Exercise Transcutaneous Oximetry of the Buttocks
— External Validation With Computed Tomography Angiography —

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Background: Exercise transcutaneous oximetry (Ex-tcPO2) is a non-invasive test for exercise-induced buttock ischemia. Prior study defined Ex-tcPO2 normal/abnormal cut-offs against arteriography but no external validation was available. The aims of this study were therefore to (1) determine the diagnostic performance of Ex-tcPO2 against CTA; (2) determine the cut-off point for detection of stenosis >75% in arteries toward the hypogastric circulation; and (3) determine the effect of chest profile classification on the diagnostic performance of Ex-tcPO2.

Methods and Results: A total of 207 patients referred for Ex-tcPO2 were analyzed. DROP during Ex-tcPO2 was compared with the CTA results. Chest-tcPO2 changes were automatically classified into pre-defined profiles representing normal or abnormal responses. Using DROP <-15 mmHg as a cut-off, Ex-tcPO2 had 80.2% sensitivity, 72.3% specificity, 43.1% PPV, 93.3% NPV and 73.9% accuracy, to detect 1 stenosis >75% in arteries toward the hypogastric circulation. Optimal DROP to detect stenosis was: −15 mmHg. The overall diagnostic performance of Ex-tcPO2 was independent of chest profile classification.

Conclusions: Ex-tcPO2 has satisfactory diagnostic performance to detect arterial stenoses towards the hypogastric circulation. Abnormal chest-tcPO2 profile does not impair the overall diagnostic performance of the test.

Key Words: Claudication; Computed tomography; Peripheral artery disease

Exercise-induced lower limb pain is a frequent symptom that can result from vascular or non-vascular (neurologic, osteoarticular) disease.¹ When due to vascular ischemia, claudication can result in distal pain, consistent with the Rose definition of arterial calf claudication² or in proximal pain (so-called buttock claudication). For distal ischemia, ankle-brachial index (ABI) is a validated non-invasive test to detect arterial lesions, but ABI is not the optimal tool to detect lesions on arterial branches that do not drive blood to the distal circulation, such as the internal iliac artery. Proximal claudication can be a particularly puzzling diagnostic issue given that lumbar spine stenosis and various musculotendinous diseases can mimic arterial claudication or be associated with it. The Society for Vascular Surgery considers that the prevalence of buttock claudication is low, and in this case recommends arterial radiology, such as computed tomography angiography (CTA), as a direct step to detect iliac artery diseases.³ Due to the risks associated with arterial imaging tests (e.g., infection, bleeding, renal failure), optimal patient selection is required.

Although a surface technique, transcutaneous oxygen pressure measurement during treadmill walking exercise (exercise transcutaneous oximetry; Ex-tcPO2) has been shown to be a simple, non-invasive, reliable method to detect exercise-induced underlying buttock ischemia.⁴ Ex-tcPO2 performed by a single trained operator was compared against arteriography.⁵ An objectively determined cut-off point for the presence of arteriographic lesions was a lowering in the decrease from rest of oxygen pressure (DROP) below −15 mmHg.⁶ External validation of the technique and confirmation of this cut-off limit with CTA, and performance by various moderately trained or untrained operators, has never been reported.

In addition to detecting lower limb ischemia, a major advantage of Ex-tcPO2 is the ability to monitor potential systemic changes in arterial oxygen partial pressure (as can result from cardiopulmonary diseases)⁷ through the recording of chest-tcPO2 changes during exercise and recovery.⁸ Using clustering analysis, we previously showed that chest-tcPO2 changes could be classified into 4 different profiles (A–D).⁹ The first 2 are normal, while the latter 2 are abnormal and are associated with exercise-induced systemic hypoxemia.

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We hypothesized that the diagnostic performance of Ex-tcPO2 against gold-standard radiology could be impaired in patients with the abnormal (C or D) profile as compared with the normal (A or B) chest profile. This has never been studied. The aims of the present study were therefore to (1) test the diagnostic performance of Ex-tcPO2 against CTA with the previously defined DROP cut-off −15 mmHg; (2) use receiver operating characteristics (ROC) to determine the diagnostic performance and cut-off point to be used to detect at least 1 stenosis >75% in arteries toward the hypogastric circulation compared with CTA; and (3) to determine the effect of chest profile classification on diagnostic performance.

**Methods**

A retrospective analysis was done of all the patients referred for Ex-tcPO2 to the Department of Vascular Investigations at the University Hospital of Angers between 1 January 2010 and 30 June 2014. During that period the Ex-tcPO2 tests were performed by numerous (n=28) moderately trained and untrained operators, while initially the technique was performed by 1 single trained operator (P.A.). From these patients, we selected only the patients who had CTA within 3 months of the exercise test and no revascularization procedure between Ex-tcPO2 and CTA. Throughout this period, arteriography was not prescribed as first-line radiology. Patients who had a history of angioplasty or bypass on the aorta, common iliac or internal iliac arteries were excluded. Also, routine biometric evaluation was systematically performed, and we recorded gender, age, treatment, presence of cardiovascular risk, and the self-reported estimation of maximum walking distance. Further, all the patients had manual measurement of ABI at rest immediately before the treadmill test.

**Exercise Test**

After a 20-min resting period, patients were installed in a room with a temperature of 21±2°C. Tests were performed...
on a treadmill, with the treadmill started flat. For the exercise period, speed and slope were increased from 0 km/h and 0% grade to 3.2 km/h and 10% grade within 1 min. Thereafter, the treadmill speed and grade were stabilized for an additional 15 min. If patients were not forced to stop within the first 16 min, the speed and grade were progressively increased from minute 16 according to the previously described protocol. This combination of constant load and increasing load protocol allows all patients to reach symptom limitation, whereas most patients stop during the constant load phase.

Patients were encouraged to perform at the highest possible speed for the longest time possible (maximum walking distance) and not to stop at pain occurrence. Exercise was discontinued on the patient’s request. All patients remained standing during a recovery period ≥10 min. Twelve-lead electrocardiogram was used to control the heart rate and to detect any arrhythmias or abnormal depolarization events during the whole exercise test procedure.

tcPO2 Measurement

Measurements were performed using 3 tcPO2 probes (TCM-400 Radiometer, Copenhagen, Denmark). A 1-point calibration to air was performed before each experiment. The calibration value was set according to actual barometric pressure. The temperature of the probe was 44.5°C to allow for maximum vasodilatation, thereby decreasing the artery-skin surface oxygen pressure gradient. Afterward, the tcPO2 measurements were automatically temperature-corrected to 37°C by the transcutaneous device. Probes were positioned on the chest and on each buttock (upper external quarter). Before fixing the electrode, the skin was cleaned and dead cells from the epidermal surface were removed by gently rubbing the skin with gauze. Once the electrodes were in position, a pre-test heating period of 10–20 min in the standing position was required to allow stable resting values to be reached. Stable values were defined as tcPO2 change <2 mmHg within 5 min. Once stable, tcPO2 recording was started for 2 min at rest with the treadmill stopped and flat. The recording continued throughout the walking period and the recovery. During the recording, data were transferred in real time to a proprietary program that automatically calculates DROP at each limb site on a 1-Hz sampling rate. DROP was calculated by subtracting chest-tcPO2 changes from tcPO2 changes (from the 2 min at rest) at the buttocks level. For analysis of each side, the lowest negative DROP reached during walking or in the recovery period was used. Ex-tcPO2 were performed and analyzed blinded to the results of CTA, when CTA was performed prior to Ex-tcPO2. The delay between the 2 tests was calculated for each patient.

Chest-tcPO2 Change Classification

At the end of each test, chest-tcPO2 changes throughout the recording were automatically tested against 4 predefined models. Each patient was classified into 1 of the 4 pre-defined categories, as previously described. The profiles A or B were considered normal, while classification into profiles C or D indicated abnormal systemic oxygenation during exercise (Figure 1). In patients with C or D profiles, it is assumed that respiratory limitation might impair walking ability and limit exercise before a measurable significant ischemia occurs at the limb level.

Exercise-Induced Buttock Ischemia

The severity of stenosis was calculated as a percentage according to the formula: (largest diameter−smallest diameter)/largest diameter×100. An occluded artery was scored as 100% stenosis. For each side (right and left), the highest percentage of stenosis among the aorta, common iliac artery, and internal iliac artery; the 3 different observers then measured the largest and the smallest diameters of theses arteries on both sides. With DROP cut-off (−15 mmHg) at the end of the walking test. (Lower panel) Computed tomography angiography of the same patient. Arrow, occluded left common iliac artery occlusion; star, permeability of the contralateral internal iliac artery.

Table 2. Accuracy of Ex-tcPO2 to Detect Stenosis >75% With DROP Cut-off −15 mmHg

<table>
<thead>
<tr>
<th>AUC</th>
<th>0.805</th>
</tr>
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<tbody>
<tr>
<td>DROP optimal cut-off (mmHg)</td>
<td>−15</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>80.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>72.3</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>43.1</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>93.3</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>73.9</td>
</tr>
</tbody>
</table>

AUC, area under curve; DROP, decrease from rest of oxygen pressure; Ex-tcPO2, exercise transcutaneous oximetry; NPV, negative predictive value; PPV, predictive positive value.
years, and 81% were male. Mean ABI was 0.75±0.28. Chest-tcPO2 profiles were normal in 119 patients (A profile, n=107; B profile, n=12), while 88 were considered abnormal (C profile, n=40; D profile, n=48). Clinical characteristics according to chest-tcPO2 profile are listed in Table 1. As shown, there was no significant difference in clinical characteristics between patients with normal and abnormal profiles. Of the 207 patients, all but 9 (4.3%) reproduced their usual lower limb symptoms on treadmill. In these 9 patients the treadmill test had to be stopped due to cardiopulmonary limitation or osteoarticular symptoms. No technical issue (probe disconnection or recording failure) was observed during the 207 Ex-tcPO2 tests (414 results). All CTA were able to be analyzed on both sides (414 results).

Eighty-seven of the 414 CTA showed at least 1 stenosis >75% in the aorta, common iliac or internal iliac arteries. Using the pre-defined DROP cut-off −15 mmHg previously proposed, Ex-tcPO2 had 80.2% sensitivity; 72.3% specificity, 43.1% positive predictive value (PPV), 93.3% negative predictive value (NPV), and resulted in 73.9% accuracy (Table 2). Figure 2 shows a typical example of Ex-tcPO2 application, with a unilateral occlusion of the left internal iliac artery in a patient with unilateral buttock claudication. A typical example of ROC curve analysis and derived distance-to-angle analysis (which allows the determination of the optimal cut-off point) is given in Figure 3. As shown, the shortest distance to the 100%/100% sensitivity/specificity angle indicates the optimal cut-off point for clinical detection, assuming an equal risk of false-positive and false-negative results. AUC were compared using STATA.

Ethics
Given that this was a retrospective analysis of medical routine, French law does not require, to date, patient informed consent. The present work was validated by the ethics committee of the University Hospital of Angers and registered under no. 2016-96.

Results
The CTA were performed before tcPO2 in 61 patients (median delay between the 2 tests, 14 days) and after tcPO2 in the other 146 patients (median delay between the 2 tests, 15 days). Mean age for the 207 patients was 65.0±11.4 years, and 81% were male. Mean ABI was 0.75±0.28. Chest-tcPO2 profiles were normal in 119 patients (A profile, n=107; B profile, n=12), while 88 were considered abnormal (C profile, n=40; D profile, n=48). Clinical characteristics according to chest-tcPO2 profile are listed in Table 1. As shown, there was no significant difference in clinical characteristics between patients with normal and abnormal profiles. Of the 207 patients, all but 9 (4.3%) reproduced their usual lower limb symptoms on treadmill. In these 9 patients the treadmill test had to be stopped due to cardiopulmonary limitation or osteoarticular symptoms. No technical issue (probe disconnection or recording failure) was observed during the 207 Ex-tcPO2 tests (414 results). All CTA were able to be analyzed on both sides (414 results).

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Discussion
The major results of the present study can be summarized as follows: (1) the accuracy of Ex-tcPO2 performed by trained and untrained operators to detect >75% stenosis...
on CTA using the previously defined cut-off point was slightly lower than that observed in our initial experience; (2) the optimal cut-off point for DROP against CTA to detect lesions toward the hypogastric circulation is similar to that in the previous study and was −15 mmHg for stenosis of >75%, confirming the previous result; and (3) contrary to the present hypothesis, abnormal chest-tcPO2 profile does not significantly impair the performance of Ex-tcPO2 to detect a proximal arterial lesion to the hypogastric vascular bed.

The present laboratory established the optimal cut-off point for DROP at −15 mmHg to obtain a sensitivity of 78.8%, specificity, 85.7%; PPV, 85.7%; and NPV, 83.9%. All parameters (sensitivity, specificity and NPV) except PPV were similar, although slightly inferior to, those determined in the initial study, which compared Ex-tcPO2 with the gold standard of that time: arteriography. To clarify the reason for this lower trend, we reviewed the CTA of all 67 apparently false-positive tests. Most of these apparent false-positive Ex-tcPO2 results related to either hypoplastic arteries or long intermediate stenosis or a distal branch thrombosis or calcifications resulting in difficult evaluations. Only a few cases were still clearly considered false positives after this new reading, but are likely to result from distal lesions or lesions of the lumbar ipsilateral arteries.

The main aim of Ex-tcPO2 is to evaluate ischemia, whereas CTA evaluates macro-anatomic lesions. For example, long intermediate stenosis can result in regional ischemia, but would be negative in the present protocol evaluation of CTA. Further, we previously showed the importance of lumbar arteries in buttock perfusion. It cannot be excluded that impaired perfusion through these pathways may result in significant ischemia despite a moderate hypogastric stenosis. Another explanation for the present relatively low PPV, is that only the main arteries were studied and not the distal branches such as the superior gluteal artery. Occlusion of a gluteal branch would possibly result in buttock ischemia but would not be accounted for in the present CTA analysis protocol. Moreover, prior meta-analysis showed that CTA underestimates arterial lesion as compared with arteriography in 15% of cases. Specifically, calcifications and CTA artifacts can make the evaluations difficult. We assume that the lower PPV observed in the present external validation study is likely to result from the imaging method (CTA vs. arteriography) rather than from the lower performance of the Ex-tcPO2 test itself. Last, another possibility is that patients referred nowadays are different from those who were referred during the our initial experience, with more complex clinical situations than 10 years ago.

Given that clinical examination is insufficiently sensitive to detect lower extremity arterial disease, non-invasive tests are necessary for the screening and follow-up of claudication. ABI at rest is recommended as the first-line non-invasive test to establish a diagnosis of peripheral artery disease. When ABI is borderline or normal, the recommendation advises post-exercise ABI. Nevertheless, ABI at rest or following exercise are both inadequate to explore the hypogastric circulation. Ex-tcPO2 seems an optimal non-invasive non-radiological investigation for the detection and follow-up of the hypogastric vascularization, despite the fact that it is measuring only surface oxygen pressure and not muscle oxygen content. Scintigraphy has a good sensitivity (81–100%) for the investigation of lower limb circulation but variable specificity (10–83%).

Furthermore, no specific validation has been done at the buttock level. Near infra-red spectroscopy had low performance compared with Ex-tcPO2. Similarly, penile pressure has a low diagnostic performance compared with arteriography. CTA is now considered as the reference imaging technique for lower limb arterial investigation. The sensitivity of CTA was 95% and specificity, 96% compared with arteriography, but CTA has some limits: the irradiation level is high and the contrast medium is nephrotoxic. Recent reviews suggested that CTA is not a first-line approach except in the case of isolated internal iliac lesions. We suggest that Ex-tcPO2 is underused to date and may help identify patients who might require radiological invasive techniques.

Many parameters may be involved in the imbalance of muscle oxygen requirement and oxygen delivery: the macrocirculation, the microcirculation, systemic hypoxemia and anemia. Variation in any of these parameters might change the absolute and/or relative tcPO2. Indeed, DROP is indexed on chest change. Therefore in the case of exercise-induced hypoxemia, it is expected that DROP might remain within normal limits if the peripheral tcPO2 decrease mimics the decrease in systemic tcPO2 (estimated via chest reference probe). As previously discussed, systemic arterial oxygen pressure influences absolute tcPO2, and changes throughout exercise in arterial partial oxygen pressure may be estimated by changes in tcPO2. Assuming that the C and D profiles reflect exercise-induced hypoxemia, we hypothesized that systemic hypoxemia may worsen the tissue oxygen imbalance at exercise and result in a non-vascular contribution to walking limitation. Although the relationship between abnormal chest profile and cardiorespiratory disease is not yet established, we generally refer such patients for cardiology investigations and repeat Ex-tcPO2 after treatment of frequently detected cardiopulmonary disease. Nevertheless, there was no significant difference in Ex-tcPO2 accuracy between normal and abnormal chest profile status, but the decreasing trend observed in the case of abnormal chest profile could reach significance in a larger population of patients.

Last, the importance of learning curves in cardiovascular stress tests has been previously shown. Thus, while the technique is progressively spreading in France and abroad, it is of interest to show that its diagnostic performance is preserved and that the cut-off point previously proposed remains identical in moderately trained or untrained hands.

Conclusions

The previously proposed DROP cut-off of −15 mmHg has been confirmed; and the diagnostic performance of Ex-tcPO2 for detecting stenosis in the arterial branches toward the hypogastric circulation is satisfactory when performed by trained and untrained operators. Abnormal chest-tcPO2 profile did not significantly change the overall diagnostic performance of Ex-tcPO2 at the buttock level. Ex-tcPO2 can help to better select patients for invasive imaging in the case of proximal claudication, or claudication of questionable vascular origin, even in moderately trained or untrained hands.

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Disclosures
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References