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Retrospective Cohort Study

Proximal Ischemia is a Frequent Cause of Exercise-Induced Pain in Patients with a Normal Ankle to Brachial Index at Rest

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Background: Excluding a vascular origin of exercise-related pain is often difficult in clinical practice. Recent papers have underlined the frequent association of concurrent lumbar spine degenerative disease and peripheral arterial disease. Furthermore, even when suspected, isolated exercise-induced proximal ischemia is difficult to diagnose. Measurement of transcutaneous oxygen pressure (tcpO2) is an interesting and accurate method to differentiate proximal (buttock) from distal (calf) regional blood flow impairment (RBFI) during exercise.

Objectives: We searched for isolated proximal-without-distal RBFI as a possible cause of claudication, in patients with borderline (ABI-b: 0.91 - 0.99) or normal (ABI-n: 1.00 to 1.40) ankle to brachial index at rest.

Study design: Retrospective cohort design study. We analyzed patients referred to our laboratory with symptom limiting claudication and an ankle brachial index within normal limits.

Settings: University-based exercise-investigation center.

Methods: Over a 12-year period, we identified 463 patients referred to our laboratory that had their lowest resting ABI between 0.90 and 1.40. The tcpO2 on chest, buttocks, and calves were recorded during treadmill walking tests (3.2 km/h, 10% slope) in 220 ABI-b and 243 ABI-n unique consecutive patients complaining of limiting claudication (each patient's ABI was the lowest of the 2 legs). Limiting claudication was defined as the reported inability to walk 1 kilometer without stopping. A DROP index (limb tcpO2-changes minus chest tcpO2-changes from rest) below -15 mmHg was used to indicate a positive result (i.e. exercise-induced RBFI).

Results: Treadmill exercise showed evidence for proximal or distal RBFI, of at least one side, in 128 out of 220 patients (58.2%) and in 86 out of 243 (35.4%) patients with ABI-b and ABI-n, respectively. Isolated proximal-without-distal RBFI was found in 32 out of the 128 (25.0 %) positive tests in ABI-b and 32 out of the 86 (37.2%) positive tests in ABI-n patients.

Limitations: Study limitations include the absence of systematic follow-up of diagnosed patients and absence of systematic search for cardio-respiratory co-morbid conditions.

Conclusion: Isolated proximal-without distal RBFI is found in approximately one out of 7 patients complaining of symptom limiting claudication with a borderline or normal resting ABI. Exercise-tcpO2 may help to discriminate patients with arterial claudication that could benefit from invasive vascular investigations and procedures.

Key Words: Claudication, diagnosis, prevalence, peripheral arterial disease, transcutaneous oxygen pressure, pathophysiology, exercise testing, arterial pressure, vascular disease

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Claudication is a frequent cause of walking limitation in elderly patients. Lumbar spine stenosis due to disk degeneration (DD) and peripheral artery disease (PAD) can often show similar symptoms. Both can result in exercise-induced lower back, buttock, or hip pain. While the patient's history will often guide the physician toward DD or PAD as the underlying cause of walking limitation, the primary diagnosis may not always be clear, and these 2 diseases are frequently associated (1,2). The measurement of the ankle to brachial index (ABI) is an easy bedside tool to detect the presence of PAD. It has high sensitivity and specificity (3-5) in the general population, and is much more accurate than pulse palpation (6,7). An ABI is often defined abnormal at 0.90 or lower. Recently, ABI values of 0.90 to 0.99 have been defined as "borderline abnormal"(8). Values above 1.40 suggest calcified or stiff arteries and are generally considered abnormal as well. Nevertheless, there are limits to the evidence provided by an ABI between 0.91 and 1.40 as an argument against the arterial origin of pain (5,9-11). Very few studies have focused on patients with claudication and an ABI at rest within the 0.91–1.40 limits (11). In proximal arterial claudication (i.e. Leriche syndrome) symptoms are generally reported as fatigue, discomfort, or sciatica rather than cramping pain, thus mimicking symptoms of non-vascular origin (pseudo-claudication). Further, proximal (i.e. lower back, buttock, hip) arterial claudication is unlikely to have an abnormal ABI if it is due to isolated lesions of the lumbar and/or hypogastric arteries (1,2). Exercise-transcutaneous oxymetry (tcpO2) is an interesting tool in the context of the present problem, since it can simultaneously detect proximal (buttock) and distal (calf) regional blood flow impairment (RBFI) at both sides during exercise, thus providing an objective argument for the origin of exertional pain (12-16). We aimed to estimate the proportion of patients whose lowest ankle to brachial index at rest was borderline (ABI-b: 0.91 - 0.99) (8,17) or normal (ABI-n: 1.00 to 1.40) and whose tcpO2 exercise test was abnormal, suggesting a vascular origin of claudication. We assumed that this proportion would be higher in patients with ABI-b than in patients with ABI-n. We hypothesised that, among these positive tests, isolated proximal without distal ischemia would be observed more frequently in patients that had prior aortic or iliac revascularisation (14,18). This latter point is of particular interest, since we assume that a normal perfusion to distal arteries may falsely lead the physician to exclude PAD as a cause of walking limitation.

Research Design and Method

Participants

A retrospective analysis over a 12-year period was performed among all new patients referred to our laboratory for claudication (19-21). As a routine, all referred patients had the following standard procedure.

Medical History

For each patient referred to the department, we used a questionnaire that inquired about previous vascular interventions at the aorto-iliac level as well as treatments for lumbar spine syndrome, hip and lumbar arthritis, and sciatica. Age, weight, height, gender, presence of diabetes, and current medications were noted from patient's file and completed by patient's interview when needed.

Symptoms by History

The questionnaire used was a French translation of the San Diego Claudication Questionnaire (SDCQ), adding hip pain as a possible location for claudication. The questionnaire was self-administrated by the patient at admission. Exercise-related pain was suspected to be of vascular origin if the pain:

A. occurred during walking,
B. did not occur when standing still or sitting,
C. did not disappear during walking, but only during the slow-down phase or discontinuation of the exercise, and
D. disappeared within 10 minutes after stopping.

From answers to the SDCQ, only the exercise- related symptoms by history which fulfilled these criteria were considered of vascular origin and used for the analysis.

ABI Measurement

When ABI was not available bilaterally from patient's file at referral, as a laboratory routine, it was measured *de-novo* after 10 minutes of rest and calculated on each side as the ratio of the lowest ankle systolic pressure to the highest brachial systolic pressure.

Treadmill Exercise Test

The treadmill tests were performed as previously described (12). The treadmill speed was progressively increased within 4 minutes up to 3.2 km/h and then maintained at this speed for a maximum of 16 minutes (~1000 m) at a 10% slope. All patients were blinded

to the distance and time walked. Maximal walking distance on the treadmill was noted at the end of each test. The patients that completed the 20-minute treadmill test were considered unlimited while walking on a treadmill.

Transcutaneous Oxygen Pressure Measurements

Measurements were performed as previously reported (12,13). We used a tcpO2 device (TCM-400 Radiometer, Copenhagen, Denmark) with 5 probes heated to 44.5°C, recorded values being automatically temperature-corrected to 37°C. Probes were positioned on the chest, on each buttock (upper external quarter), and approximately 4 cm above each ankle. The data were transferred every 5 seconds to a custom-made computer program that automatically calculated the decrease from rest of oxygen pressure (DROP) at each limb site. The DROP index was calculated as previously described (12) by subtracting chest-tcp02 changes to tcp02-changes at the limb levels. For the analysis, the lowest negative value of the DROP index ($DROP_m$) during or in the 10 minutes post-exercise was used. $DROP_m$ remains normal in case of systemic exercise-induced hypoxemia and is thus expected to reflect local cutaneous hypoxemia resulting from underlying RBFI. Last, according to our previous observation, at both the proximal and distal level a $DROP_m$ value below negative 15 mmHg was defined as abnormal, indicating a regional blood flow impairment (RBFI) during exercise. This value has been shown to provide highly accurate results as compared to arteriography at both the proximal and distal level (12,13). Lastly, the lowest of the 4 DROPm values was used as an index of severity of RBFI during exercise.

Symptoms on Treadmill

The questionnaire used was the same as the one used at admission. During the test, participants were encouraged to signal any trouble that interfered with their ability to perform the test, such as dyspnea, dizziness, or pain of any kind. As before the treadmill test, only the exercise- related symptoms during the treadmill testwhich fulfilled pre-defined vascular-type criteria were used for the analysis.

Inclusion Criteria

Over the studied period we selected all consecutive patients that had:

1. lowest resting ABI between 0.90 and 1.40;
2. stable symptoms in the last 3 months before their visit; and
3. limiting claudication, as defined as the self-reported inability to walk 1000 m without stopping.

Analysis of Data

Statistical evaluation was performed using SPSS V 12.0F software (Cary, NC). Values were expressed as the means ± SD. We considered *P* values <0.05 to be statistically significant. NS is a non-significant statistical difference. Proportions are calculated with 95% confidence intervals. Comparisons between ABI-b and ABI-n participants were performed using the unpaired Student's t tests for numerical variables and Chi^2 test for binary variables. Concordance between symptoms by history and on the treadmill was studied with the Kappa coefficient. Last, proximal claudication is frequent in patients that have undergone revascularization procedures at the proximal (aorto-iliac or aorto-femoral) level bypassing the hypogastric vascular bed (14). Thus we studied the relative risk of having an isolated proximal RBFI in patients that have had a revascularisation at the aortic or iliac level as compared to nonoperated patients in the ABI-b and ABI-n groups.

Results

Within the study period, 3,120 exercise-tcpO2 tests were performed among 2,209 different consecutive patients. Among these 2,209 patients, 818 had stable symptoms for at least 3 months and an ABI between 0.90 and 1.40. More than half of these latter patients (n = 463) reported walking limitation, thus fulfilling inclusion criteria.

Participants

Among the patients studied, 278 (60.0%) were referred by vascular physicians, 62 (13.4%) by rheumatologists of orthopedic surgeons, 4 (0.8%) by neurologists, the other 119 (25.7%) by their general physician.

Among the 463 studied patients, 80 (17.2%) had a history of surgery or angioplasty at the aorto-iliac level, 24 (5.2%) had a history of hip or lumbar spine surgery for spinal stenosis, 139 (30.0%) had been treated medically for disk degeneration or hip arthritis, and 26 (5.6%) were primarily diagnosed with lower limb neuropathy either due to diabetes or chronic alcohol abuse. Characteristics of included patients are reported in Table 1.

As shown, patients were dominantly males and most were treated for the primary or secondary prevention of cardiovascular disease.

Tests Results

Symptoms by History

Although patients often complained of multiple localization of pain, the major limiting symptoms were infra-inguinal in ABI-b (n=143; 65.0%) and ABI-n (n = 156; 64.2%) patients. Pain was reported in the lower back in 18 ABI-b and 33 ABI-n patients, in the buttock(s) in 32 ABI-b and 31 ABI-n patients, and in the hip(s) in 27 ABI-b and 23 ABI-n patients.

Symptoms on Treadmill

All but 44 patients reported lower limb symptoms on the treadmill that were generally consistent with the symptoms that they reported by history as shown in Table 2: Kappa was 0.475 in ABI-b ($P < 0.001$) and was 0.653 in ABI-n ($P < 0.001$). Twelve patients remained asymptomatic on the treadmill. The most frequent non-limb symptoms limiting exercise were dyspnea and/or chest pain.

Table 1. *Characteristics of the patients in each group*

	Borderline ABI	Normal ABI	*P* value
N	220	243	
Age (yrs)	62.3±11.3	64.0±12.6	0.12
Stature (cm)	168±9	168±10	0.70
Weight (kg)	79±17	80.0±16	0.69
Walking speed over 10 m (km/h)	3.8±0.6	3.7±0.7	0.20
Lowest ankle to brachial index	0.94±0.03	1.08±0.08	<0.0001
Lowest of the 4 DROP values (mmHg)	-22.4±15.0	-15.1±11.2	<0.0001
Heart rate (beats/min)	80±16	79±17	0.33
Male	182	193	0.36
Systolic blood pressure (mmHg)	142±2	140±20	0.26
Duration of the treadmill test (sec)	340±295	358±306	0.54
History of aortic or iliac surgery or angioplasty	46	37	0.11
History of lumbar spine or hip surge	11	13	0.17
Previous treatment for Rheumatic	63	76	0.53
Lower limb neuropathy	8	18	0.06
Anticoagulant or Antiplatelet drugs	160 (73%)	160 (66%)	0.11
Beta blockers	53 (24%)	67 (28%)	0.39
Anti-diabetic	43 (20%)	52 (21%)	0.62
Cholesterol lowering drugs	116 (53%)	116 (48%)	0.28
Anti hypertensive	120 (55%)	141 (58%)	0.45
Anti-inflammatory or analgesic drugs	47 (21%)	55 (23%)	0.74

ABI: ankle to brachial index"

Table 2. *Reproduction of symptoms on treadmill in patients with a borderline or normal ankle to brachial index (ABI).*

		Symptoms by history			
		Borderline ABI		Normal ABI	
		Proximal	Distal	Proximal	Distal
Symptoms on treadmill	Proximal	44	14	65	5
	Distal	27	122	8	134
	Non limb symptoms or no symptoms	6	7	14	17

TcpO2 Results

Exercise-tcpO2 was positive ($DROP_m$ below negative 15 mmHg) suggesting exercise-induced RBFI at least on one of the 4 sites in 128 of the 220 patients with ABI-b (58.2%) and 86 of the 243 patients with ABI-n (35.4%): $P < 0.001$. Results are shown in Table 3. It is of interest to note that isolated proximal (buttock) RFBI was found in 32 of 128 (25%) of the positive tests in ABI-b patients and in over one-third (32 of 86; 37.2%) of the positive tests in ABI-n patients, between group $chi^2 = 3.7$, $P = 0.06$.

History of Aortic or Iliac Revascularisation

Ischemia at one or more sites was found in 38 of the 49 patients (78%) with ABI-b, and in 17 of the 34 patients (50%) with ABI-n that had a prior history of aortic or iliac revascularization. Among these, the presence of isolated proximal RBFI without distal RFBI was observed as a possible cause of claudication in 17 (34.6%) of the patients with ABI-b and 10 (29.4%) of the patients with ABI-n that had prior bypass or stent at the aortic or iliac level. Thereby, the relative risk of the presence of isolated proximal RBFI in the presence vs. absence of prior aortic or iliac revascularisation was 3.96 (2.13-7.81) $P < 0.0001$ in patients with ABI-b and 2.79 (1.45-5.47), $P < 0.01$ in patients with ABI-n.

Discussion

Key Results

Major results can be summarized as follows:

- Overall, 46.2 % of all tests were found consistent with a significant abnormal tcpO2 response (RBFI) during exercise consistent with a vascular origin of claudication despite an ABI within the 0.91-1.40 range.
- The percentage of RBFI was higher in the ABI-b than in the ABI-n group.
- Claudication with proximal, without distal, RBFI was observed in approximately one out of seven of the patients included in this study.
- A history of aortic or iliac revascularisation increases the likelihood of positive isolated proximal without distal RFBI.

This is one of the largest ever-reported series (n=64) of isolated proximal without distal RBFI in patients with symptom-limited claudication with a normal or borderline ABI at rest.

Interpretation

Overall Prevalence of Positive Tests and Isolated Proximal RFBI

Approximately half (46.2%) of the patients included in the study had a RBFI with exercise, confirming a vascular participation to their walking impairment. This is much higher than the proportion of positive post-exercise ABI (31%) observed by Stein et al (11). The difference is very likely in that we detected proximal ischemia by use of the exercise tcpO2 protocol. Indeed, the prevalence of distal RBFI (with or without associated proximal RBFI) in the present population was 32.4%. This result is very close to the result previously observed with post-exercise ABI, and supports the use of tcpO2 in the present study. Claudication resulting from isolated proximal-without-distal RBFI is rarely reported in the general population, found as only isolated observations or very small series (22,23). Previous reports have demonstrated that isolated proximal ischemia can mimic symptoms of neurological or musculoskeletal origin (22,24) and may result in isolated distal symptoms in approximately 15% of the cases (25). In practice, proving the vascular origin of claudication in proximal-without-distal ischemia is not easy. Frequently in obese patients, optimal complete ultrasound investigation of the arterial tree is often not obtained at the hypogastric level. Further, our local experience is that in most patients, even in the presence of proximal claudication, the patency and presence/absence of stenosis of the hy-

Table 3. *Localization of regional blood flow impairment (RFBI) during exercise-tcpo2 in patients with a borderline or normal ankle to brachial index (ABI).*

	Borderline ABI (N=220)	%	Normal ABI (N=243)	%	*P* Value
No RFBI	92	41.8	157	64.6	<0.0001
Distal RFBI only	35	15.9	26	10.7	NS
Proximal+ distal RFBI	61	27.7	28	11.5	<0.0001
Proximal RFBI only	32*	14.5	32	13.2	NS

pogastric arteries is not reported in the ultrasound file (26). Various diagnostic tools have been proposed to assess proximal ischemia such as penile pressure (27), near infra-red spectroscopy (28), or thallium scintigraphy (29). To date, we think that tcpO2 is the most accurate and validated technique (12).

Prevalence of Abnormal Exercise-TCPO2 in ABI-b vs. ABI-n Patients

Not surprisingly, the prevalence of positive exercise tcpO2 results was higher in ABI-b than in ABI-n. For patients with ABI lower than 1.00, the mortality rate increases almost linearly with the decrease in ABI (30). Consistently, estimation of sub-clinical atherosclerosis by carotid artery intima-media thickness shows a progressive increase from normal ABI (1.10-1.29), low-normal ABI (1.00-1.09), borderline ABI (0.90-0.99) to ABI <0.90 (17). With these data in mind, it is expected that isolated proximal lesions should be more prevalent and more severe (as reflected in the lowest DROPm) in ABI-b than ABI-n patients.

Patients with a History of Aortic and Iliac Procedures

Overall more than half of patients with a history of aortic or iliac bypass had a positive tcpO2 result consistent with a vascular origin of claudication. The proportion exceeded 75% in those with ABI-b. In these previously revascularized patients, one could suggest that it is expected that arterial claudication should be frequent, rapidly suspected, and easily proved. We think that it is not the case. The proportion of isolated proximal RFBI in this population was particularly high as compared to the rest of the population, approximately one-third. Our experience is that peripheral examination and investigations are often normal as a result of an apparently perfectly patent procedure, leading to the exclusion of an arterial origin of the walking impairment and resulting in prolonged diagnostic erring. Indeed, we have previously shown that proximal claudication is a frequent finding and frequently misdiagnosed in patients with aorto-bi-femoral bypasses (14,18).

Limitations

Systemic hypoxemia can be an exacerbating cause of muscle oxygen deficit during exercise (31-33) but was not specifically studied in the present study. Frequently in vascular patients, cardiac limitation can occur as a limiting co-morbid condition. The low proportion (< 7%) of patients reporting limitation related to non-lower limb symptoms was expected from the selection criteria of the study but does not exclude that walking capacity was worsened by non-arterial factors. Arterial stiffness was likely an explanation of normal resting ankle pressure measurements (9,10) in some patients of the present study. This is one of the reasons why exercise-tcpO2 and not post-exercise ABI is performed as a primary routine in our laboratory, in patients with claudication. Arterial stiffness occurs frequently in diabetic patients. Interestingly the proportion of patients treated for diabetes was not different between the ABI-b and ABI-n groups of this study. Last, the retrospective characteristic of the study may be suggested as a limitation.

Generalizability

In patients with claudication, a vascular origin of walking impairment should not be excluded on the basis of a normal or borderline ABI. A vascular origin with abnormal exercise-tcpO2 was found in half of such patients. Approximately one-third of these positive results related to isolated proximal arterial regional blood flow. This last observation is the most likely explanation for the high prevalence of positive tests compared to previous reports. Indeed proximal-without-distal RBFI is likely difficult to detect even with post-exercise ABI.

Areas for Future Research

The most common cause of PAD is atherosclerosis obliterans. ABI measurements are largely used for the diagnosis of PAD but can remain normal in patients with claudication. Exercise-tcpO2 is a complex and time-consuming technique as compared to post-exercise ABI, and is not done routinely in most vascular clinics. Nevertheless, exercise-tcpO2 is efficient and accurate for the non-invasive detection of proximal ischemia. As such, this technique may help to discriminate patients with arterial claudication that may benefit from invasive arterial investigations and procedures. A cost-effectiveness study of this technique as an additional clinical tool in patients with ABI-b or ABI-n values is required.

Further, lumbar spine stenosis (LSS) is frequent in the elderly. Some clinical characteristics might distinguish vascular from neurogenic claudication (Table 4), but the management of chronic exercise-induced pain often remains challenging (34). Specifically, on the one hand, the normal limit to be used to assess the presence of LSS is still a subject of debate among osteo-articular specialists, while on the other hand, proving the vas-

Table 4. *Typical clinical characteristics suggesting vascular and neurogenic claudication*

	Vascular	Neurologic
History of aorto-iliac revascularisation	Yes	No
Acute onset of first event	No	Yes
Relief of pain after walking	< 10 min	> 10min
Relief of resting pain while standing still	Yes	No
Abnormal Romberg test	No	Yes
Dysesthesia, paresthesia, Intermittent priapism	No	Yes
Absent pulse, Abnormal Ankle pressure or arterial bruit	Yes	No
Pain at spinal mobilisation	No	Yes
Unexplained urinary disturbance	No	Yes
Wide-based gait	No	Yes

cular origin of walking-induced buttock claudication remains a difficult issue with routine non-invasive tools for the vascular physicians. LSS may induce exercise limitation and claudication. More than 30 000 interventions for LSS are performed each years in USA, for a total cost over $10 billion (35). Of interest is the fact that the treatment of lumbar spine syndrome by surgery is acknowledged to provide only modest long term improvement of symptoms (36,37). Whether a significant part of these nonsatisfactory functional results could be due to undiagnosed proximal isolated RBFI is a fascinating issue for future research.

Conclusion

Isolated proximal-without distal RBFI is found in approximately one out of 7 patients complaining of symptom limiting claudication with a borderline or normal resting ABI. Exercise-tcpO2 may help to discriminate patients with arterial claudication that could benefit from invasive vascular investigations and procedures.

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