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**Investigation of arterial claudication with transcutaneous oxygen pressure at exercise: Interests and limits.**

Pierre ABRAHAM, Pierre RAMONDOU, Jeanne HERSANT, Wendsèndaté Yves SEMPORE, Mathieu FEUILLOY, Samir HENNI.

**Short title**

Ex-TcpO<sub>2</sub> in lower extremity artery disease

**Corresponding author.**

Pierre ABRAHAM, M.D., Ph.D. Department of physiology, University hospital, Angers, France, and LUNAM University, INSERM 1083/CNRS 6015, Faculty of Medicine, Angers, France.

Fax : +33 241 35 35 93; Telephone: +33 241 35 40 93 Email address: piabraham@chu-angers.fr

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#### ABSTRACT:

Transcutaneous oxygen pressure (TcpO<sub>2</sub>) measurement has been used for years at rest in patients with lower extremity artery disease. It was proposed for exercise testing (Ex-TcpO<sub>2</sub>) in the 80s to evaluate regional blood flow impairment (RBFi) at the proximal and distal levels simultaneously and on both sides, in case of claudication. It was suggested that the use of a chest electrode was mandatory to show that decreases in TcpO<sub>2</sub> at the limb level resulted from limb RBFi and not from a systemic pO<sub>2</sub> decrease of cardiopulmonary origin (exercise-induced hypoxemia). Unfortunately, a major pitfall of Ex-TcpO<sub>2</sub> was the low absolute reliability of the regional perfusion index (RPI: ratio of limb to chest values) and the technique was almost abandoned until 2003, when the DROP index (Decrease from rest of oxygen pressure: limb changes minus chest changes from rest) was proposed. The DROP mathematical formula makes TcpO<sub>2</sub> results independent from the absolute pO<sub>2</sub> starting values, improving reliability of Ex-TcpO<sub>2</sub> as compared to the RPI. Since then, Ex-TcpO<sub>2</sub> has been of renewed interest. The present paper addresses the physiology of Ex-TcpO<sub>2</sub>, interpretation of its results, and common misunderstandings about its use.

**KEY WORDS:** Diagnosis; Treadmill testing; oxygen; claudication; Peripheral artery disease; Exertional limb pain

## **Introduction**

Transcutaneous oxygen pressure (TcpO<sub>2</sub>) measurement at rest has been used for years and recommended by international guidelines in the evaluation of patients with lower extremity artery disease (LEAD) and critical limb ischemia. The analysis of oxygen partial pressure relies either on electrochemical (Clark-type) probes or photo-reactive sensors that measure oxygen partial pressure at the skin surface. The former technique is a classical electrochemical oxydo-reduction between a platinum cathode and a silver anode. For the latter technique, the light from a green LED excites the sensor spots in the matrix layer to emit fluorescence. If the sensor spot encounters an oxygen molecule, the excess energy is transferred in a non-radiative way, quenching the fluorescence signal. The degree of quenching correlates to the partial pressure of oxygen in the matrix, which is in dynamic equilibrium with oxygen in the sample. These photo-reactive sensors must be differentiated from the near infrared spectroscopic approach that reports local tissue saturation and not partial pressure. Beyond its use at rest in patients with severe LEAD, TcpO<sub>2</sub> can be used at exercise (Ex-TcpO<sub>2</sub>) in patients complaining of lower-limb exercise-induced pain suspected of arterial origin. Interest in Ex-TcpO<sub>2</sub> and use is increasing. The present paper addresses the physiology of Ex-TcpO<sub>2</sub>, interpretation of its results and common misunderstandings about its use.

## **Why is this old technique of renewed interest?**

Coming back to a historical point, TcpO<sub>2</sub> has been used for years at rest but scarcely during exercise, specifically as a diagnostic test. First attempts of Ex-TcpO<sub>2</sub> started in the eighties [1, 2]. Following these initial publications few authors have reported the use of Ex-TcpO<sub>2</sub> [3-6], with the rapid evidence that the technique was attractive because it allowed recording throughout exercise. The use of a chest electrode

rapidly appeared also of particular interest to confirm that a local inadequate oxygen supply to fulfill oxygen demand is only related to a severely impaired blood flow supply and not from a moderately impaired blood flow supply but with low blood oxygen content. This was attained through the calculation of the regional perfusion index (RPI: limb values divided by chest values) The result was a non-unit percentage. Nevertheless, the variability of chest TcPO<sub>2</sub> at rest in patients with LEAD is high (standard deviation of 12.3 mmHg as shown in Figure 1). Further, the reliability of absolute TcPO<sub>2</sub> results in test retest recording is fair at best. Thereby, TcPO<sub>2</sub> was unsatisfactory with the use of the RPI [1, 2] because the RPI ratio suffered the added variability of chest and limb absolute values and was dependent on the transcutaneous gradient [7].

In 2003, the “Decrease from Rest of Oxygen Pressure” (DROP) was proposed for the interpretation of exercise results. The DROP accounts for changes from rest at each of the limb probes minus changes from rest at a chest reference probe [8]. The DROP is expressed in mmHg and is by-construction independent of the initial transcutaneous gradient (which is assumed to be constant over time within an experiment) [8]. This proposed DROP index improves test-retest reliability [7]. The arterial systemic PO<sub>2</sub> in normal or diseased patients may either increase (due to improved ventilation/perfusion ratio during moderate exercise) or decrease (due to the obstructive or diffusive lesions in the lungs) during exercise. Previous studies have proven that although the transcutaneous to arterial PO<sub>2</sub> difference may change from one probe to another (figure 1 lower panel), this difference remains constant during moderate exercise within an experiment, thus allowing for a continuous monitoring of PaO<sub>2</sub> absolute changes overtime (although not providing absolute instantaneous values) [9, 10]. For example, during exercise a decrease of 20 mmHg of buttocks TcPO<sub>2</sub> might result in either stable thoracic reading associated with a 20 mmHg decrease of buttocks values or inversely of stable buttocks value with a 20 mmHg systemic PaO<sub>2</sub> decrease. In the first case DROP would be –20 mmHg whereas it would be zero in the second case since buttocks changes directly reflect systemic changes. Inversely stable absolute buttock values could

result in a negative DROP value if thoracic (and then systemic)  $PO_2$  increases. For another example, the absence of increase of buttocks values while thoracic Tc $PO_2$  increases by 20 mmHg, likely are due to lower extremity hypo-perfusion and would result in a DROP value at that buttock of -20 mmHg. Thoracic absolute changes were then added or subtracted to buttocks changes depending on their increase or decrease during exercise. A typical example of the interest of a chest reference analysis is provided in figure 2.

### **How should Ex-Tc $PO_2$ be performed?**

As previously noted, a minimum of two probes (the chest reference and one or more limb probes) is required. Various devices are available in the European market with prices ranging 20 to 60 K€ depending on the number of channels (up to 8). Once the probes are positioned (avoiding area of skin concavity), a period of 15 to 20 minutes is required to reach local heating. Then, we record a resting reference period of 2 minutes before treadmill is started. The DROP has been validated for constant load protocols only. The usual protocol is 3.2 km/h and 10% slope, but specific slow procedures (2 km) may be proposed without dramatically altering the results for patients that do not tolerate the 3.2km/h speed [11]. A recovery period of 10 minutes generally allows DROP to return to zero. A DROP not returned to zero at the end of the recovery period may indicate the need for further recovery time, or may be indicative of a measurement drift. Last, computer availability has allowed the development of real time recording from different devices and real time calculation of results issued from Tc $PO_2$  probes as shown in figure 3 [12]. For the interpretation, we found minus 15 mmHg as the optimal cutoff point to discriminate normal from abnormal results at both the buttock and calf level [7, 8, 13]. We also use this limit at the thigh or foot although it has not been validated for these localizations. A DROP that remains superior to minus 15 mmHg when exercise is stopped, that abruptly decreases below minus 15 mmHg

after exercise and then returns slowly to zero suggests that despite the presence of a significant ischemia walking limitation might be of a non-vascular origin (as in the example shown in figure 2).

### **Is searching for buttock ischemia with Ex-TcpO2 really useful?**

The initial study using the DROP index proposed the use of Ex-TcpO2 as a non-invasive diagnostic tool for buttock claudication [7]. Although buttock claudication is assumed to be relatively rare, non-calf claudication has been estimated to be found in 3 to 6 % of patients with leg pain [14]. Proximal ischemia (as measured at the buttock level with Ex-TcpO2) may result in buttock, hip or lower back pain or pseudo-sciatica. Further, the ability to estimate exercise-induced proximal ischemia is becoming of greater interest due to both iatrogenic reasons (e.g.: intentional occlusion of the internal iliac arteries to reduce bleeding within the genital tract) and to the fact that new endovascular procedures have made isolated lesions of internal iliac arteries accessible to treatment (in case of isolated internal iliac stenosis). Further, proximal claudication occurs frequently in patients with aorto-bi-femoral bypasses [15]. The fact that lower limb ultrasound investigations are within normal limits, does not preclude the possibility that a proximal claudication/ischemia exists because visualization of the hypogastric artery is sometimes difficult in routine evaluation [16]. In many cases, proximal claudication remains a delayed diagnosis [15, 17]. It is of interest to note that the number of treated isolated iliac artery lesions increased with the number of Ex-TcpO2 tests performed in our service [17]. Last, we recently reported that in patients with low back pain at exercise, many patients had buttock (+/- low back) ischemia while walking, suggesting that proximal ischemia could be an underestimated cause of chronic exercise-related low back pain [18].

### **Diabetes affects mainly small rather than large vessels. Is the technique accurate in diabetic patients?**

Results of Ex-TcpO<sub>2</sub> in diabetic versus non diabetic patients with claudication of suspected vascular origin [6] found that patients with diabetes show reduced walking capacity on the treadmill, more cardio-respiratory symptoms, and more frequent distal ischemia than patients without diabetes, with no difference in the prevalence of ischemia at the buttock level[6]. Interestingly, the evaluation of DROP values for each decimal of ankle brachial arterial pressure index seems to be similar in diabetic and non-diabetic patients [19].

#### **How can TcpO<sub>2</sub> being a surface value account for muscle abnormal perfusion?**

TcpO<sub>2</sub> is not a measure of muscle flow but of local oxygen pressure in the skin. The local heating to 43-45 °C is expected to abolish eventual skin vasoconstriction resulting from adrenergic stimulation and facilitate oxygen diffusion from sub-cutaneous tissues. Nevertheless, it is clear that TcpO<sub>2</sub> does not measure muscle oxygen pressure in the muscle, nor the absolute value of arterial oxygen pressure at the skin level. As previously discussed, a transcutaneous gradient exists resulting in surface pO<sub>2</sub> being lower than tissue pO<sub>2</sub>. TcpO<sub>2</sub> at rest is used for critical limb ischemia but not in LEAD patients with claudication because their perfusion at rest may be not altered. At exercise, the local tissue PO<sub>2</sub> reflects the adequacy/inadequacy of the oxygen delivery versus the oxygen demand of the tissue. Then TcpO<sub>2</sub> should be regarded as being an indication of the oxygen supply/demand mismatch of the small region of tissue underlying the electrode and expected to indicate regional blood flow impairment.

#### **What are the reasons for positive Ex-TcpO<sub>2</sub> results when other non-invasive investigations (such as ultrasound) are negative?**

At the proximal level, we have shown that ultrasound which is generally used as a routine investigation in LEAD fails to detect many arterial lesions in patients with proximal claudication [16]. TcpO<sub>2</sub> can be



frequently abnormal in patients with a normal resting ankle to brachial index (ABI). Approximately 30% of the patients with arterial claudication and a normal ABI have a decrease below 0.9 after exercise [20]. There is a debate about the normal limit to be used for ankle pressures after exercise [21]. Nevertheless, whatever the limit used for ankle pressures, the specific interest is that TcpO<sub>2</sub> can measure buttock flow impairment. Indeed, we showed that isolated proximal ischemia is found in 25.0 % and 37.2% of patients with claudication and a borderline ABI or a normal ABI at rest patients with a normal ankle to brachial index at rest [22] and is also a frequent cause of exercise-induced pain in patients with normal post-exercise (ABI or ankle pressure decrease) recordings [23].

#### **What are the reasons for negative Ex-TcpO<sub>2</sub> when ultrasound or imaging results are positive?**

The presence of radiographically significant arterial lesions is not necessarily proof that they are responsible for the clinical symptoms. On the one hand, there is no reason that all severe arterial lesions or occlusions should result in regional ischemia due to the presence of collateral (vicariate) vessels. On the other hand, due to the frequent association of osteo-articular lumbar or hip lesions and proximal vascular diseases (as clearly illustrated by the studies of L Kauppila) [24, 25], there are numerous situations where proximal exercise induced pain may be of non-vascular origin in vascular patients. Then a negative Ex-TcpO<sub>2</sub> shall not exclude the presence of lesions but suggest that an arterial participation to pain is unlikely. Further, it was also shown that isolated proximal –non-calf- ischemia can induce pain involving the calf while calf DROP result remains within normal limits [26]. Another important issue is that pain in claudication results from the misfit between oxygen demand (to cover exercise requirement) and oxygen delivery by blood flow to the active muscles. The prevalence of known or unknown chronic airway diseases is far from being rare in LEAD patients [27]. Impairment in oxygen content (systemic hypoxia) or decreased ability to transport oxygen (anemia) may worsen walking impairment in patients with moderately affected arteries. Exercise hypoxemia in such a population (high prevalence of former

smokers or obese patients) is expected as a possible explanation of the oxygen delivery impairment. This is important because the primary issue of muscle is the oxygen delivery and not the sole inflow. If flow is not optimal and associated to abnormal oxygen content, then the muscle will suffer during exercise. It is very important to keep in mind that the calculation of the DROP accounts for systemic PO<sub>2</sub> changes through the subtraction of chest values from limb values. The result of this is that limb DROP index will remain almost zero if the decrease in local surface PO<sub>2</sub> mimics the decrease in chest surface PO<sub>2</sub> as both result from a systemic decrease in arterial PO<sub>2</sub>. We estimated that Ex-TcpO<sub>2</sub> reveals abnormal systemic oxygenation during exercise in approximately 15% of the patients referred for claudication of suspected vascular origin [28]. This is one of the mechanisms underlying the fact that although most patients with a normal ABI at rest but an abnormal post exercise ABI are positive for Ex-TcpO<sub>2</sub>, few have a normal Ex-TcpO<sub>2</sub> investigation [23].

#### **How does Ex-TcpO<sub>2</sub> compare to other techniques associated with exercise tests such as post-exercise ABI, NIRS or penile pressure?**

Concerning ABI, the issue is that both tests cannot be performed simultaneously because TcpO<sub>2</sub> recovery is in the standing position while ABI at rest or post-exercise must be recorded strictly lying down. One could argue that patients could lie after walking with TcpO<sub>2</sub> in place. Unfortunately, this is impossible when buttock probes are used (as in our routine). Another suggestion would be to disconnect TcpO<sub>2</sub> at maximal exercise and measure ABI but this is not recommended both because TcpO<sub>2</sub> may decrease after exercise is stopped and the recovery to baseline DROP (zero) is an important quality control endpoint of Ex-TcpO<sub>2</sub>. Further, the normal limits to be used in Ex-TcpO<sub>2</sub> have been clearly defined at the calf and buttock [8, 13], while there is no consensus as to the normal limit to be used for post exercise ABI [21]. Thereby, if one aims at analyzing the additional value of TcpO<sub>2</sub>, what normal limit for exercise ABI should be used? According to previous authors, 13.6% of patients have arterial stiffness

[20]. Before it results in non-compressible arteries, stiffness may lead to an overestimation of ABI. There is strictly no reason why stiffness should interfere with results at rest and would not interfere with post exercise results. Then, using a technique independent from arterial stiffness such as TcpO2 is of major interest. The same issue exists about post-exercise arrhythmia that may preclude the use or precision of ABI but does not preclude the use of TcpO2. Overall, the time required performing a walking test with post-exercise ABI or a test with TcpO2 is not dramatically different and the technique can detect hypoxemia, can measure proximal ischemia, and is insensitive to artifacts or to arterial stiffness. This does not mean that post-exercise ABI is useless, because ABI remains cheaper, technically easier, and more accessible than TcpO2. Nevertheless, Tcpo2 seems to provide some valuable additional results when compared to ABI at rest or after exercise [29].

Although it is claiming to measure muscle values, which is a great advantage as compared to surface TcpO2, NIRS measures saturation and the sigmoidal relationship of saturation to pressure for oxygen is an important pitfall for the technique. Further, it was previously shown with local heating at rest, that skin perfusion is an important determinant of NIRS value[30]. The use of NIRS on the buttocks might not be a favorable site for NIRS measurement due to subcutaneous fat thickness. This might explain a lower performance as compared to Ex-TcpO2, at least at the buttock level [31].

The penile brachial index could be used routinely in male subjects for buttock claudication. However, we showed that penile pressure is not relevant to detect abnormal hypogastric perfusion in patients with proximal claudication [32].

### **Should Ex-TcpO2 be used in routine?**

Obviously, TcpO2 is largely used for critical limb ischemia and, to date, scarcely used as a diagnostic tool in patients with claudication. There can be several rationales behind using Ex-TcpO2 measurements for

assessing LEAD patients with claudication [3, 33-35]. Optimal diagnostic indications include: Buttock claudication; Claudication of disputed vascular origin (in case of comorbid conditions such as osteo-articular disease); excessive severity of symptoms in perspective of hemodynamic results or imaging with an aim of detecting exercise-induced systemic hypoxemia). The first experience in the United States has been reported [36, 37] as well as that of the 10 university hospitals that are performing Ex-TcpO<sub>2</sub> as a diagnostic tool in France [38]. This French study has allowed estimation of the clinical cost-benefit of the original approach in the diagnostic routine of patients with claudication [38]. To date we have reported our experience of the first 5000 tests [17], and we are performing more than 500 tests per years in our routine investigation of patients with claudication of suspected arterial origin, atypical claudication, non-calf claudication or claudication of debatable vascular origin. Clearly the technique is time consuming, shall remain limited to referral centers and is unlikely to develop as a routine tool in the general practice. Nevertheless, it seems important that physicians of various specialties are aware of this original approach. Presently, non-vascular specialists (internal medicine practitioners, orthopedic surgeons or rheumatologists) represent approximately 1/8 of referral physicians in our experience.

### **Conclusion and directions for the future.**

Many clinical points still need to be clarified about the use of Ex-TcpO<sub>2</sub>. Among these, its position among other tools in the diagnostic algorithm of exertional limb pain of suspected vascular origin, the population that should undergo this procedure, its correlation with biochemical markers of ischemia, its interest in the follow-up of rehabilitation in arterial claudication, its eventual ability to predict the functional results of revascularization. The TcpO<sub>2</sub> technique itself is simple and can be performed by a technician or a nurse under medical supervision. New devices are expected with portable tools to facilitate recordings in the community, but duration remains limited by the risk of prolonged local heating. New implantable probes may allow prolonged recordings in the future but will require

validation at exercise. To our opinion, diagnostic exercise testing in general, and diagnostic Ex-TcpO<sub>2</sub> specifically, remain largely underused in patients reporting walking impairment suspected of a vascular origin. Claudication is an exercise-related symptom. Thereby, we believe that relying on resting investigation to diagnose and evaluate patients suffering lower limb exertional pain should no longer be the dominant practice.

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PA, MF, SH reviewed and corrected the draft. All authors have critically reviewed the manuscript on the scientific content and have approved the final version of the manuscript.

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## FIGURE LEGENDS

Figure 1: Distribution of chest absolute values among the patients studied in our laboratory (Upper panel) and Bland-Altman representation of the left to right absolute value difference (lower panel) when two chest probes are used simultaneously in the same patients. As shown, the standard deviation (SD) for the site to site difference is in the same range as the SD of absolute chest value.

Figure 2: Typical example of TcPO<sub>2</sub> DROP changes (B1) in a patient complaining of left calf claudication due to the occlusion of the left superficial femoral artery (A1). Of interest is that the chest changes during exercise show a dramatic decrease of the reference value (C1) suggesting the coexistence of exercise induced hypoxemia as a worsening factor of oxygen availability and a possible associated cause of walking limitation. After angioplasty, the femoral artery is patent (A2), the ischemia of the left calf has disappeared (B2) as well as calf claudication, but walking distance is not improved and the patient now complains of dyspnea and the chest change still records exercise-induced hypoxemia (C2) due to pulmonary emphysema and micro nodular diffuse parenchymatous lesions (D).

Figure 3: Schematic representation of the principles of exercise oximetry. Probes are positioned on the upper external square of both buttocks and on the lower third of both calves. The chest probe can be placed either on the right or left scapular area. Whatever absolute starting values are, by construction DROP at rest is zero and the analysis of chest changes is based only on pattern and not absolute results.

Fig 1 :

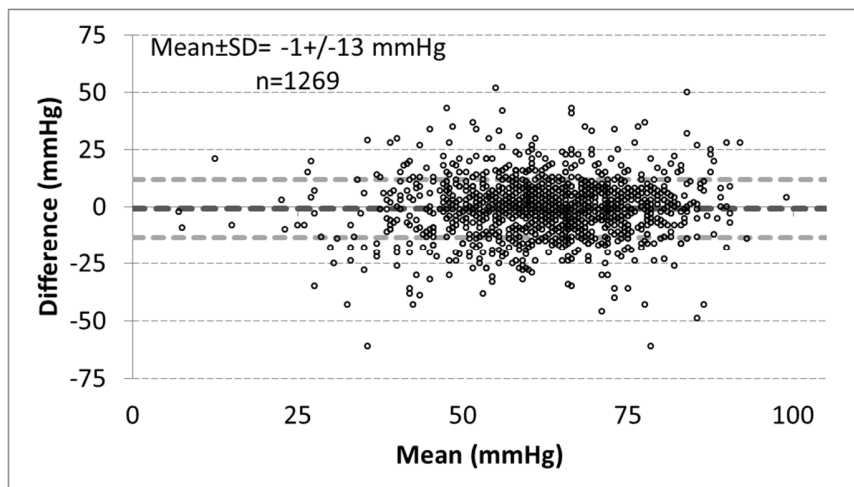
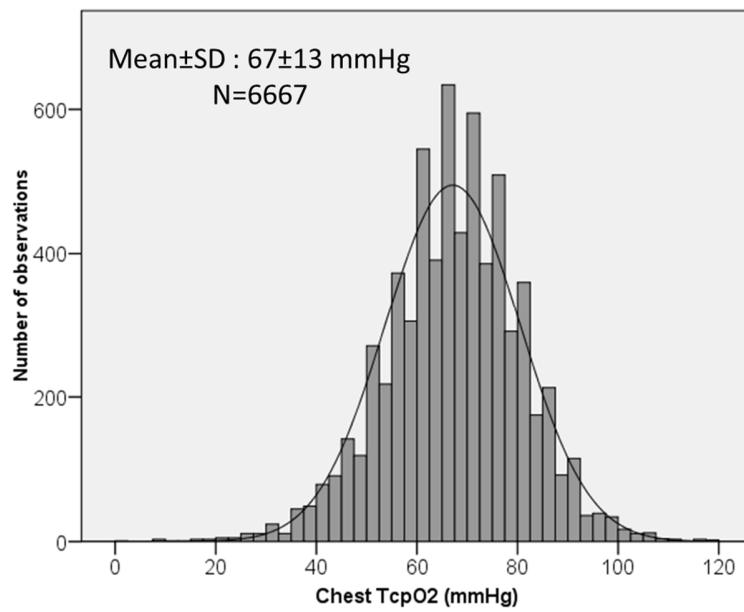


Figure 2

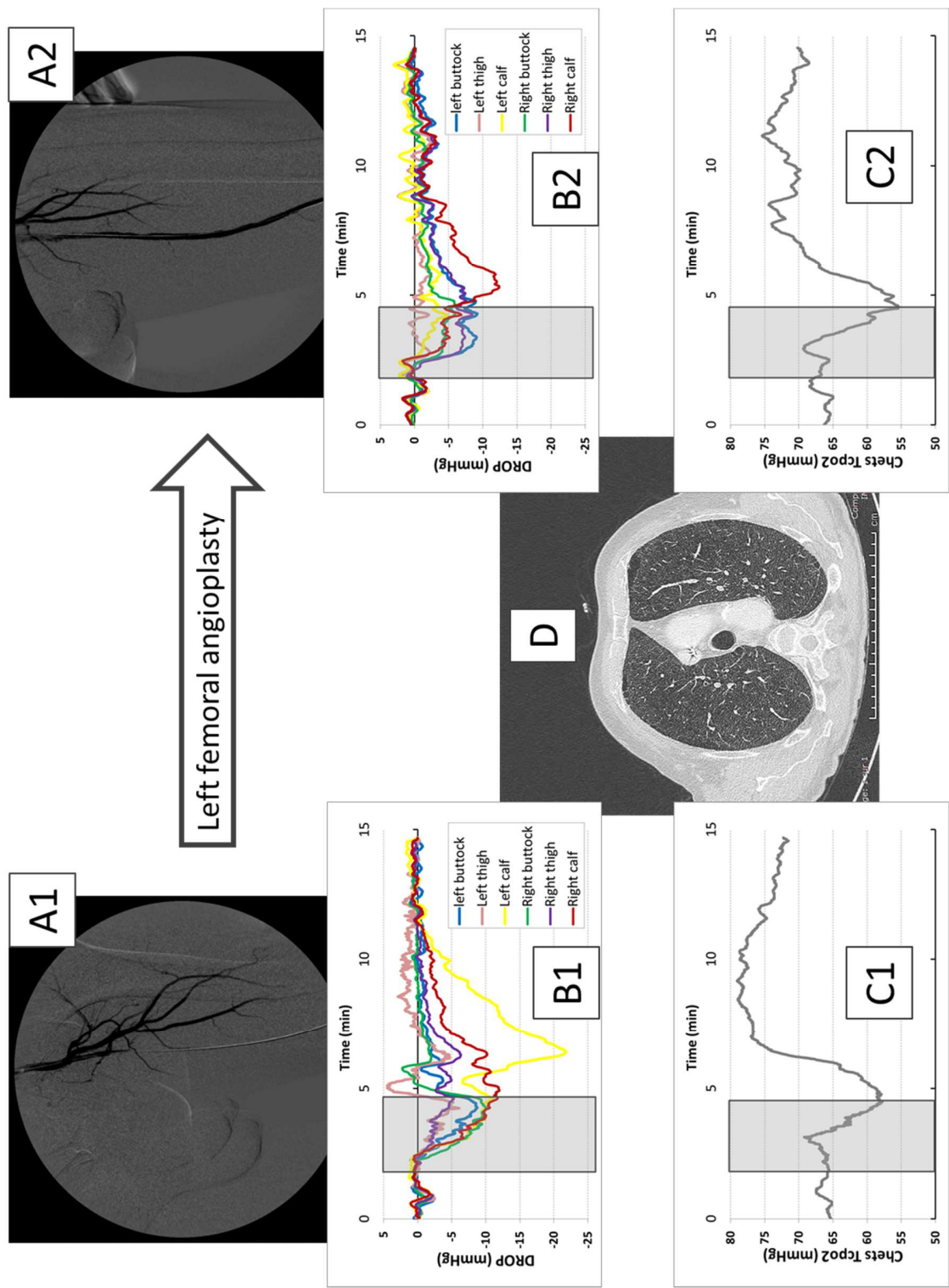


Figure 3:

