively (both $p < 0.05$) [24]. The author suggested that patients were “*prone to*
235 *exaggerate any discomfort they had been suffering from in lower body parts*” [24]. This explanation
236 remains possible but is somewhat inconsistent with the observation that patients underestimate buttock
237 pain by history in comparison with the effective prevalence of buttock claudication on the treadmill
238 [5]. In our experience, patients justify the fact that they did not spontaneously report proximal pain
239 before the vascular tests because they often consider that such pains are unlikely to be of vascular
240 origin. In most studies, LEAD diagnosis is based on ABI determination [20-23]. Although in
241 epidemiological studies this simple method is an accurate tool to predict LEAD, 7% to 50% of patients
242 with claudication have a normal ABI at rest [21, 23]. Besides, more than 30% of patients with normal
243 ABI at rest have an abnormal ABI after exercise [25]. Furthermore, ABI measurement can neither
244 detect exercise-related ischemia nor its exact location (proximal or distal).

245 Aside from ABI determination, the evaluation of limb ischemia can be performed by near infra-red
246 spectroscopy (NIRS) that has gained an increasing interest in vascular medicine [26-30]. This
247 technology could theoretically be used simultaneously in calves, thighs and buttock but, to the best of
248 our knowledge, has never been used this way until now. Although NIRS claims to measure deep tissue
249 (muscle) blood flow [28], it is largely influenced by skin blood flow [31]. Further, the normal response
250 of NIRS in healthy subjects is a decrease in the various NIRS-derived parameters. Thus, $TcpO_2$ has the

251 major advantage of allowing an estimation of regional perfusion impairment, throughout exercise
252 procedures, simultaneously at buttocks, thighs, and calves. In the present study, this technology
253 allowed the detection of ischemia in a large number of asymptomatic patients. Strikingly, no
254 significant ischemia could be detected in around 50 symptomatic patients with a pathological ABI at
255 rest, but we previously demonstrated that in almost half of the cases this resulted from the coexistence
256 of limitation of non-LEAD origin [19, 32].

257 To the best of our knowledge, only one study has hitherto focused on calf and non-calf claudication in
258 perspective of calf and non-calf lower limb ischemia. In this study, duplex ultrasound was compared
259 to self-reported leg symptoms in 701 patients with claudication. In patients with calf pain, the authors
260 observed 237 legs with proximal lesions, 372 legs with distal lesions and 72 legs with both proximal
261 and distal lesions [33]. Thus, patients with distal pain had a wide variety of anatomic lesion location,
262 as in the present study.

263 There are limitations to the present study. First, it is possible that walking on treadmill with a slope
264 induces more proximal symptoms than walking on a flat surface. Second, we believe that many
265 patients link their proximal symptoms to co-morbid conditions (e.g. arthritis, osteo-articular pain,
266 sciatica) and consider that reporting these symptoms to the vascular physician before the test is
267 inappropriate. Third, males are overrepresented in our population. We have no clear explanation for
268 this and had already noted that in the past. Nevertheless, this may limit the generalizability of our
269 results to the general population. Last, due to the initial focus of our laboratory towards typical
270 claudication of vascular origin, a recruitment bias could be suggested. However, such a bias seems
271 unlikely since patients selected for the present study complained of typical calf vascular-type
272 symptoms.

273 In conclusion, patients reporting exertional limb pain affecting only the calf may have non-calf
274 claudication on a treadmill and frequently show not-only-calf ischemia. This is important when
275 planning reeducation and when assessing the effectiveness of preventive or curative treatments taken
276 by patients with claudication. As shown in the graphical abstract online, almost a quarter of the

277 patients with calf pain by history and on a treadmill do not have calf ischemia while their ABI is
278 abnormal at rest. Whether or not this could explain the relatively fair to poor correlations observed in
279 the studies of biochemical consequences of claudication in the literature is a fascinating issue for
280 future studies. On the other hand, almost half of the patients with an ABI not < 0.90 have non-calf
281 ischemia (buttock and/or thigh pain) that is more likely detectable by exercise TcpO₂ than by post-
282 exercise ABI. Finally, exercise TcpO₂ allows segmental analysis of the lower limb and thus provides
283 original models for the study of the biochemical consequences of ischemia in patients with
284 claudication [34].

285

286 DECLARATION OF COMPETING INTERESTS

287 P. Abraham has benefited from a loan of TcpO₂ devices from Perimed, Radiometer and Medicap
288 companies and is member of an advisory board for the Profusa company. The other authors have no
289 conflict of interest to report.

290

291

292 AUTHORS' CONTRIBUTIONS

293 P. Ramondou : Investigation, Review & Editing; W. Y. Semporé : Investigation, Review & Editing C.
294 Guilleron : Investigation, Review & Editing; J. Hersant : Investigation, Review & Editing; S. Henni :
295 Conceptualization, Resources, Review & Editing, Supervision N. Ouedraogo : Investigation, Review
296 & Editing; P. Abraham : Conceptualization, Writing - Original Draft, Project administration. All
297 authors have validated the manuscript in its final form.

298

299

300

301 ACKNOWLEDGEMENTS

302 The authors thank Mathieu Feuilloy, Stéphanie Maréchal and Marine Mauboussin as well as the
303 “Maison de la Recherche Clinique” of Angers for their technical help.

304

305 REFERENCES

306 [1] G. A. Rose, The diagnosis of ischaemic heart pain and intermittent claudication in field
307 surveys, *Bull World Health Organ*,27 (1962) 645-658.

308 [2] G. C. Leng,F. G. Fowkes, The Edinburgh Claudication Questionnaire: an improved version of
309 the WHO/Rose Questionnaire for use in epidemiological surveys, *J Clin Epidemiol*,45 (1992) 1101-
310 1109.

311 [3] P. Abraham, J. Picquet, B. Vielle, D. Sigaudou-Roussel, F. Paisant-Thouveny, et al.,
312 Transcutaneous oxygen pressure measurements on the buttocks during exercise to detect proximal
313 arterial ischemia: comparison with arteriography, *Circulation*,107 (2003) 1896-1900.

314 [4] P. Bouye, J. Picquet, V. Jaquinandi, B. Enon, G. Leftheriotis, et al., Reproducibility of
315 proximal and distal transcutaneous oxygen pressure measurements during exercise in stage 2 arterial
316 claudication, *Int Angiol*,23 (2004) 114-121.

317 [5] V. Jaquinandi, J. Picquet, P. Bouye, J. L. Saumet, G. Leftheriotis, et al., High prevalence of
318 proximal claudication among patients with patent aortobifemoral bypasses, *J Vasc Surg*,45 (2007)
319 312-318.

320 [6] P. Abraham, Y. Gu, L. Guo, K. Kroeger, N. Ouedraogo, et al., Clinical application of
321 transcutaneous oxygen pressure measurements during exercise, *Atherosclerosis*,276 (2018) 117-123.

322 [7] P. Abraham, P. Ramondou, J. Hersant, W. Y. Sempore, M. Feuilloy, et al., Investigation of
323 arterial claudication with transcutaneous oxygen pres, *Trends Cardiovasc Med* (2020).

- 324 [8] B. D. Duscha, J. L. Robbins, W. S. Jones, W. E. Kraus, R. J. Lye, et al., Angiogenesis in
325 skeletal muscle precede improvements in peak oxygen uptake in peripheral artery disease patients,
326 *Arterioscler Thromb Vasc Biol*,31 (2011) 2742-2748.
- 327 [9] A. E. Harwood, S. King, J. Totty, G. E. Smith, N. Vanicek, et al., A systematic review of
328 muscle morphology and function in intermittent claudication, *J Vasc Surg*,66 (2017) 1241-1257.
- 329 [10] J. Henriksson, E. Nygaard, J. Andersson, B. Eklof, Enzyme activities, fibre types and
330 capillarization in calf muscles of patients with intermittent claudication, *Scand J Clin Lab Invest*,40
331 (1980) 361-369.
- 332 [11] E. Jansson, J. Johansson, C. Sylven, L. Kaijser, Calf muscle adaptation in intermittent
333 claudication. Side-differences in muscle metabolic characteristics in patients with unilateral arterial
334 disease, *Clin Physiol*,8 (1988) 17-29.
- 335 [12] G. Mahe, F. Catillon, Q. Tollenaere, P. Jehannin, A. Guilcher, et al., Discordance of peripheral
336 artery disease diagnosis using exercise transcutaneous oxygen pressure measurement and post-exercise
337 ankle-brachial index, *Sci Rep*,10 (2020) 7419.
- 338 [13] G. Mahe, N. Ouedraogo, J. Marchand, B. Vielle, J. Picquet, et al., Self-reported estimation of
339 usual walking speed improves the performance of questionnaires estimating walking capacity in
340 patients with vascular-type claudication, *J Vasc Surg*,54 (2011) 1360-1365.
- 341 [14] W. Sempore, P. Ramonou, J. Hersant, M. Feuilloy, C. Guilleron, et al., Specific slow tests are
342 not mandatory in patients with extremely short standard (3.2km/h 10% slope) tests durations during
343 exercise oximetry., *Clinical Physiology and Functional Imaging* (2020) (in press).
- 344 [15] P. Abraham, C. Colas-Ribas, I. Signolet, M. Ammi, M. Feuilloy, et al., Transcutaneous
345 Exercise Oximetry for Patients With Claudication- A Retrospective Review of Approximately 5,000
346 Consecutive Tests Over 15 Years, *Circ J*,82 (2018) 1161-1167.
- 347 [16] P. Abraham, J. Picquet, P. Bouye, P. L'Hoste, B. Enon, et al., Transcutaneous oxygen pressure
348 measurements (tcpO₂) at ankle during exercise in arterial claudication, *Int Angiol*,24 (2005) 80-88.

- 349 [17] S. Henni, C. Colas-Ribas, I. Signolet, M. Feuilloy, P. Abraham, et al., Multiprobe devices for
350 exercise transcutaneous oxymetry in patients complaining claudication: interest and limits of unusual
351 probe positions, *Int Angiol*,35 (2016) 557-564.
- 352 [18] P. Abraham, Software analysis of transcutaneous oxygen pressure measurements at exercise in
353 patients with arterial claudication, *Atherosclerosis*,278 (2018) 328-329.
- 354 [19] C. Colas-Ribas, I. Signolet, S. Henni, M. Feuilloy, F. Gagnadoux, et al., High prevalence of
355 known and unknown pulmonary diseases in patients with claudication during exercise oximetry: A
356 retrospective analysis, *Medicine (Baltimore)*,95 (2016) e4888.
- 357 [20] M. M. McDermott, S. Mehta,P. Greenland, Exertional leg symptoms other than intermittent
358 claudication are common in peripheral arterial disease, *Arch Intern Med*,159 (1999) 387-392.
- 359 [21] L. Manzano, D. Garcia-Diaz Jde, C. Suarez, J. M. Mostaza, M. Cairols, et al., Thigh and
360 buttock exertional pain for the diagnosis of peripheral arterial disease, *Eur J Intern Med*,20 (2009)
361 429-434.
- 362 [22] M. H. Criqui, J. O. Denenberg, C. E. Bird, A. Fronek, M. R. Klauber, et al., The correlation
363 between symptoms and non-invasive test results in patients referred for peripheral arterial disease
364 testing, *Vasc Med*,1 (1996) 65-71.
- 365 [23] J. C. Wang, M. H. Criqui, J. O. Denenberg, M. M. McDermott, B. A. Golomb, et al.,
366 Exertional leg pain in patients with and without peripheral arterial disease, *Circulation*,112 (2005)
367 3501-3508.
- 368 [24] B. B. Basgoz, I. Tasci, B. Yildiz, C. Acikel, H. K. Kabul, et al., Evaluation of self-
369 administered versus interviewer-administered completion of Edinburgh Claudication Questionnaire,
370 *Int Angiol*,36 (2017) 75-81.
- 371 [25] R. Stein, I. Hriljac, J. L. Halperin, S. M. Gustavson, V. Teodorescu, et al., Limitation of the
372 resting ankle-brachial index in symptomatic patients with peripheral arterial disease, *Vasc Med*,11
373 (2006) 29-33.

- 374 [26] A. W. Gardner, P. S. Montgomery, M. Wang, C. Chen, M. Kuroki, et al., Vascular
375 Inflammation, Calf Muscle Oxygen Saturation, and Blood Glucose are Associated With Exercise
376 Pressor Response in Symptomatic Peripheral Artery Disease, *Angiology*,70 (2019) 747-755.
- 377 [27] W. B. Baker, Z. Li, S. S. Schenkel, M. Chandra, D. R. Busch, et al., Effects of exercise
378 training on calf muscle oxygen extraction and blood flow in patients with peripheral artery disease, *J*
379 *Appl Physiol* (1985),123 (2017) 1599-1609.
- 380 [28] A. G. Koutsiaris, Deep tissue near infrared second derivative spectrophotometry for the
381 assessment of claudication in peripheral arterial disease, *Clin Hemorheol Microcirc*,65 (2017) 275-
382 284.
- 383 [29] T. Komiyama, A. Onozuka, T. Miyata,H. Shigematsu, Oxygen saturation measurement of calf
384 muscle during exercise in intermittent claudication, *Eur J Vasc Endovasc Surg*,23 (2002) 388-392.
- 385 [30] A. Andrade-Lima, G. G. Cucato, W. J. R. Domingues, A. H. Germano-Soares, B. R.
386 Cavalcante, et al., Calf Muscle Oxygen Saturation during 6-Minute Walk Test and Its Relationship
387 with Walking Impairment in Symptomatic Peripheral Artery Disease, *Ann Vasc Surg*,52 (2018) 147-
388 152.
- 389 [31] S. L. Davis, P. J. Fadel, J. Cui, G. D. Thomas,C. G. Crandall, Skin blood flow influences near-
390 infrared spectroscopy-derived measurements of tissue oxygenation during heat stress, *J Appl*
391 *Physiol*,100 (2006) 221-224.
- 392 [32] I. Signolet, S. Henni, C. Colas-Ribas, M. Feuillo, J. Picquet, et al., Prevalence and Causes of
393 Normal Exercise Oximetry in the Calf in Patients with Peripheral Artery Disease and Limiting Calf
394 Claudication, *Eur J Vasc Endovasc Surg*,51 (2016) 572-578.
- 395 [33] M. van Zitteren, P. W. Vriens, J. M. Heyligers, D. H. Burger, M. J. Nooren, et al., Self-
396 reported symptoms on questionnaires and anatomic lesions on duplex ultrasound examinations in
397 patients with peripheral arterial disease, *J Vasc Surg*,55 (2012) 1025-1034 e1022.

398 [34] I. Signolet, P. Abraham, S. Chupin, M. Ammi, N. Gueguen, et al., Mitochondrial complex I
399 defect resulting from exercise-induced lower limb ischemia in patients with peripheral arterial disease,
400 J Appl Physiol (1985),125 (2018) 938-946.

401

402 FIGURES LEGENDS

403 **Figure 1.** Flowchart of the selection of the patients.

404

405 **Figure 2.** Distribution of pain and ischemia locations during the treadmill test among (A) patients self-
406 reporting calf claudication, and (B) leg-by-leg analysis.

407 The proportions of pathological ankle to brachial indexes (ABI) are also indicated. For analyses,
408 undetermined ABI were included in the $ABI > 0.9$ subgroups since they represented only 3.7% (6/160)
409 of patients and 6.4% (20/314) of legs. CS: calf symptoms, NCS: non-calf symptoms, CI: calf ischemia,
410 NCI: non-calf ischemia

411

412 TABLES

413 **Table 1.** Study population's characteristics according to symptoms on treadmill and presence/location of ischemia.

414

415		Total	CS,	CS,	NCS,	Other	<i>p</i> value ^a
416			CI	NCI or CI+NCI	CI or CI+NCI		
417		n = 584	n = 114	n = 185	n = 19	n = 266	
418							
419	Age (years)	65.6 ± 11.4	66.2 ± 12.2	65.3 ± 7.6 ^{ns}	69.5 ± 7.7 ^{ns}	65.4 ± 9.2 ^{ns}	0.4251
420	Male gender (n, %)	461 (78.9)	87 (76.3)	166 (89.7)*	13 (65) ^{ns}	195 (73.3) ^{ns}	0.0002
421	Weight (kg)	76.6 ± 15.8	74.7±15.5	78.3 ± 11.5 ^{ns}	76.7 ± 14.7 ^{ns}	76.3 ± 13.0 ^{ns}	0.2911
422	Height (cm)	169 ± 8	169±9	170 ± 5 ^{ns}	166 ± 6 ^{ns}	168 ± 7 ^{ns}	0.0288
423	Body mass index (kg/m ²)	26.9 ± 4.9	26.0 ± 4.7	27.2 ± 3.7 ^{ns}	27.6 ± 4.7 ^{ns}	27.0 ± 4.0 ^{ns}	0.1833
424	Ankle brachial index (6 missing)	0.77 ± 0.24	0.74 ± 0.19	0.70 ± 0.17 ^{ns}	0.70 ± 0.19 ^{ns}	0.84 ± 0.20***	< 0.0001

425	Ankle brachial index < 0.90 (n, %)	424 (72.6)	98 (86.0)	152 (82.2) ^{ns}	16 (84.2) ^{ns}	158 (59.4)****	< 0.0001
426	Time to walk 10 meters at usual pace (s)	9.7 ± 2.2	9.3 ± 1.7	9.4 ± 1.3 ^{ns}	10.3 ± 1.6 ^{ns}	9.9 ± 1.7 ^{ns}	0.0145
427	Resting heart rate (beats/min)	80 ± 15	78 ± 15	81 ± 12 ^{ns}	77 ± 9 ^{ns}	81 ± 12 ^{ns}	0.1332
428	Ongoing treatments						
429	Antiplatelet agents (n, %)	473 (81.0)	98 (86.0)	160 (86.5) ^{ns}	15 (78.9) ^{ns}	200 (75.2) ^{ns}	0.0099
430	Antihypertensive drugs (n, %)	365 (62.5)	72 (63.2)	125 (67.6) ^{ns}	12 (63.2) ^{ns}	174 (65.4) ^{ns}	0.2926
431	Cholesterol lowering drugs (n, %)	410 (70.2)	82 (71.9)	139 (75.1) ^{ns}	15 (78.9) ^{ns}	174 (65.4) ^{ns}	0.1156
432	Anticoagulants (n, %)	48 (8.2)	8 (7.0)	13 (7.0) ^{ns}	3 (15.8) ^{ns}	24 (9.0) ^{ns}	0.5263
433	Beta blockers (n, %)	200 (34.2)	41 (36.0)	64 (34.6) ^{ns}	8 (42.1) ^{ns}	87 (32.7) ^{ns}	0.8120
434	Medical history						
435	Cerebrovascular disease	113 (19.3)	16 (14.0)	36 (19.5) ^{ns}	3 (15.8) ^{ns}	58 (21.8) ^{ns}	0.7103
436	Coronary artery disease	25 (4.3)	3 (2.6)	10 (5.4) ^{ns}	1 (5.3) ^{ns}	11 (4.1) ^{ns}	0.3567

437	Other non-lower limb vascular diseases	71 (12.2)	10 (8.8)	25 (13.5) ^{ns}	2 (10.5) ^{ns}	34 (12.8) ^{ns}	0.6416
438	Diabetes mellitus (n, %)	157 (27.0)	26 (22.8)	61 (33.0) ^{ns}	3 (15.8) ^{ns}	67 (25.2) ^{ns}	0.1103
439	Active smokers (n, %)	141 (24.1)	24 (21.1)	53 (28.6) ^{ns}	4 (21.0) ^{ns}	60 (22.6) ^{ns}	0.3765
440	Past history of revascularization (n, %)	159 (27.2)	20 (17.5)	68 (36.8)**	9 (47.4)*	62 (23.3) ^{ns}	0.0002
441	Symptoms by history						
442	Duration of self-reported symptoms (y)	3.1 ± 5.6	3.4 ± 5.4	2.6 ± 2.2 ^{ns}	3.6 ± 3.5 ^{ns}	3.3 ± 3.2 ^{ns}	0.5034
443	Self-reported symptoms left calf (n, %)	435 (74.5)	79 (69.3)	141 (76.2) ^{ns}	16 (84.2) ^{ns}	199 (74.8) ^{ns}	0.4144
444	Self-reported symptoms right calf (n, %)	439 (75.2)	81 (71.1)	138 (74.6) ^{ns}	15 (78.9) ^{ns}	205 (77.1) ^{ns}	0.6327

445

446 CS: calf symptoms, NCS: non-calf symptoms, CI: calf ischemia, NCI: non-calf ischemia, DROP: decrease from rest of oxygen pressure

447 ^a*p* value of means comparison between the four subgroups by one-way ANOVA.

448 ns, non-significant; * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$; **** $p < 0.0001$: statistical significance of mean differences between patients with isolated calf
449 pain and distal ischemia (CS,CI) and the three other groups by Tukey's multiple comparisons test.

450 **Table 2.** Results of the treadmill test.

451		Total	CS,	CS,	NCS,	Other	<i>p</i> value ^a
452			CI	NCI or CI+NCI	CI or CI+NCI		
453							
454		n = 584	n = 114	n = 185	n = 19	n = 266	
455							
456	Maximal walking time (s)	603 ± 440	656 ± 464	519 ± 326*	569 ± 416 ^{ns}	643 ± 391 ^{ns}	0.0134
457	Transcutaneous oxygen pressure (TcpO ₂)						
458	Chest TcpO ₂ at rest (mmHg)	64 ± 12	66 ± 13	62 ± 10 ^{ns}	65 ± 8 ^{ns}	65 ± 10 ^{ns}	0.0217
459	Minimal chest TcpO ₂ (mmHg)	59 ± 12	61 ± 13	57 ± 9 ^{ns}	59 ± 9 ^{ns}	60 ± 9 ^{ns}	0.0582
460	Chest TcpO ₂ decrease > 5 mmHg (n, %)	199 (34.1)	39 (34.2)	56 (30.3) ^{ns}	7 (36.8) ^{ns}	97 (36.5) ^{ns}	0.5878
461	DROP left buttock (mmHg)	-13 ± 10	-8 ± 4	-19 ± 8*****	-7 ± 2 ^{ns}	-12 ± 7***	< 0.0001
462	DROP right buttock (mmHg)	-13 ± 11	-7 ± 4	-20 ± 9*****	-6 ± 2 ^{ns}	-11 ± 7**	< 0.0001
463	DROP left thigh (mmHg)	-12 ± 10	-7 ± 3	-17 ± 9*****	-7 ± 3 ^{ns}	-11 ± 6**	< 0.0001

464	DROP right thigh (mmHg)	-13 ± 12	-7 ± 3	-18 ± 9****	-8 ± 2 ^{ns}	-12 ± 8****	< 0.0001
465	DROP left calf (mmHg)	-20 ± 14	-21 ± 12	-26 ± 12**	-22 ± 8 ^{ns}	-15 ± 9****	< 0.0001
466	DROP right calf (mmHg)	-21 ± 15	-21 ± 12	-27 ± 12**	-18 ± 9 ^{ns}	-16 ± 11*	< 0.0001
467	DROP left buttock < -15 mmHg (n, %)	172 (29.5)	0 (0)	111 (60.0)****	0 (0) ^{ns}	61 (22.9)****	< 0.0001
468	DROP right buttock < -15 mmHg (n, %)	168 (28.8)	0 (0)	106 (57.3)****	0 (0) ^{ns}	62 (23.3)****	< 0.0001
469	DROP left thigh < -15 mmHg (n, %)	143 (24.5)	0 (0)	89 (48.1)****	0 (0) ^{ns}	54 (20.3)****	< 0.0001
470	DROP right thigh < -15 mmHg (n, %)	144 (24.7)	0 (0)	84 (45.4)****	0 (0) ^{ns}	60 (22.6)****	< 0.0001
471	DROP left calf < -15 mmHg (n, %)	311 (53.3)	73 (64.0)	137 (74.0) ^{ns}	16 (84.2) ^{ns}	85 (31.9)****	< 0.0001
472	DROP right calf < -15 mmHg (n, %)	317 (54.3)	80 (70.2)	139 (75.1) ^{ns}	10 (52.6) ^{ns}	88 (33.1)****	< 0.0001
473	Symptoms on treadmill						
474	Left buttock pain (n, %)	33 (5.7)	0 (0)	0 (0) ^{ns}	4 (21.0)***	29 (10.9)****	< 0.0001
475	Right buttock pain (n, %)	34 (5.8)	0 (0)	0 (0) ^{ns}	5 (26.3)****	29 (10.9)***	< 0.0001
476	Left thigh pain (n, %)	69 (11.8)	0 (0)	0 (0) ^{ns}	10 (52.6)****	59 (22.2)****	< 0.0001
477	Right thigh pain (n, %)	81 (13.9)	0 (0)	0 (0) ^{ns}	10 (52.6)****	71 (26.7)****	< 0.0001
478	Left calf pain (n, %)	372 (63.7)	73 (64.0)	141 (76.2) ^{ns}	12 (63.2) ^{ns}	146 (54.9) ^{ns}	< 0.0001
479	Right calf pain (n, %)	390 (66.8)	81 (71.1)	134 (72.4) ^{ns}	13 (68.4) ^{ns}	162 (60.9) ^{ns}	0.0509

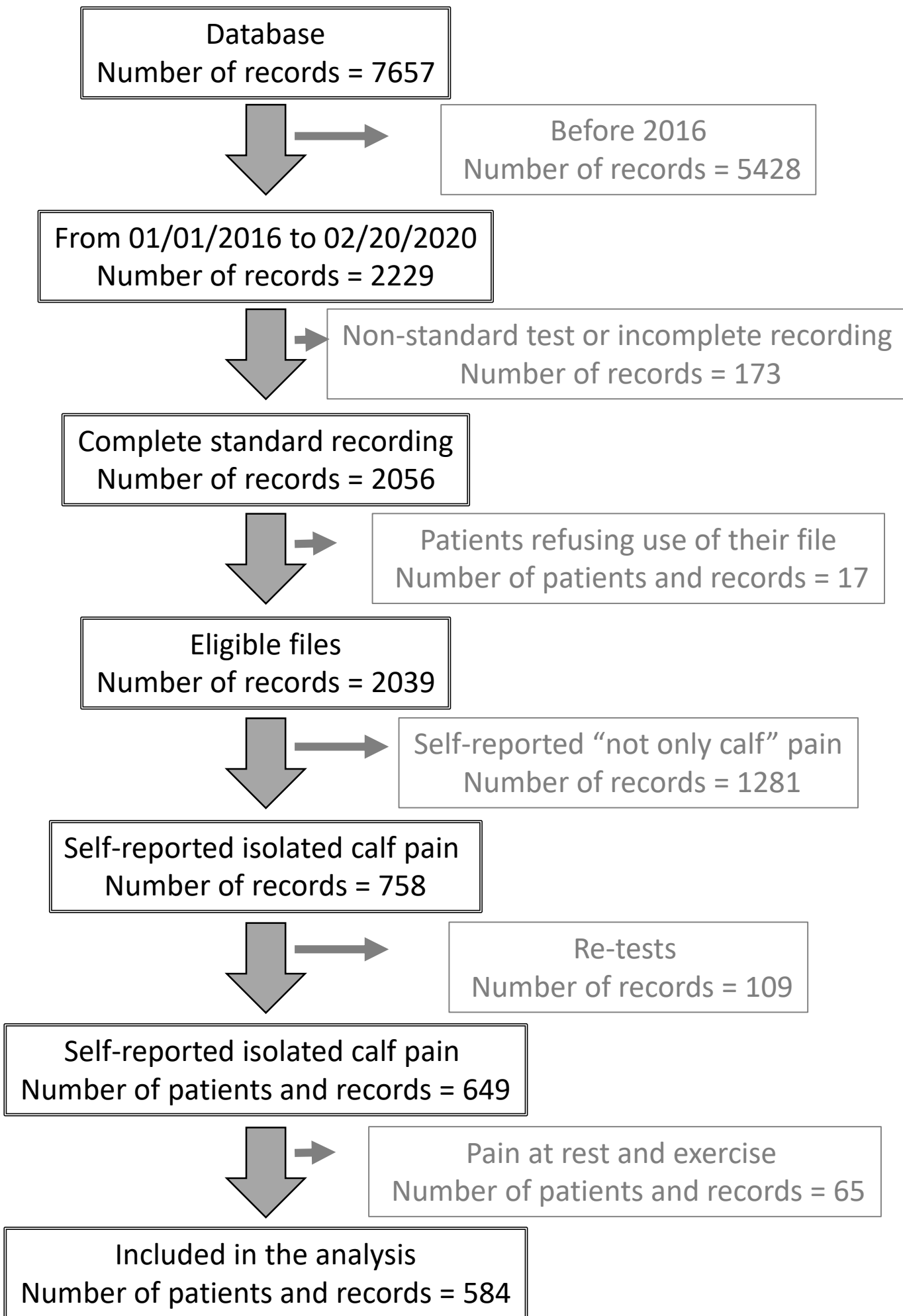
480

481 CS: calf symptoms, NCS: non-calf symptoms, CI: calf ischemia, NCI: non-calf ischemia, DROP: decrease from rest of oxygen pressure

482 ^a*p* value of means comparison between the four subgroups by one-way ANOVA.

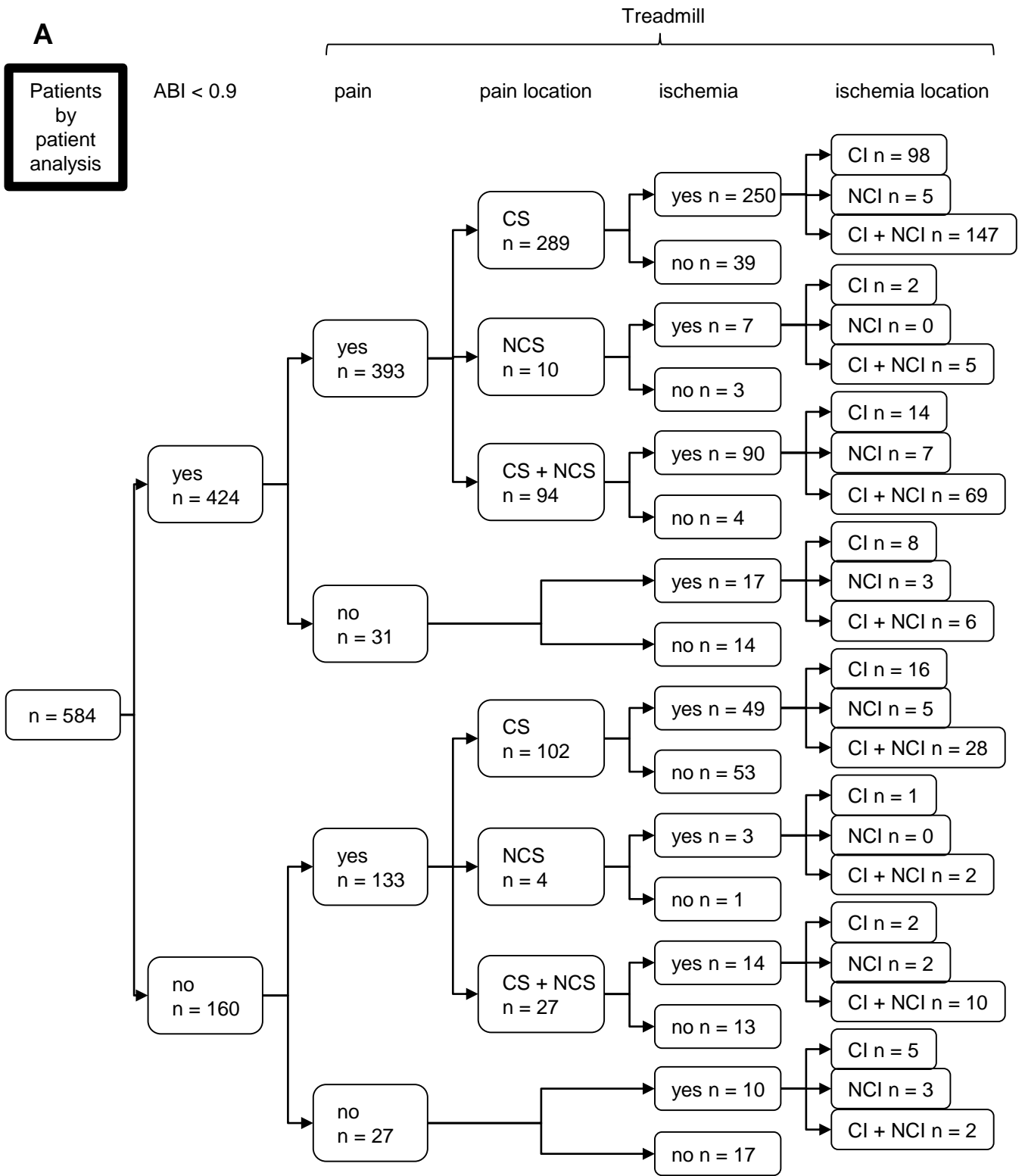
483 ns, non-significant; * *p* < 0.05; ** *p* < 0.005; *** *p* < 0.0005; **** *p* < 0.0001 : statistical significance of mean differences between patients with isolated calf

484 pain and distal ischemia (CS,CI) and the three other groups by Tukey's multiple comparisons test.



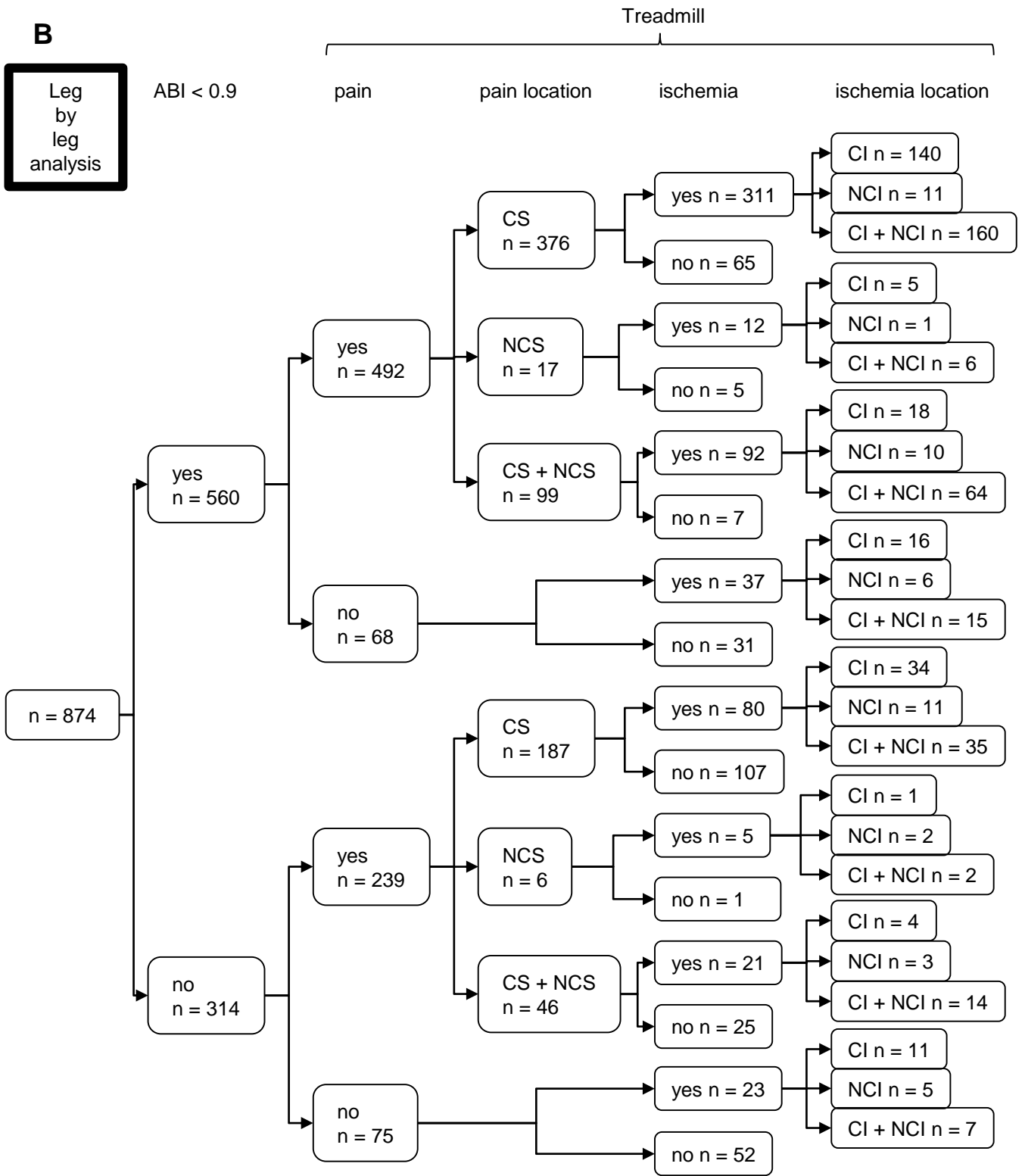
A

Patients by patient analysis



B

Leg
by
leg
analysis



Comparison of symptoms and ischemia observed on a treadmill in patients complaining of isolated vascular-type calf pain by history

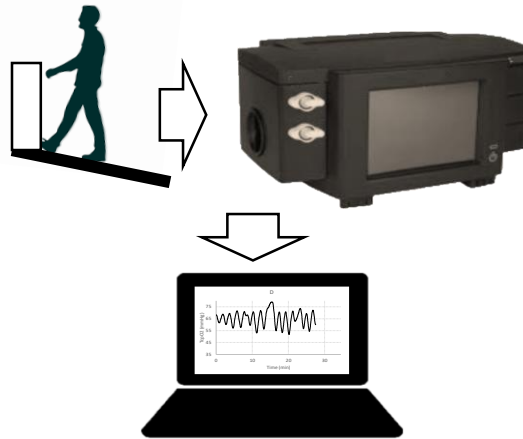
Database : 2229 records of patients referred for treadmill test since 2016

Edinburgh Claudication Questionnaire & ABI : Ankle brachial index

Exclusions: patients' refusal, incomplete records, retests, non-isolated CS, pain at rest

584 new patients complaining of isolated vascular type calf pain by history

Transcutaneous oxygen pressure



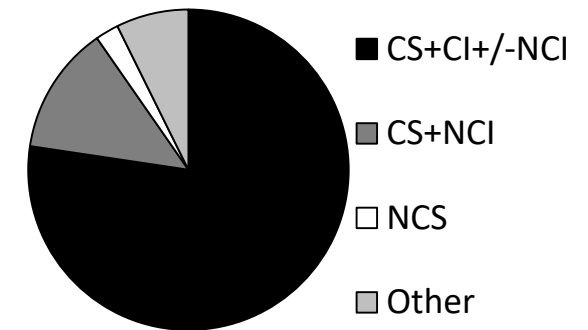
Ischemia (I): DROP < -15 mmHg

&

Symptoms (S) on treadmill

Analyses for calves (C) and for buttocks or thighs (NC)

ABI < 0,90, n=424



ABI not < 0,90, n=160

