Transcutaneous Exercise Oximetry for Patients With Claudication
— A Retrospective Review of Approximately 5,000 Consecutive Tests Over 15 Years —

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Background: Exercise transcutaneous oximetry (Ex-tcPO2) is used to argue for the vascular origin of lower limb pain, especially at the proximal level, where the diagnosis of peripheral artery disease can be difficult. This study analyzed the principal indications, mean results, and limitations of Ex-tcPO2, as well as the relationship between the annual number of Ex-tcPO2 tests and internal iliac artery (IIA) revascularizations.

Methods and Results: Data from our first 15 years’ experience (3,631 patients, 5,080 tests) with Ex-tcPO2 were analyzed retrospectively using the minimal value of the decrease from rest of oxygen pressure ($\text{DROP}_{\text{min}}$). We had 99.7% of expected $\text{DROP}_{\text{min}}$ results. The proportion of tests showing isolated proximal unilateral or bilateral ischemia ranged from ~5% to ~20%. A gradual increase with time was observed in both the annual number of Ex-tcPO2 tests (from 0 to ~500 per year) and the annual number of IIA revascularizations performed (from 0 up to 18 per year). At least 85% of patients (77/91) showed function improvement after IIA revascularization.

Conclusions: Ex-tcPO2 (using $\text{DROP}_{\text{min}}$) provides an objective argument for exercise-induced ischemia, bilaterally at the distal and/or proximal level. Using Ex-tcPO2 has improved our diagnostic performance and markedly changed our therapeutic decisions, specifically for proximal claudication. The increased number of Ex-tcPO2 tests is associated with an increased number of IIA revascularizations, although a causal relationship was not proven.

Key Words: Claudication; Exercise transcutaneous oximetry; Peripheral artery disease; Revascularization

International guidelines state that in case of typical or atypical symptoms suggestive of lower extremity artery disease, the treadmill test should be considered for diagnostic confirmation and/or baseline quantification of functional severity. Despite this recommendation, exercise testing is a largely underused approach in arterial claudication. Exercise in the laboratory is a very efficient way of reproducing symptoms and quantifying walking impairment in patients with lower-limb peripheral artery disease (PAD). Although the Rutherford classification of PAD severity originally relied on the ability to walk for 5 min on a treadmill, treadmill testing is rarely done in routine clinical practice.

When exercise testing is performed, the most widely used technique to monitor changes in lower limb hemodynamics is recording of the post-exercise ankle-brachial index (ABI). This easy and cost-effective method improves the detection of PAD. Unfortunately, there are many limitations to post-exercise ABI (1) it can only be measured following, and not during, exercise; (2) it requires the patient to lie down (which is not always comfortable for patients with dyspnea); (3) it is sensitive to arrhythmia and arterial stiffness; (4) it cannot account for lesions on branches, such as the internal iliac artery (IIA); (5) it cannot be measured in case of skin ulcers; (6) it cannot differentiate proximal from distal lesions; (7) the normal post-exercise ABI limits to be used are debatable; and (8) it is relatively insensitive to the hemodynamic improvement observed after rehabilitation.

Other available approaches include, among others, thallium scintigraphy, near infra-red spectroscopy, and exercise transcutaneous oximetry (Ex-tcPO2). This latter technique was proposed in the 1980s using the regional perfusion index (RPI; the ratio of limb to chest values), but
was abandoned due to a reliability issue. Indeed, the test-retest absolute value for tcPO2 is highly variable (due to microvascular heterogeneity of the skin), whereas the absolute changes over time are highly reproducible. In 1999 we tested (and published in 2003) a new formula to express the results of Ex-tcPO2 and to get rid of absolute value variability, namely the “decrease from rest of oxygen pressure” (DROP) index. We showed that this DROP index (limb changes from rest minus chest changes from rest) markedly improves the accuracy and reliability of the technique compared with the previously proposed RPI.11,12 We defined normal limits to be used and validated the technique against gold-standard arteriography at the calf and buttock level,11,12 or computed tomography angiography.13 We showed that Ex-tcPO2 also accounts for eventual systemic arterial oxygen pressure changes through the use of the chest electrode.14

Since 2000 we have progressively integrated Ex-tcPO2 in our diagnostic routine of claudication as a tool to argue for the vascular origin of exercise-induced pain, specifically at the proximal level. Ex-tcPO2 was initially performed in highly selected patients for whom usual techniques and/or post-exercise ABI were negative or impossible. With time, Ex-tcPO2 has rapidly become systematic in our laboratory and the technique of choice in the diagnostic exercise approach of walking-induced impairment, associated with claudication. In recent years, the technique has progressively developed in other laboratories in France15 and abroad.16

Herein we report a retrospective analysis of our first 15 years’ experience with Ex-tcPO2 testing. We focus on the progressive development, principal indications, and mean results observed with the technique over these 15 years, as well as on the limitations of the technique. Because the usual investigations of proximal exercise-induced ischemia lack accuracy,17 we hypothesized that the development of the Ex-tcPO2 technique would increase the number of patients detected with atypical claudication showing isolated proximal ischemia and therefore the number of IIA revascularizations performed over the same period.

Methods

Since 2000, all Ex-tcPO2 tests have been systematically recorded in a database. In the present study we reviewed the database of Ex-tcPO2 tests from 1 January 2000 to 31 December 2015. Over this period, few changes have been made in our procedures, and these changes are described in the following paragraphs. In the present retrospective analysis, we studied all the Ex-tcPO2 tests performed in the Laboratory for Vascular Investigations in Angers (France).

Routine, on arrival, patients were asked to complete a questionnaire regarding their medical history, including current medications and symptoms, using either the San Diego claudication questionnaire (until 2009)18 or the Edinburgh claudication questionnaire (since 2010).19 Then, patients were admitted to the test room. Their usual walking speed was measured over 10 m in the corridor between the waiting room and the test room. All patients who were able to walk these 10 m in less than 15 s were assigned to the standard Ex-tcPO2 protocol. Patients who walked slower were given a lower speed protocol, as detailed below. Before each treadmill test, age, body weight, stature, and ABI were retrieved from the patient files and, when needed, measured by trained, certified staff. Self-completed questionnaires were checked for completion and completed if required. The ABI for each patient was calculated as the ratio of the lowest measurable ankle pressure to the highest arm pressure.

The tcPO2 measurements were performed using 5 single-probe Tyna TCM3 devices until 2006 and a 5-probe TCM 400 device thereafter (both from Radiometer, Copenhagen, Denmark). Ex-tcPO2 tests were performed in an air-conditioned room (temperature 21±2°C; mean±SD). A 1-point calibration to air was performed before each experiment. The calibration values were set according to actual barometric pressure. The temperature of the probe was 44.5°C to allow maximal vasodilation, thereby decreasing the arterial-to-skin pressure gradient. Thereafter, the tcPO2 measurements were automatically temperature corrected to 37°C by the transcutaneous device. One probe served as the control on the chest, 1 probe was positioned on each buttck, 4–5 cm back from the bony prominence of the trochanter, and the last 2 probes were placed 4–5 cm above the external ankle malleolus. In recent years we often used a 6th probe in other, non-standard, locations. Results for this 6th probe have been reported elsewhere.20

Before fixing the electrodes to the skin with double-sided adhesive rings, dead cells from the epidermal surface were removed by gently rubbing the skin with a rough tissue. Once the probes were in position, a pretest 10-min heating period in the standing position was required to allow steady state resting values to be reached. All tests were performed under electrocardiogram (ECG) monitoring.

The standard treadmill test was performed with changes in speed and grade as follows. The treadmill was stationary and flat for a 2-min resting period, then the incline was rapidly increased from flat to 10% while the speed was increased to reach 3.2 km/h (in 60-s increments until 2004, and 15-s increments since 2005). This transition aimed at facilitating the adaptation of patients to walking on the treadmill. Thereafter, patients were tested at a constant speed of 3.2 km/h at a 10% incline until exhaustion, all the while encouraged to report their symptoms and perform to their highest possible speed and duration. Until 2009, if no limitation occurred after 15 min walking at a constant speed, the exercise was stopped. Since 2010, after 15 min at a constant speed, the speed and incline of the treadmill were increased progressively at 1-min intervals, as described previously.12 This second phase was proposed so that all patients reached their limit despite the absence or presence of only moderate symptoms. Of the few patients who ‘naturally’ took ≥15 s to walk 10 min in the corridor before the Ex-tcPO2 test, the increase in treadmill speed was limited to 2 km/h. None of these slow-walking patients could walk for more than 15 min on treadmill.

In all cases, the treadmill test was stopped: (1) at the absolute maximal walking distance at the patient’s request; and (2) for medical reasons in the case of persistent severe arrhythmia, dyspnea, or dizziness. Post-exercise recovery consisted of the patient standing still on a flat treadmill for a minimum of 10 min. A test was considered valid if the patient was able to walk for at least 15 s at the constant speed.

The tcPO2 values were recorded for 2 min in the standing position (before the treadmill was started), during the walking period and for at least 10 min in the standing position following the end of the exercise test. All data were recorded on a computer with a sample rate of at least 1 Hz (through a 16-bit analogue output on the TCM3’s and on
Results

Seven of the referred patients could not undergo the scheduled Ex-tcPO2 due to a pretest diagnosis of unstable angina, severe tachycardia associated with anemia, osteoarticular disease, or a severe vagal response at the beginning of the test. Thus, 5,080 tests were performed on 3,631 patients between 1 January 2000 and 31 December 2015 (Figure 1). Over time, there was a progressive increase in the number of tests performed each year, leading to approximately 10 tests being performed per week in recent years (Figure 2A). Most patients were referred to our laboratory by vascular specialists (angiologists, vascular surgeons, cardiologists). To date, approximately 1 in 8 patients are referred from physicians of other specialities, which, in order of decreasing frequency, are: GPs or internal medicine physicians, neurologists or spinal surgeons, rheumatologists, and other specialties.

Most patients underwent only 1 test (n=2,709). Of those patients that underwent more than 1 test, 608 patients had 2 tests, generally before and after medical treatment or revascularization. The remaining 314 patients had 3 or more tests as a follow-up of their disease over time. The characteristics of the patients when first referred to the laboratory are given in the Table. Briefly, the patients were predominantly male and with a mean age of 63 years. Most, but not all, were receiving antiplatelet or anticoagulant treatment, because some had not been diagnosed with PAD at the time of referral. ABI was available in the database for 3,129 of 3,631 patients (502 ABI values were missing).

consent from individual patients.

The tcPO2 values for each probe were averaged over the 2 min of the resting period and used as baseline. Changes in tcPO2 from baseline over the time of the test at the level of the buttocks and calves were corrected for eventual changes at the chest level from baseline. The resulting DROP index (limb changes minus chest changes from baseline) is a negative value (in mmHg). The lowest DROP value observed throughout the test (DROPmin) was used for analysis. Previously, we showed that a DROPmin lower than −15 mmHg was to be considered an abnormal result, indicative of exercise-induced regional blood flow impairment (RBFI). In addition, the hospital database (including the departments of vascular surgery and radiology) was searched from 1 January 2005 to 31 December 2016 for codes for all revascularizations, as well as IIA revascularization (angioplasty with or without stenting or surgery). Before 2005, the search was performed manually in surgery files. The year of revascularization was noted. Once identified, files from follow-up visits were analyzed to retrieve the functional results of revascularization. Codes included: asymptomatic; persistent symptoms with improved walking ability; no improvement or worsened; and lost to follow-up.

Values are reported as the mean±SD or as the number of observations and percentages (with 95% confidence intervals [CIs]). Statistical significance was defined as 2-tailed P<0.05. The present study conformed to the principles of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the University Hospital in Angers (Reference no. 2016-86). As a retrospective analysis of routine clinical procedures and according to French law, this present study did not require digital transfer from the TCM 400). The tcPO2 values for each probe were averaged over the 2 min of the resting period and used as baseline. Changes in tcPO2 from baseline over the time of the test at the level of the buttocks and calves were corrected for eventual changes at the chest level from baseline. The resulting DROP index (limb changes minus chest changes from baseline) is a negative value (in mmHg). The lowest DROP value observed throughout the test (DROPmin) was used for analysis. Previously, we showed that a DROPmin lower than −15 mmHg was to be considered an abnormal result, indicative of exercise-induced regional blood flow impairment (RBFI).
indications for the ex-tcPO2 test. Indeed, the initial indications were more restrictive and limited to claudication of atypical localization or severity. It is of interest to note that most tests showed proximal and distal RBFI rather than only distal RBFI, highlighting the importance of quantifying or reported non-feasible). A lowest ABI of <0.90 was observed in 2,201 patients (70.3%; 95% CI 68.7–71.9), in 34 patients (1.1%; 95% CI 0.8–1.5) the lowest ABI was >1.30 (all arteries were incompressible).

Overall, the 5,080 tests should result in 25,400 measurements (1 chest plus 4 limbs per patient) and in 20,320 DROPmin values (4 per patient). Technical problems encountered during the procedure included 2 electronic transmission failures (between the tcPO2 device and the computer) resulting in a total absence of recording, 5 chest probes disconnecting during the test resulting in no calculable DROP result for the 4 limb probes, and 17 probes disconnecting on 1 peripheral recording. Thus, technical failures were observed in <0.5% of tests. As a result, the database included 20,275 DROPmin values, representing 99.8% (95% CI 99.7–99.8) of expected results.

On a patient-by-patient basis, the proportion of negative tests was almost constant over time, representing approximately one-quarter of the tests undertaken (Figure 2B). This includes both patients seen after revascularization and patients with claudication of doubtful or debatable vascular origin. Although the absolute number of tests showing isolated proximal unilateral or bilateral RBFI increased, the proportion of such tests was close to 20% initially, but this has decreased progressively to ~10%. This decrease is to an increase in the total number of tests performed each year, in association with a progressive extension of the indications for the ex-tcPO2 test. Indeed, the initial indications were more restrictive and limited to claudication of atypical localization or severity. It is of interest to note that most tests showed proximal and distal RBFI rather than only distal RBFI, highlighting the importance of quantify-
Ex-tcPO2 and IIA Revascularizations

At the proximal level (n=134 [16.0%; 95% CI 13.6–18.7] vs. n=302 [10.8%; 95% CI 9.7–12.0], respectively; P<0.001) or at the proximal and distal levels (n=512 [61.2; 95% CI 57.8–64.6] vs. n=1,409 [50.4; 95% CI 48.5–52.3], respectively; P<0.001). Finally, the development of the tcPO2 tech-

Figure 4. Exercise transcutaneous oximetry recordings from 6 patients (A–F). On all traces, the gray shaded area indicates the time patients were required to walk. Vertical red lines are event markers and the red horizontal indicates the –15 mmHg normal limit. In some patients, a 6th probe was used (gray lines). Results from this 6th probe were not analyzed in the present study. “Phase d’effort” is exercise period and “Seuil” is limit for normal response.
nique since 2000 has led to approximately 500 Ex-tcPO2 tests performed each year in our laboratory.

Meanwhile, the number of IIA revascularizations performed has increased notably (Figure 3). Although the few IIA revascularizations performed between 2000 and 2008 were rarely diagnosed by Ex-tcPO2, most IIA revascularizations performed since 2009 (>75%) were detected by Ex-tcPO2. This underlines the effect of Ex-tcPO2 in the therapeutic intervention. Among the revascularized patients, 8 were lost to follow-up. For the others, over a mean follow-up period of 4.6 months (range 3–42 months), 52 were asymptomatic (62.7%; 95% CI 52.9–72.3), 25 reported improved symptoms (30.1%; 95% CI 21.3–40.7), and 6 reported no improvement or a worsening of symptoms (7.2%; 95% CI 3.1–15.2).

Typical examples of tcPO2 recordings at the chest and limb levels in 6 different patients are shown in Figure 4, showing different types of recordings.

Discussion

Although claudication is an exercise-induced symptom, most clinicians rely on history, resting ABI, and ultrasound imaging to argue for, or rule out, the presence of PAD and its contribution to walking impairment. Nevertheless, there are many challenging clinical situations, including: (1) typical claudication concurrently associated with comorbid conditions, thus questioning the contribution of the vascular disease alone to walking impairment; (2) the absence of symptoms concordant with the severity of the lesions as estimated by invasive or non-invasive vascular imaging; and (3) atypical claudication not fulfilling vascular-type criteria and buttock claudication. Furthermore, current follow-up of treatments (specifically rehabilitation) lacks objective estimation of hemodynamic improvement, because ABI generally does not improve after rehabilitation.6 Specifically, routine ultrasound lacks sensitivity in proximal claudication,17 leading to the recommendation that invasive imaging should be a first-line approach in these cases.21,22 We believe that a functional test linking symptoms to exercise-induced proximal RBFI is stronger evidence of the contribution of PAD to the symptoms than the sole presence of a stenosis of the IIA observed on imaging. In our usual practice, and in an increasing number of referral centers in France, Ex-tcPO2 has become an efficient tool to better select those patients who should be referred for contrast-injected invasive imaging. The Mayo Clinic (Rochester, NY, USA) has recently reported its first cases of Ex-tcPO2 testing and is thereby the first American center developing this specific approach.16 We believe that Ex-tcPO2 is an accurate, non-invasive test to better select patients who may require invasive imaging, and a prospective study should be performed to prove this assumption.

Initially, we developed Ex-tcPO2 to try to fill the gap between imaging and symptoms, to search for buttock ischemia and to find an objective argument to support the role of PAD in the symptoms reported by the patient. Furthermore, we assumed that patients report symptoms on their most painful area and that Ex-tcPO2 would allow us to visualize areas of asymptomatic ischemia. Thus, Ex-tcPO2 is expected to better estimate the importance and diffusion of exercise-induced RBFI on both sides and at the proximal and distal levels simultaneously. The present study confirms the very high feasibility of these measurements, with fewer than 3 per 1,000 measurement failures.

Until 2000, most cases of buttock claudication reported in the literature were isolated observations or small case series,22,23 suggesting that buttock claudication may be a rare occurrence. We think that it is likely that buttock claudication is actually underdiagnosed, as was shown for patients with aorto-bi-femoral bypasses.24,25 The results of the present study confirm that the prevalence of RBFI at the proximal level is significantly higher in patients with a history of any degree of lower-limb revascularization compared with the rest of the population, and demonstrate the particular application of this technique.

The present study does have some limitations. First, we do not report common iliac revascularizations, whereas we have observed isolated proximal ischemia in isolated common iliac artery lesions. Our assumption is that those would have been detected with resting or post-exercise ABI. The absence of post-exercise ABI could also be suggested as a limitation, but it is unlikely that the ABI could detect isolated IIA lesions, and penile pressure showed low accuracy in this context.26 Further, herein we report functional but not hemodynamic results of revascularizations; the hemodynamic results have been reported previously.27–29

Finally, the present work does not provide any proof of a causal relationship between the development of Ex-tcPO2 tests and the increased number of IIA revascularizations. There are several possible explanations for this. First, our ability to diagnose proximal ischemia has resulted in diagnoses that probably remained undiagnosed in the past. Second, the percutaneous transluminal angioplasty technique has largely developed in the same period of time, facilitating the treatment of arteries that were of complex surgical access and would probably have been left untreated in the past. Third, our report on the evidence of a high rate of isolated proximal ischemia after aorto-bi-femoral bypass28,30 has changed the technique our surgeons use in the revascularization of at least one of the IIA during surgery, which they did not pay attention to in the past. Whether or not there is a causal relationship between the development of Ex-tcPO2 tests and the increased number of IIA revascularizations cannot be defined. The present study is the largest ever reported series of Ex-tcPO2 tests and IIA revascularizations from a single center.

Conclusions

Ex-tcPO2 is an accurate test to diagnose proximal RBFI during exercise, as can result from lesions of the common or internal iliac arteries. The present retrospective study illustrates the concomitant development of Ex-tcPO2 and the number of IIA revascularizations performed in a single center. Although the need of multiple tcPO2 electrodes makes the initial expense accessible only to specialized vascular units, neither nuclear administrative agreement nor radiation detection apparatus are required. Thereby, we think that the use of Ex-tcPO2 shall develop rapidly.

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Conflict of Interest

The authors declare no conflicts of interest.
References


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