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# Oxymétrie transcutanée : état des lieux et nouvelles applications

Jeanne Hersant

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# THÈSE DE DOCTORAT DE

L'UNIVERSITÉ D'ANGERS

ÉCOLE DOCTORALE N° 605

*Biologie Santé*

Spécialité : médecine vasculaire *CNU 51-04*

Par

**Jeanne HERSANT**

**Oxymétrie transcutanée : état des lieux et nouvelles applications**

Thèse présentée et soutenue à Angers, le 06 janvier 2022

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## Rapporteurs avant soutenance :

Gabrielle SARLON      Professeur des Universités – Praticien Hospitalier, Université de Marseille  
Xavier BERARD        Professeur des Universités – Praticien Hospitalier, Université de Bordeaux

## Composition du Jury :

Président : Pierre ABRAHAM      Professeur des Universités – Praticien Hospitalier, Université d'Angers  
Examineurs : Francine THOUVENY      Praticien Hospitalier, Université d'Angers  
Examineurs : Alessandra BURA RIVIERE      Professeur des Universités – Praticien Hospitalier, Université de Toulouse  
Dir. de thèse : Samir HENNI      Professeur des Universités – Praticien Hospitalier, Université d'Angers



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« En persévérant, on arrive à tout »  
Théocrite

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# INTRODUCTION GENERALE

## 1. Le réseau vasculaire, pourquoi la microcirculation ?

Le rôle de l'appareil circulatoire, outre la thermorégulation, est le transport du sang, des substrats énergétiques et de l'oxygène, d'un secteur à l'autre de l'organisme. Ce système complexe est régulé par des mécanismes locaux et systémiques (1). L'exploration morphologique et fonctionnelle de la circulation artérielle se fait par de nombreuses techniques de mesures parmi lesquelles les ultrasons jouent un rôle prédominant, mais d'autres techniques existent telles que : l'oxymétrie tissulaire, le laser, la spectrométrie infrarouge. Cette thèse va développer plus précisément l'une d'entre elle : **l'oxymétrie transcutanée** (2-5).

D'un point de vue physiopathologique, il est important de comprendre que la vitesse d'écoulement est inversement proportionnelle à la surface de section cumulée des vaisseaux. Cette surface de section vasculaire augmente depuis le secteur artériel vers le secteur capillaire ; elle diminue à nouveau du secteur capillaire vers le secteur veineux, ce qui est représenté sur l'illustration ci-dessous.

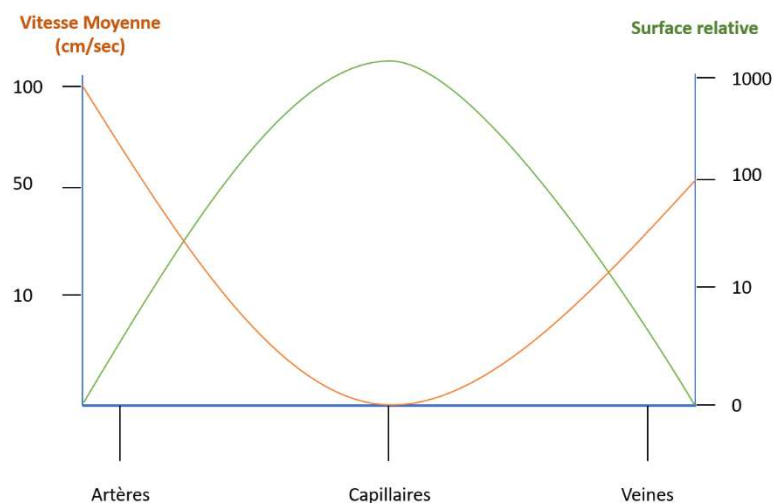


Illustration 1 : représentation de la relation entre la vitesse d'écoulement et la surface de section des vaisseaux, inspiré du Chapitre physiologie et exploration de la circulation artérielle - EMC

La quantité de liquide qui pénètre et ressort du système vasculaire est identique. Le débit de l'ensemble des capillaires est similaire à celui de l'ensemble de l'arbre artériel macrovasculaire : c'est le principe de redistribution. Les propriétés capillaires, notamment sa surface de section élevée, entraîne une diminution des vitesses. La vitesse d'écoulement de sang dans les capillaires est en règle générale inférieure à 0.1 cm/s (contre 40 à 50cm/sec dans l'arbre artériel macrovasculaire), ce ralentissement étant favorable aux échanges entre le sang et les tissus interstitiels.

La microcirculation constitue donc grâce à ces différents points une surface d'échange importante et facilement accessible à l'étude dans certaines de ses localisations, notamment du fait de son caractère superficiel au niveau de la surface cutanée.

## 2. Ischémie

### 2.1. Définition et physiopathologie

L'ischémie est le procédé traduisant l'inadéquation besoin/apport d'oxygène aux muscles. Elle résulte d'une altération du débit, de manière constante (au repos) ou intermittente (à l'effort) lorsqu'il existe une incapacité en cas d'augmentation des besoins énergétiques de la cellule de faire face à ces besoins. L'apport sanguin aux tissus périphériques est présent pour fournir à la fois les substrats énergétiques et l'oxygène nécessaire afin de dégrader ces substrats énergétiques en aérobose. Fondamentalement, ce n'est pas tant le débit sanguin qui importe mais bien le débit d'oxygène. Dans un contexte d'exercice, la consommation d'oxygène du muscle va augmenter de façon quasi linéaire avec le niveau d'exercice fourni et ce débit d'oxygène constitue le produit du débit artériel et de la différence artérioveineuse en oxygène.

### 2.2. Moyens d'exploration

Dans le cadre de l'exploration, il existe deux sous-parties à distinguer : l'ischémie expérimentale, pour laquelle nous ferons un bref rappel, et l'ischémie spontanée, dont l'étude a nourri les travaux de cette thèse.

L'ischémie expérimentale est principalement retrouvée dans le champ des mesures visant à évaluer la fonction endothéliale. À travers différents systèmes de mesures (laser speckle, étude de la pulsatilité), il est étudié la réaction vasculaire, notamment l'hyperhémie post-ischémique (après création d'une ischémie régionale par garrot) ou la vasodilatation endothélium dépendante ou indépendante (iontophorèse à l'acétylcholine).

Les inconvénients de ces techniques d'ischémies expérimentales sont notamment la tolérance parfois limitée du garrot pendant quelques minutes. Des travaux récents, de notre équipe ont tenté de remplacer ces ischémies régionales par des ischémies locales avec un dispositif d'appui très localisé et d'observer, après retrait du système, l'hyperhémie post-ischémique. L'intérêt de cette technique est d'être totalement indolore pour le patient et d'enregistrer des réponses de pic d'hyperhémie qui sont proportionnelles à la durée d'application de la pression et à la force d'application (6).

À côté de ces ischémies expérimentales, il y a le contexte de l'exploration de l'ischémie spontanée que l'on peut observer dans certaines situations cliniques et qui correspond comme mentionné dans la définition soit à la diminution du débit sanguin de repos soit à l'incapacité du débit sanguin d'augmenter les flux locaux pour permettre de couvrir les besoins énergétiques de la cellule lors de la réalisation d'un effort.

L'exploration fonctionnelle de l'ischémie en clinique peut être réalisée via l'utilisation de questionnaires, qui permettent d'établir la tolérance fonctionnelle de l'ischémie vis à vis de l'apparition de symptômes (questionnaire de Rose) ou des conséquences fonctionnelles en termes de capacités fonctionnelles (questionnaire de Welch).

L'exploration fonctionnelle de l'ischémie peut également être réalisée via différentes explorations :

- La première utilisée, même si elle est peu fonctionnelle, est l'imagerie avec réalisation d'écho-doppler qui permettra de visualiser les lésions vasculaires et leur retentissement hémodynamique (analyse des vélocimétries et des spectres dopplers). C'est également le cas de l'angioscanner ou de l'angioRM qui



permettent une étude morphologique mais où le caractère fonctionnel est peu développé hormis pour l'IRM avec le développement de la perfusion, par l'utilisation de séquence T2\*. En fonction du niveau d'exercice fourni, il est possible de démasquer des déficits perfusionnels. Néanmoins il n'existe pas, pour le moment, d'intérêt diagnostique à révéler une atteinte infra clinique, qui n'apporte pas d'information complémentaire par rapport à la clinique de l'ischémie. Il existe peu d'application encore développée dans le contexte d'AOMI et sa disponibilité est difficile.

- En seconde intention, la réalisation d'une artériographie permet une analyse hémodynamique et morphologique.
- La réalisation des IPSc (index de pression systolique de cheville), dont l'intérêt n'est plus à démontrer. Le débit circulatoire correspond à la différence de pression divisée par les résistances à l'écoulement : ( $Q=Pa-Pv/R$ ). En clinique, l'outil le plus largement utilisé pour l'évaluation de l'ischémie est l'évaluation des différences de pression. Cet examen constitue une évaluation clinique fonctionnelle de l'importance et de la sévérité d'une AOMI.

$$\text{IPSc} = \frac{\text{Plus haute pression systolique de cheville}}{\text{Plus haute pression systolique brachiale}}$$

≤ 0.40	Severe PAD	1.01 – 1.40	Normal
0.41 – 0.90	Mild to moderate PAD	>1.40	Incompressible artery
0.91 – 1.00	Borderline	<sup>1</sup> Chaudru, Eur J Vasc Endovasc Surg, 2015	

**Illustration 2** : représentation de la réalisation d'IPSc avec valeurs seuils décrit par Chaudru et al (7)

- Scintigraphie au thallium : au cours d'un exercice on injecte une dose de thallium dont la distribution dans les tissus va dépendre de la perfusion locale. Il sera réalisé deux imageries : une imagerie de perfusion puis quelques heures plus tard une imagerie de redistribution
- L'oxymétrie de repos ou d'effort qui sera détaillée dans un chapitre ci-dessous

### 2.3. Situations cliniques

La principale situation en médecine vasculaire, où l'exploration de l'ischémie s'est développée, est l'artériopathie avec son atteinte d'effort (claudication) et de repos (ischémie critique). Cela s'explique d'un point de vue physiopathologique car il a été largement démontré que le débit musculaire est rigoureusement proportionné à la force musculaire exercée au niveau des muscles striés squelettiques c'est pourquoi cette ischémie spontanée correspond principalement à la pathologie athéromateuse.

D'autres pathologies rencontrées en médecine vasculaire sont le résultat d'un état d'ischémie : c'est par exemple le cas dans le syndrome du défilé thoraco-brachial où il existe une compression majoritairement intermittente, dynamique du paquet vasculo-nerveux dans la zone de traversée thoraco-brachiale. Nous développerons notamment, au cours de cette thèse l'évaluation de l'ischémie artérielle résultant de cette compression par étude de la microcirculation via la réalisation d'une oxymétrie dynamique.

## 3. Oxymétrie transcutanée

### 3.1. Historique

D'un point de vue physiopathologique, il existe deux approches afin de mesurer l'oxygène :

- La **saturation tissulaire**, qui repose sur des techniques dérivées de la spectroscopie dans le proche infrarouge et dont le principe est l'émission d'ondes lumineuses rouge et infrarouges, absorbées par l'hémoglobine selon qu'elle est oxydée ou pauvre en oxygène. Différentes longueurs d'onde sont utilisées, selon les appareils, pour retrouver la saturation tissulaire.
- La **pression partielle en oxygène** ou mesure transcutanée de la pression en oxygène (TcPO<sub>2</sub>) qui est une technique non invasive permettant de mesurer l'oxygène diffusant à travers la peau, reflet de la perfusion microcirculatoire des tissus superficiels environnants et c'est cette technique que nous allons aborder au cours de ce travail.

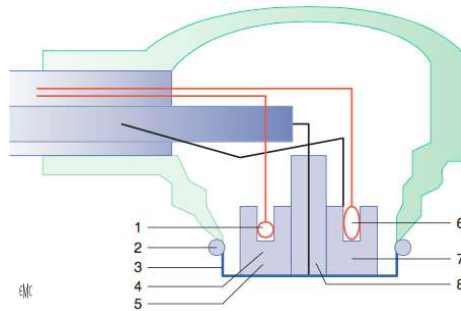
L'oxymétrie a été développée dans les années 1970 initialement pour la surveillance des hypoxies et de l'état respiratoire global en néonatalogie(3). En 1985, Baker et al ont tenté de déterminer si elle pouvait prédire, en continu et de manière non invasive, la pression partielle en oxygène au niveau systémique (PaO<sub>2</sub>) des patients. Cependant, lorsque le capteur a été placé sur des patients en état de choc, les valeurs de TcPO<sub>2</sub> étaient bien inférieures aux valeurs de PaO<sub>2</sub> et la technique a donc été remise en question. Pourtant, le capteur signalait que le patient était en état de choc, avec une hypoxie tissulaire. Cette mauvaise interprétation reposait sur la confusion entre l'hypoxémie due à une fonction pulmonaire médiocre et l'hypoxie tissulaire résultant d'une diminution du débit sanguin périphérique dans le choc. La TcPO<sub>2</sub> dépend des apports en O<sub>2</sub> (DO<sub>2</sub>) et donc des trois mécanismes permettant d'augmenter le DO<sub>2</sub> : l'augmentation du débit cardiovasculaire (Q), de la quantité d'hémoglobine (Hb), et les apports en oxygène pour obtenir une pression partielle en oxygène au niveau systémique (PaO<sub>2</sub>) plus importante, mais également pour augmenter la part d'oxygène libre dissout dans le sang (inférieure à 2% en situation normale).

$$DO_2 = Q \times (Hb \times SaO_2 \times 1,34) + (PaO_2 \times 0,003)$$

### 3.2. Principe

La TCPO<sub>2</sub> est enregistrée grâce à une électrode polarographique, dite de Clark. Celle-ci est composée d'une cathode en platine, entourée d'une anode en argent baignant dans une solution hydroélectrolytique, et recouverte d'une membrane de polyéthylène perméable à l'oxygène. L'électrode est fixée hermétiquement à la peau grâce à une bague de fixation adhésive. Puis, elle chauffe la peau localement à 44°C afin de créer une hyperhémie cutanée et de rendre ainsi l'examen plus discriminant. Effectivement, à l'état basal, la PO<sub>2</sub> cutanée est très basse (3 à 4 mmHg) et aucune différence significative de PO<sub>2</sub> ne pourrait être enregistrée entre une peau bien vascularisée et une peau ischémique. Une solution hydroélectrolytique servant d'interface entre l'électrode et la surface cutanée permet la dissolution de l'oxygène traversant l'épiderme. L'oxygène qui diffuse à travers la peau va

générer un courant électrique par réaction d'oxydo-réduction. Le courant électrique généré dépend de la quantité d'oxygène capté par l'électrode.



**Figure 1.** Électrode polarographique de type Clark améliorée. 1. Anneau circulaire de maintien de la membrane; 2. membrane de polypropylène perméable à l'oxygène; 3. anode d'argent entourant la cathode; 4. chambre d'électrolyte; 5. résistance contrôlant la température de l'électrode; 6. solution d'électrolytes contenant les ions chlorures; 7. cathode en platine; 8. élément chauffant.

Illustration 3 : Schéma de fonctionnement d'une électrode de Clark (8)



Illustration 4 : Moniteur de TCPO2 et électrode Clark.

*L'électrode utilisée est celle de Radiometer Copenhagen (une seule marque disponible). Le système est relié à un moniteur (Radiometer ou Perimed).*

La courbe obtenue au début de l'examen est la suivante :

- Les valeurs sont d'abord hautes et correspondent à la PO<sub>2</sub> de l'air ambiant, avant mise en place de l'électrode sur le support
- Puis elles baissent progressivement jusqu'à leur niveau de base
- Ces mesures vont augmenter lors du chauffage par hyperhémie jusqu'à leur niveau maximal (après 15-20minutes)
- C'est à ce moment que l'enregistrement est débuté.

S'il existe une baisse initiale faible ou une remontée rapide des valeurs il faudra rechercher un défaut d'étanchéité du matériel.

Plusieurs situations peuvent modifier l'interprétation des résultats :

- Une inflammation cutanée ou une infection cutanée qui peuvent entraîner une hyperhémie et augmenter les valeurs de l'examen
- Un œdème ou un épaissement cutané qui va limiter la diffusion de l'oxygène et donc possiblement diminuer les valeurs de TCPO<sub>2</sub>
- L'état respiratoire peut modifier l'interprétation de l'examen. En effet, l'existence d'une hypoxie sera responsable d'une baisse de la TCPO<sub>2</sub> au niveau tissulaire, d'où son utilisation historique première en néonatalogie pour surveillance de l'oxymétrie des enfants
- L'insuffisance cardiaque pourra engendrer une diminution du débit de perfusion tissulaire ou les valeurs pourront être diminuées du fait de l'existence d'œdème sur une insuffisance cardiaque congestive.
- La présence d'un diabète déséquilibré peut modifier les valeurs de TCPO<sub>2</sub> sans présence d'une ischémie
- L'anémie ainsi que les troubles rhéologiques vont également modifier les données de l'examen.

L'interprétation dépend donc du contexte clinique.

Différents tests de sensibilisation existent et seront explicités dans les sous-parties suivantes :

- Test d'hyperhémie post-ischémique
- Test postural
- Test d'inhalation d'oxygène
- Test d'effort sur tapis roulant

Cette technique de TCPO<sub>2</sub> ne permet en revanche pas d'explorer les conséquences de cette ischémie, notamment histologiques.

### **3.3. Utilisations**

Après avoir posé le principe ainsi que les limites techniques de cet examen dans l'évaluation de l'ischémie, nous allons détailler ses différentes utilisations.

#### **3.3.1. TCPO<sub>2</sub> couplée à une épreuve de marche**

Dans ce contexte, la TCPO<sub>2</sub> permet un enregistrement continu de l'altération du flux sanguin régional en fesses, cuisses et mollets de manière simultanée chez les patients claudicants (9, 10). L'intérêt spécifique de la technique est d'apporter des valeurs mesurables continues à différents niveaux de manière bilatérale et pendant un exercice ainsi que son temps de récupération.

La technique de calcul du DROP (decrease from rest of oxygen pressure) extraite des valeurs absolues de TCPO<sub>2</sub> en fesses, cuisses et mollets en utilisant une sonde thoracique de référence a été validé en 2018 par ABRAHAM et al (11, 12). La valeur la plus basse de ces changements de DROP au cours de l'exercice est un reflet de la sévérité de la détérioration du flux sanguin régional. Le DROP minimal < -15mmHg est utilisé pour définir l'ischémie (13).

Cette épreuve place le malade en situation de gêne clinique à l'effort. Elle représente a priori le test le plus spécifique pour reproduire et analyser la claudication artérielle, ainsi que pour étudier le comportement vasculaire après l'effort.

Afin que le test de marche diagnostique soit le plus reproductible possible, les conditions qui entourent le malade et influencent les résultats du test ont été standardisées. Le tapis roulant permet une marche sur un sol qui se dérobe sous les pas, selon une vitesse et selon une pente qui peuvent être modifiées :

- o La pente est de 10 % dans la majorité des centres
- o La vitesse de déroulement peut être fixée à 3,2 km/h

Cela correspond à la vitesse qui convient à plus de la moitié des sujets examinés, sans provoquer d'impossibilités à la marche, mais suffisante pour déclencher la claudication (14). D'autres protocoles sont possibles, avec vitesse et pente progressivement augmentées.

Le test de marche est stoppé lorsque la claudication apparaît, ou bien lorsque la distance maximale prédéterminée est effectuée sans claudication, ou si apparaît un événement intercurrent gênant ou contre-indiquant la poursuite de l'effort. S'agissant d'un test d'effort, en général pratiqué chez un sujet athéromateux, il convient de respecter certaines précautions et contre-indications (15)

Lorsque l'épreuve de marche est terminée, il convient de continuer à réaliser une mesure des pressions distales après l'effort. Les résultats exprimés au terme de l'examen sont : le pourcentage de diminution maximale de la pression distale par rapport à la pression de repos (obtenu le plus souvent à la première minute qui suit l'arrêt de l'effort) ; le temps de récupération de la valeur de la pression basale.

La mesure des IPSc post effort, couplée à l'épreuve de marche sur tapis, permet d'évaluer le retentissement hémodynamique de lésions artérielles. Une chute des IPSc en post effort immédiat est considérée comme étant significative au-delà de 20% et est en faveur d'une artériopathie oblitérante des membres inférieurs (16).

L'intérêt de la TCPO2 d'effort est de mieux analyser la claudication artérielle sur le plan diagnostique, avec un apport notamment important dans le cadre des ischémies d'effort proximale (lombaire ou fessière) (17), liée à une artériopathie aorto-iliaques, dont l'exploration en écho-doppler est le plus souvent difficile (18, 19) et ainsi de mieux adapter la décision thérapeutique.

### 3.3.2. TCPO2 de repos

Le principe de l'utilisation de la TCPO2 reste le même. Cependant, des tests de sensibilisation ont été développés afin de s'affranchir de l'incertitude liée au gradient transcutané de l'oxygène. En effet, une valeur absolue plutôt basse peut correspondre, soit à une PO2 tissulaire plutôt élevée associée à un gradient transcutané important, soit à une PO2 tissulaire faible associée à un gradient transcutané faible. Ces tests permettraient aussi de pallier le manque de reproductibilité de la mesure en valeur absolue.

L'examen se déroule donc comme tel :

- Enregistrement des valeurs en position allongée
- Réalisation d'un test de surélévation du membre à au moins 30° qui suggèrera un mauvais pronostic de cicatrisation, en cas de baisse de TcPO2 supérieure à 15mmHg

- Puis mise du patient assis, position jambes pendantes : la hauteur de la colonne sanguine va alors participer à l'augmentation de la pression de perfusion distale. En cas d'existence d'une ischémie sévère, ce test permet d'évaluer les capacités de recrutement d'oxygène tissulaire et de réserve hémodynamique.
- Puis position de repos en décubitus

Il s'agit du protocole classique mais d'autres tests existent :

- Le test d'hyperhémie post ischémique ou réactionnelle est utile pour évaluer le tonus vasomoteur, mesurer le retentissement microcirculatoire de lésions occlusives et définir la zone frontière entre ischémie d'effort et ischémie permanente marquée par l'augmentation des temps de latence. Une occlusion à pression supra systolique est pratiquée à la cheville durant 4 min, le signal post-ischémique est ensuite enregistré pendant 6 à 10 min. Les paramètres à noter sont la valeur de TcPO<sub>2</sub> maximale résultant de l'hyperémie et le temps nécessaire à la récupération permettant de définir une pente de restitution post ischémique et un temps de demi-retour au plateau (T50) qui est normalement de l'ordre d'une minute.
- L'épreuve d'inhalation d'oxygène qui consiste en une oxygénothérapie à haut débit (9 à 10L/min au masque à haute concentration pendant 10 minutes) permettant ainsi d'élever la TcPO<sub>2</sub> à plus de 100 mmHg chez le sujet sain. L'absence d'augmentation de la TCPO<sub>2</sub> aux membres inférieurs signerait un pronostic défavorable en termes de survie et de sauvegarde de membre. Selon Scheffler et Rieger (20), ce test évalue la réserve circulatoire, régulée par l'ouverture et la fermeture des shunts artériovoineux lorsque la PaO<sub>2</sub> artériolaire augmente sous l'effet de l'oxygène inhalé.

Cependant, force est de constater que la mise sous oxygène à forte dose pendant une durée certaine n'est pas sans risque de décompensation chez des patients insuffisants respiratoires. Il conviendrait donc de réduire au maximum ce temps d'inhalation. Contrairement aux autres centres qui relèvent la valeur absolue de la TcPO<sub>2</sub> sous oxygène à la fin du test, nous enregistrons, au CHU d'Angers, durant toute la durée du test, les variations de la PO<sub>2</sub> transcutanée au niveau du thorax et des membres inférieurs, ce qui a par conséquent permis d'extraire des données de morbi-mortalité sur les profils de courbes thoraciques qui seront explicités au cours d'un article présenté ci-dessous.

## 3.4. Intérêt de la TCPO<sub>2</sub>

### 3.4.1. Quantification de la sévérité de l'ischémie

Au repos, les valeurs limites sont les suivantes :

- >65mmHg : normales
- 30-65 mmHg : ischémie d'effort
- < 30mmHg : ischémie chronique permanente
- < 10 mmHg : ischémie critique

Il s'agit de valeurs qui permettent de quantifier la sévérité de l'artériopathie présentée par les patients.

### 3.4.2. Aide au pronostic de l'AOMI chronique sévère et de l'ischémie critique

La réalisation d'une TCPO2 de repos chez les patients en ischémie sévère peut avoir une valeur pronostique intéressante :

- S'il existe une possibilité à la revascularisation : les valeurs de TCPO2 jambes pendantes ont une bonne valeur pronostique avec un seuil à 40 mmHg, au-dessus duquel 80% des patients à un an ont gardé un appui talonnier contre 40% si les valeurs de TCPO2 étaient inférieures à 40mmHg (21)
- S'il n'existe pas de possibilité de revascularisation, la valeur seuil est de 30 mmHg. En deçà le potentiel de cicatrisation spontané basé sur une prise en charge médicale pure longue et coûteuse est très faible. Cela peut aider le praticien dans sa décision thérapeutique et notamment dans la réalisation d'une amputation.

Les valeurs recueillies en position de repos allongé, vont permettre de déterminer un niveau d'amputation avec une probabilité de cicatrisation faible lorsque les valeurs sont en-dessous de 20mmHg

## CADRE GENERAL DES TRAVAUX DE THESE

Les travaux autour de l'exploration fonctionnelle au CHU d'Angers ont débuté dans les années 90, principalement dans son exploration d'effort. Dans un premier temps, ces travaux étaient centrés sur des études utilisant les IPSC chez le sportif. L'approche s'est diversifiée par l'utilisation de la TCPO2 (*transcutaneous oxygen pressure*) développée dans les années 2000.

Les différents travaux réalisés au sein du service ont notamment permis de développer cet outil simple, original et fiable permettant de s'affranchir des limites historiques de la technique et d'améliorer la performance de la technique dans le but initial d'une confirmation para clinique de l'existence d'une ischémie proximale chronique des membres inférieurs. Dans un second temps, les études du service ont visé à approcher les mécanismes physiopathologiques de cette ischémie, d'étudier sa prévalence, et d'apporter de nouvelles stratégies thérapeutiques pour pouvoir la prévenir et parfois la traiter. Après validation informatique et technologique ainsi que validation externe, cela a pu être appliqué à d'autres pathologies et l'on a pu avoir une vision différente afin d'objectiver d'autre apport de cette exploration que l'étude de l'ischémie dans la cadre de l'artériopathie.

Lors de l'utilisation d'une technique, il convient parfois de prendre du recul afin de pouvoir s'intéresser aux données recueillies non principales pourtant primordiales et d'exporter le processus à d'autres champs d'applications. Nous avons pu appliquer ce principe dans différentes situations cliniques impliquant la TCPO2.

Nous rapporterons donc successivement des études qui visent à

- Evaluer le temps de récupération et les facteurs influençant cette récupération dans un contexte d'exploration d'effort, dans les localisations anatomiques hors mollet : cuisses et fesses.  
*Calf and non-calf hemodynamic recovery in patients with arterial claudication: implication for exercise training*
- Valider l'utilisation de la TCPO2 dynamique dans une nouvelle pathologie : Le syndrome du défilé thoraco-brachial  
*Microvascular response to the Roos test has excellent feasibility and good reliability in patients with suspected Thoracic Outlet syndrome*  
*Comparison of transcutaneous oximetry with symptoms and arteriography in thoracic outlet syndrome*
- S'intéresser à l'apport de l'enregistrement continu de la sonde thoracique dans le cadre de la TCPO2 de repos notamment dans les contextes mouvements sinusoïdaux suggérant la présence d'une dyspnée de Cheyne-Stokes ainsi que l'impact sur l'évaluation de la morbi-mortalité du patient  
*Sinusoidal changes in transcutaneous oxygen pressure, suggesting Cheyne-Stokes respiration, are frequent and of poor prognosis among patients with suspected critical limb ischemia*



# ARTICLES DE LA THESE PUBLIES

## 1. Explorations des membres inférieurs à l'exercice

### *Calf and non-calf hemodynamic recovery in patients with arterial claudication: Implication for exercise training*

#### Contexte :

Il a déjà été démontré dans le cadre de l'AOMI que la réalisation d'un nouvel exercice après une période de repos, pouvait reproduire les symptômes plus rapidement si la récupération hémodynamique n'était pas optimale (22). La détermination du temps de récupération hémodynamique a toute sa place dans les programmes de rééducation afin de déterminer le temps de pause nécessaire pour une récupération hémodynamique optimale avant le prochain effort de marche.

Les études publiées auparavant se sont focalisées sur la récupération hémodynamique au niveau du mollet alors que les ischémies des autres territoires sont fréquentes même chez les patients présentant uniquement des symptômes de mollet (23). De plus, chez les patients présentant une symptomatologie de mollet, la concordance entre le niveau d'ischémie et les symptômes présents lors du test d'effort n'est présent que dans moins de 20% (24). Il est donc possible que le temps de récupération hémodynamique nécessaire ne soit pas le même dans les autres territoires : cuisses, fesses.

L'hypothèse principale était que la durée de récupération hémodynamique en TCPO2 serait inférieure à 10 minutes en comparaison à la durée des douleurs dans la définition même de claudication (25). Les autres hypothèses étaient les suivantes : le temps de récupération est proportionnel à la sévérité de l'ischémie et au temps de marche ; le temps de récupération au mollet excède le temps de récupération sur les autres niveaux surtout chez les patients présentant une claudication de mollet ; l'importance de l'ischémie et le temps de récupération serait plus important aux mollets que dans les autres territoires principalement chez les patients présentant une claudication de mollet. Nous souhaitons également analyser les facteurs influençant ce temps de récupération.

#### Matériel et méthode :

Les valeurs de TCPO2 ont été enregistrées en fesses, cuisses et mollets durant un test d'effort à 3,2km/h et avec une pente à 10%. Il a été calculé le temps de récupération afin d'atteindre 50% de récupération totale et 90% de récupération totale des valeurs de TCPO2 depuis l'arrêt de l'effort. Une analyse de régression a ensuite été réalisée afin de déterminer les facteurs associés aux temps de récupération à 50% puis 90%.

#### Résultats :

132 patients ont été étudiés, 18,2% rapportaient une douleur isolée hors mollet. 792 valeurs de temps de récupération ont été obtenues : 3 valeurs soit 0,4% étaient au-delà de 10 minutes pour le temps de récupération à 50% et 23 soit 2,9% étaient à plus de 10 minutes pour le temps de récupération à 90%. Il existe une corrélation faible entre les 792 valeurs de DROP minimal et les temps de récupération à 50% et 90%. Les DROP minimaux les plus bas et le BMI étaient significativement associés au temps de récupération à 50% et à 90%. L'âge, le sexe, l'utilisation de beta bloquants et la durée de la période de marche n'étaient pas des facteurs associés au temps de récupération.

Conclusion :

La prévalence des claudications hors mollet reste variable dans les précédentes études (26-28). La durée de dissipation de la douleur est constamment plus courte que la normalisation hémodynamique (18). Comme attendu, le temps de récupération était inférieur à 10 minutes et corrélé à la sévérité de l'ischémie et au MWT (temps de marche maximal). La médiane de récupération hémodynamique à 50% est de 2 minutes et à 90% de moins de 10 minutes.



## Calf and non-calf hemodynamic recovery in patients with arterial claudication: Implication for exercise training

Jeanne Hersant<sup>a</sup>, Pierre Ramondou<sup>a</sup>, Jean Picquet<sup>b,c</sup>, Mathieu Feuilloy<sup>d</sup>, Pierre Abraham<sup>b,e,\*</sup>, Samir Henni<sup>a,b</sup>

<sup>a</sup> Vascular Medicine, University Hospital, Angers, France

<sup>b</sup> MitoVasc Institute UMR CNRS 6015/INSERM 1083, Faculty of Medicine, Angers University, France

<sup>c</sup> Thoracic and Vascular Surgery, University Hospital, Angers, France

<sup>d</sup> School of Electronics (ESEO), Angers, France

<sup>e</sup> Sports Medicine, University Hospital Center, Angers, France

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### ABSTRACT

**Background:** Previous studies in patients with arterial claudication have focused on calf hemodynamic recovery. We hypothesized that the duration of hemodynamic recovery with TcpO<sub>2</sub> at calf and non-calf levels would be shorter than 10 min. We analyzed the factors that influence the recovery time.

**Methods:** We monitored limb changes minus chest changes from rest (DROP) of transcutaneous oximetry on buttocks, thighs and calves, during and following a treadmill test (3.2 km/h; 10% grade). We calculated the time required to reach 50% (50%RT) and 10% (90%RT) of minimal DROP value (DROPm) from walking cessation. Regression analyses were used to determine the factors associated to 50%RT and 90%RT.

**Results:** Of the 132 patients studied, 18.2% reported isolated non-calf pain by history. Of the 792 recovery time values, only 3 (0.4%) and 23 (2.9%) were in excess of 10 min for 50%RT and for 90%RT, respectively. A weak correlation was found between each of the 792 DROPm and 50%RT ( $r = -0.270, p < 0.001$ ) as well as for 90%RT ( $r = -0.311, p < 0.001$ ). Lowest DROPm and BMI (but not age, sex, the use of beta-blockers, the duration of the walking period) were associated to both 50%RT and 90%RT.

**Conclusion:** Although recovery duration correlates significantly with the severity of ischemia of the same location, a wide discrepancy exists and the longest recovery time does not always correlate to the localization of the most severe ischemia. Non-calf ischemia should be measured when one aims at objectifying the biological effects of exercise or the effects of treatments on recovery from exercise.

### 1. Introduction

Lower limb pain while walking is a frequent symptom in elderly patients. In vascular medicine, vascular type claudication in patients with lower extremity artery disease (LEAD) has been defined for years as a lower limb pain or discomfort, that is absent at rest and disappears within 10 min when exercise is stopped (Leng and Fowkes, 1992). We previously showed that, when walking de-novo after a period of rest, patients may reproduce their symptoms earlier if hemodynamic

recovery is not optimal (Le Faucheur et al., 2010). This is one of the proposed explanations for the curvilinear relationship between maximal walking distance and the preceding duration of the stop that was observed on global positioning system recordings of community walking in patients with claudication (Le Faucheur et al., 2010). Then, determination of the duration of hemodynamic recovery could be of interest in rehabilitation programs, to define the optimal duration of recovery before the next walking. Most studies performed on hemodynamic recovery in LEAD patients have focused on calf, although non-calf

**Abbreviations:** ABI, Ankle to brachial systolic pressure index; BMI, Body mass index; DROP, Decrease from Rest of Oxygen Pressure; DROPm, Lowest DROP value recorded during or following exercise; LEAD, Lower extremity artery disease; MWT, Maximum walking time; NIRS, near infrared spectrometry; RBFi, Regional blood flow impairment; SD, Standard deviation; TcpO<sub>2</sub>, Transcutaneous oxygen pressure; 50%RT, Time required for DROP to reach 50% of the lowest value; 90%RT, Time required for DROP to reach 10% of the lowest value.

\* Corresponding author at: Centre Hospitalier Universitaire, 4 rue Larrey, 49 933 Angers Cedex 9, France.

E-mail address: [piabraham@chu-angers.fr](mailto:piabraham@chu-angers.fr) (P. Abraham).

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ischemia is frequent, even in patients with calf-only symptoms (Ramondou et al., 2020). We also previously showed that among patients complaining isolated calf pain a perfect concordance with symptoms on treadmill and underlying ischemia (calf pain only and calf ischemia only) was observed in only 19.5% of the cases (Signolet et al., 2016). It is possible that in some patients, in the recovery period non-calf ischemia may last longer than calf ischemia and that calf hemodynamic recovery may not be the proof that lower limb ischemia has recovered in non-calf areas, but this point has never been studied.

Transcutaneous oxygen pressure (TcPO<sub>2</sub>) recordings allows the monitoring of lower limb regional blood flow impairment (RBFi) at the buttocks, thighs and calves levels simultaneously, in patients with claudication (Abraham et al., 2005; Abraham et al., 2003; Henni et al., 2016). The specific interest of the technique is to provide continuous measurable values at different limb levels bilaterally and throughout the walking and recovery periods.

We hypothesized that: 1/ The duration of hemodynamic recovery with TcPO<sub>2</sub> would be shorter than 10 min, consistently with the duration of pain in the definition of arterial claudication; 2/ Recovery time would be proportional to the severity of exercise-induced ischemia and/or duration of walking. 3/ The recovery duration at the calf would exceed the duration of recovery at non-calf levels specifically in patients complaining calf claudication. 4/ Ischemia and recovery time would be higher at the calf than non-calf localizations, specifically in patients with calf-claudication by history; 5/ We analyzed the factors that influence the recovery time.

## 1. Material and methods

### 1.1. Study population

We used exercise TcPO<sub>2</sub> as a routine among all patients referred to our laboratory for exercise-induced claudication of suspected arterial origin (Abraham et al., 2005; Abraham et al., 2003; Henni et al., 2016; Abraham et al., 2018a). At arrival, all subjects had to fill a questionnaire about their age, gender, ongoing treatment, past history, presence or absence of significant history (active smoking, diabetes mellitus, hypercholesterolemia, arterial hypertension, lower limb vascular surgery). Patients also self-completed the Edinburgh claudication questionnaire. While patients were admitted to the test room, the time required to walk 10 m in the corridor at usual speed was recorded to estimate their ability to walk on treadmill at the goal speed. Stature and weight were recorded to calculate body mass index (BMI: kg/m<sup>2</sup>). When not available in the recent patient file, ankle to brachial index (ABI) on each leg was measured as the ratio of the highest systolic blood pressure in each ankle from the right and left posterior tibial or dorsalis pedis arteries, divided by the highest brachial systolic blood pressure. The lowest of the two legs ABI was recorded for each patient. An ABI < 0.90 was considered positive results for the presence of stenoses on the arterial tree toward the ankle. Missing or non-compressible values were encoded negative.

### 1.2. Exercise tests

Patients that were able to walk 10 m in less than 15 s were proposed a standard treadmill procedure consisting in a transition phase of 1 min from flat grade and 0 km/h, to 3.2 km/h and 10% slope. In the absence of limiting symptoms, after 15 min the speed and grade were increased by steps of 1 min until exhaustion or limiting symptoms, as previously described (Mahe et al., 2011a). For patients that were unable to walk the 10 m in 15 s the speed was limited to 2 km/h only. We recorded maximum walking time (MWT). Walking was performed under 12 lead electrocardiographic supervision, and was stopped on patient's request or in case of medical indication (e.g.: severe arrhythmia).

### 1.3. TcPO<sub>2</sub> measurements

We used eight 44.5 °C heated probes on PF5010 device (Perimed; Stockholm, Sweden) connected to a computer preinstalled with the AcqTcPO<sub>2</sub> program that automatically calculated the decrease from rest of oxygen pressure (DROP) from absolute EX-tcPO<sub>2</sub> values, for buttocks, thighs and calves using the left chest probe as a reference (Abraham, 2018; Abraham et al., 2018b). The right chest probe was used for DROP calculations, except in cases of disconnection of the right chest probe, of a history of right thoracotomy, or of the presence of a stenosis or occlusion of the right sub-clavicular artery. In these cases the left chest results were used. The DROP index (Decrease from Rest of Oxygen Pressure) corresponds to the limb changes from rest minus chest changes from rest. By construction, DROP is zero before exercise and it returns to zero at the end of the recovery period. The nadir value of DROP changes (DROP<sub>m</sub>) recorded during or following exercise was used as an estimation of the severity of regional blood flow impairment (RBFi).

After a pre-heating period of at least 15 min, DROP values from both buttocks, both thighs and both calves were recorded for 2 min at rest, throughout exercise and for a minimum of 10 min during recovery. If the DROP value was not returned to zero within the 10 min of the recovery period, recovery was extended to 15 min or 20 min if necessary.

A minimal DROP value (DROP<sub>m</sub>) < -15 mmHg during or following walking was used to define the presence of ischemia (Abraham et al., 2018b). We calculated the time required to reach 50% of its minimal value (50%RT) or 10% of its minimal value (90%RT). These 50%RT and 90%RT were calculated from the end of the walking period, even if DROP<sub>m</sub> occurred during the recovery period.

### 1.4. Inclusion criteria and ethical approval

As a routine, patients were systematically recalled that their recording and medical database can be used for research purposes and of their right to deny such a use. If patients deny, this was recorded in the hospital database but according to French law, this analysis of routine practice does not require written individual consent. The database was ethically approved and was fully declared to national authorities. The present analysis of the recording and database received local ethics committee approval with reference 2020/42 and conforms to the Declaration of Helsinki. It was registered to the American National Institutes of Health database [clinicaltrials.gov](https://clinicaltrials.gov) under reference NCT04376099. For the present work, we analyzed all the patients referred for exercise-tcPO<sub>2</sub> during the first semester of 2018. Exclusion criteria were: No recording in the database (denied use of the medical file, or missing recording despite a TcPO<sub>2</sub> test), absence of TcPO<sub>2</sub> (test not performed for technical reasons or contra-indication to the test), corrupted recording (recovery period not recorded, recording failure), non-standard probe positioning or missing limb probe, duplicate recording, or absence of ischemia on any of the 6 limb probes.

### 1.5. Statistical analysis

Population description was dichotomized into patients with calf pain by history (With or without associated non-calf symptoms) and patients with non-calf claudication only.

Recovery time and distribution (Gaussian/non-Gaussian) was performed with rounding the recovery duration by intervals of 30 s.

The coefficient of correlation of recovery time to DROP<sub>m</sub> with the hypothesis that recovery time would be proportional to the severity of exercise-induced ischemia and/or duration of walking.

We determined the graphical relationship between the lowest calf vs. non-calf DROP<sub>m</sub> and highest calf vs. non-calf 50%RT and 90%RT for the whole group and for patients with calf claudication assuming the longest recovery would be associated to the lowest DROP<sub>m</sub> values, and compared the ischemia and recovery times on calf and non-calf localizations with Wilcoxon paired tests.

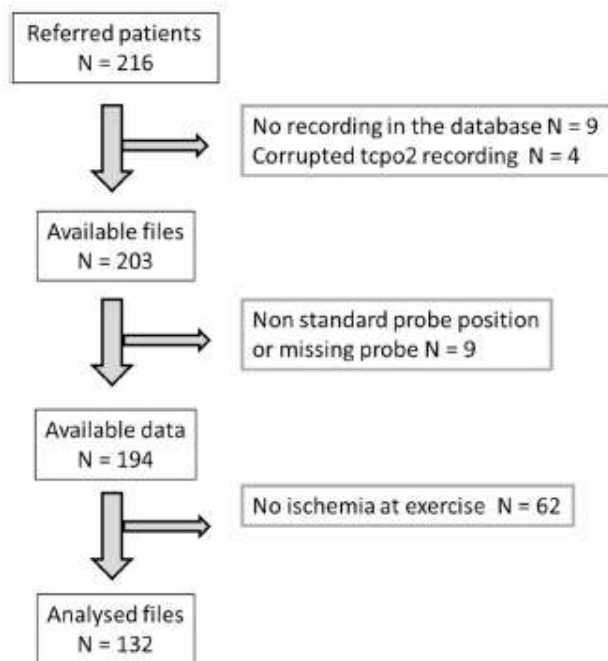


Fig. 1. Flowchart of the study.

We performed a multi-variate determination of the factors that influence the recovery times with step by step linear regression analyzing, using Lowest DROPm age, resting arterial systolic pressure, sex, body mass index, use of beta-blockers, maximal walking time as potential explanatory variables.

Statistical analyses were performed using SPSS (IBM SPSS statistics V15.0, Chicago USA). Results are reported as mean ± standard deviation (SD). Comparison between groups was performed with unpaired t-test from numerical data and Chi test for categories. For all statistical tests, a 2-tailed probability level of  $p < 0.05$  was used to indicate statistical significance. Non-significant results are reported as NS.

### 3. Results

Among the 216 patients referred for treadmill tests during the study period, exclusion criteria resulted in 132 files that were available for the analysis in the present study as shown in Fig. 1. Population characteristics are reported in Table 1. As shown, we had a relatively large proportion (18.2%) of patients that reported isolated non-calf pain by history. Few differences were found between patients that reported calf (±non-calf) pain and those that reported non-calf pain only, specifically on ABI. Nevertheless of interest is to note that the proportion of patients with calf (±Non-calf) pain that had non-calf ischemia was high and almost similar to the proportion of patients reporting non-calf pain only but that showed calf ischemia. Examples of recording and recovery time calculations are shown in Fig. 2, illustrating the fact that DROPm may occur after the end of the walking period, and that the location showing the lowest DROPm value is not necessarily the one having the longest recovery times.

As shown in Fig. 3, the duration of hemodynamic recovery with TcpO2 was shorter than 10 min consistently with the clinical definition of claudication in most patients. Of the 792 recovery time values, only 3 (0.4%) and 23 (2.9%) were in excess of 10 min (600 s) for 50%RT and for 90%RT, respectively. The times required for 95% of recorded values to reach 50%RT and 90%RT were 5.83 min and 9.80 min, respectively.

On a univariate basis, a very weak although significant correlation was found between each of the 792 DROPm and 50%RT ( $r = -0.270$ ,  $p$

Table 1

Characteristics of the patients and results for the exercise test. TcpO2 is transcutaneous oxygen pressure and DROP is for decrease from rest of oxygen pressure.

		Total	Calf pain ± non-calf pain by history	Isolated non-calf pain by history	p
		N = 132	N = 108	N = 24	
<b>Patients characteristics</b>					
Age	years	64.6 ± 9.6	64.5 ± 9.4	64.8 ± 11.0	0.581
Male gender	Nb (%)	110 (83)	90 (83)	20 (83)	1.000
Body weight	kg	76.5 ± 15.3	75.1 ± 15.4	82.7 ± 13.2	0.027
Height	cm	167 ± 8	170 ± 8	171 ± 9	0.610
BMI	kg/m <sup>2</sup>	26.5 ± 5.0	26.0 ± 4.8	28.5 ± 5.3	0.025
Systolic blood pressure	mmHg	136 ± 17	136 ± 18	138 ± 16	0.932
Diastolic blood pressure	mmHg	77 ± 10	77 ± 11	80 ± 9	0.964
ABI	-	0.70 ± 0.25	0.68 ± 0.27	0.78 ± 0.16	0.102
<b>Ongoing treatments</b>					
Antiplatelet agents	Nb (%)	118 (89)	97 (90)	21 (88)	0.739
Antihypertensive drugs	Nb (%)	83 (63)	65 (60)	18 (75)	0.174
Cholesterol lowering drugs	Nb (%)	95 (72)	75 (69)	20 (83)	0.171
Anticoagulants	Nb (%)	9 (7)	6 (6)	3 (13)	0.222
Beta blockers	Nb (%)	45 (34)	35 (32)	10 (42)	0.387
<b>Symptoms by history</b>					
Self-reported symptoms: calves	Nb (%)	108 (82)	108 (100)	0 (0)	0.000
Self-reported symptoms: non calves	Nb (%)	74 (56)	50 (46)	24 (100)	0.001
<b>Tcpo2 values at rest</b>					
Chest	mmHg	62 ± 14	62 ± 12	62 ± 15	0.869
Left buttock	mmHg	64 ± 14	64 ± 14	64 ± 12	0.815
Left thigh	mmHg	69 ± 12	69 ± 12	69 ± 10	0.892
Left calf	mmHg	67 ± 11	67 ± 11	67 ± 9	0.753
Right buttock	mmHg	64 ± 12	64 ± 12	64 ± 12	0.884
Right thigh	mmHg	71 ± 10	70 ± 10	72 ± 9	0.467
Right calf	mmHg	69 ± 13	70 ± 12	68 ± 17	0.443
<b>Treadmill test</b>					
Duration of walking	years	572 ± 430	558 ± 427	635 ± 448	0.426
Left buttock DROP min	mmHg	-17 ± 13	-16 ± 11	-22 ± 15	0.051
Left thigh DROP min	mmHg	-15 ± 13	-15 ± 13	-15 ± 10	0.829
Left calf DROP min	mmHg	-23 ± 14	-24 ± 14	-17 ± 8	0.013
Right buttock DROP min	mmHg	-17 ± 13	-16 ± 11	-23 ± 19	0.023
Right thigh DROP min	mmHg	-16 ± 12	-16 ± 11	-17 ± 14	0.874

(continued on next page)

Table 1 (continued)

		Total	Calf pain ± non-calf pain by history	Isolated non-calf pain by history	p
		N = 132	N = 108	N = 24	
Right calf DROP min	mmHg	-21 ± 11	-22 ± 12	-16 ± 7	0.012
Non-calf ischemia	Nb (%)	97 (73)	74 (69)	23 (96)	0.006
Calf ischemia	Nb (%)	117 (89)	100 (93)	17 (71)	0.002
Maximal non calf 50%RT	sec	206 ± 123	207 ± 128	203 ± 101	0.907
Maximal calf 50%RT	sec	219 ± 121	220 ± 118	217 ± 136	0.932
Maximal non-calf 90%RT	sec	387 ± 187	377 ± 183	398 ± 166	0.172
Maximal calf 90%RT	sec	393 ± 167	434 ± 200	366 ± 174	0.395

< 0.001) as well as for 90%RT ( $r = -0.311$   $p < 0.001$ ). As a result of this weak correlation, and as shown in Fig. 4, the calf was the location of maximal severity of ischemia and simultaneously of the longest recovery time in only 41 (30.1%) for 50%RT and 46 (34.8%) and 90%RT, and in only 40 (37.0%) for 50%RT and 44 (40.7%) for 90%RT, of the whole 132 patients, and of the 108 patients that complained calf claudication by history, respectively. Last, on the average the duration of 50%RT and 90% RT at the calf level, were not superior to non-calf 50%RT and 90% RT:  $p = 0.191$  and  $p = 0.676$ , respectively.

Last, multivariate analysis showed that for 50%RT, only lowest DROPm and BMI were associated to the duration of 50% recovery. The  $r$  correlation coefficient was 0.241 ( $p < 0.01$ ), and standardized  $b$  coefficient were  $-0.240$  ( $p = 0.005$ ) for lowest DROPm and 0.169 ( $p = 0.047$ ) for BMI. The analysis for 90%RT found that the  $r$  correlation coefficient was 0.411 ( $p < 0.001$ ), with standardized  $b$  coefficient being  $-0.348$  ( $p = 0.002$ ) for lowest DROPm, 0.202 ( $p = 0.014$ ) for BMI, and  $-0.204$  ( $p = 0.015$ ) for systolic blood pressure. Neither age, sex, the use of beta blockers, nor the duration of the walking period played a significant role in the models.

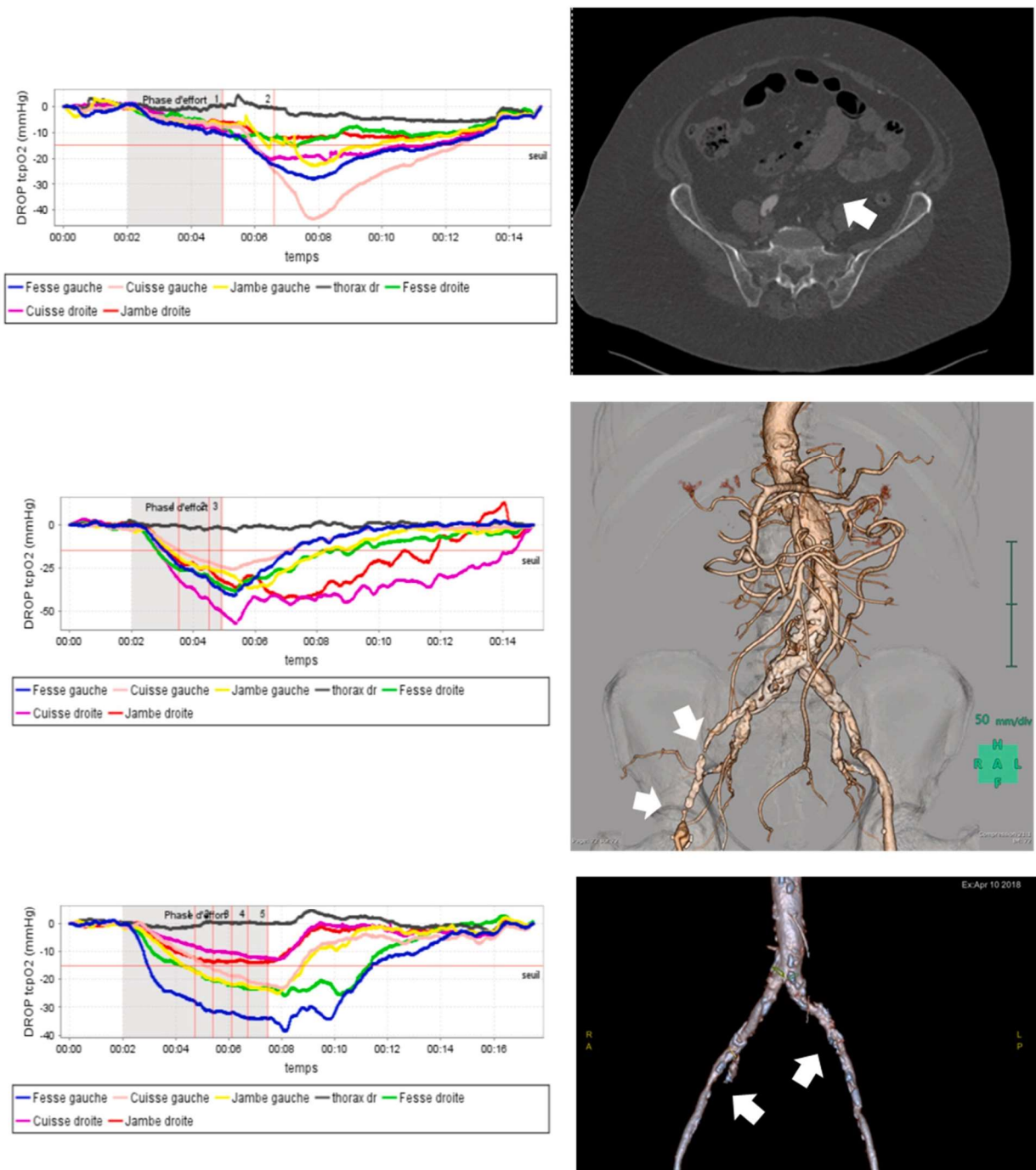
#### 4. Discussion

The prevalence of non-calf claudication is highly variable in previous studies (Manzano et al., 2009; McDermott et al., 1999; Criqui et al., 1996; Wang et al., 2005), and calf pain remains the dominant symptom in intermittent claudication. Almost all studies analyzing hemodynamic recovery in patients with claudication have focused on calf only. To the best of our knowledge, no study has ever compared hemodynamic results in the recovery period after exercise at the proximal (non-calf) and distal (calf) levels simultaneously. This aspect is of particular importance in accompanying and advising patients with claudication to wait for a sufficient period of time to allow forthcoming walking period following recovery from previous exercise-induced ischemic pain.

Dissipation of pain could appear as the most intuitive and easy way of estimating hemodynamic normalization after exercise. The problem arises from the fact that duration of pain dissipation is constantly shorter than hemodynamic normalization (Fouasson-Challoux et al., 2017). Further studies of pain dissipation provide some puzzling results. While studying claudication recovery time after a progressive, graded treadmill protocol (2 mph, 0% grade with 2% increase every 2 min), Addison et al. reported that LEAD patients with sarcopenia had higher claudication recovery time ( $592 \pm 98$  s vs  $395 \pm 29$  s;  $P < 0.05$ ) than did individuals without sarcopenia (Addison et al., 2018). The issue here is that the results imply that almost half of the patients with sarcopenia did not fulfill vascular type claudication because their recovery time was

superior to 10 min. Further, Garner et al. while studying the dissipation of claudication pain after walking with various treadmill grades found significant differences in time to onset of claudication and time to maximal claudication pain, but strictly no effect on time needed for claudication pain to dissipate (Gardner, 1993). Last, the estimation of pain dissipation remains subjective and objective measurable markers should probably be preferred. One of the simplest way of estimating recovery in claudication is to use heart rate as a surrogate measurable marker of peripheral hemodynamic recovery in LEAD patients. Fecchio et al. suggested that most heart rate recovery indices were reproducible and reliable in patients with claudication following maximal graded treadmill exercise (Fecchio et al., 2018). We showed that heart rate recovery is dependent on both the severity and diffusion of lower limb ischemia as assessed with Tcpo2 (Mahe et al., 2011b). Nevertheless, heart rate recovery is sensitive to fitness (Watson et al., 2017), and highly dependent of cardiac dysfunction or of presence of diabetes (Gharacholou et al., 2012). Last, heart rate provides no information on a leg-by-leg basis and on the localization of ischemia.

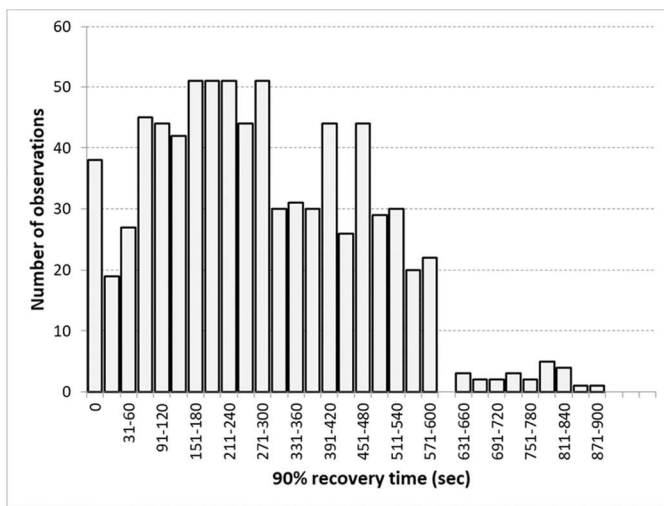
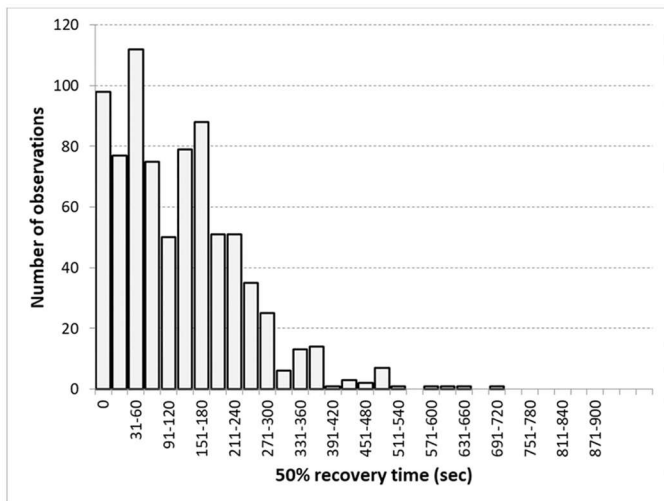
Lower limb hemodynamic measurements seem preferable for the direct estimation of post exercise recovery from ischemia. The measurement of ankle to brachial systolic pressure index (ABI) is largely used as an easy tool for estimating hemodynamic responses to exercise in LEAD patients (Stein et al., 2006). Although many studies report the fall in ABI value immediately at the end of exercise (Armstrong et al., 2017; Hammad et al., 2015), only few have studied the duration of this ABI fall and the recovery time to pre-exercise values. Sakurai et al. showed that after treadmill exercise (2.4 km/h and 10% grade), the recovery time for ABI to reach 90% of its pre-exercise value was superior to 10 min in most of patients (Sakurai et al., 1997). Average values as high as 15.6 to 28.3 min were observed in LEAD patients (without or with micro-albuminemia) after treadmill walking (2.4 km/h 12% slope) (Matsushita et al., 1996). Of interest is to note that recovery time for ABI seems to be influenced by the duration of constant load walking while the decrease in ABI from its pre-exercise value was not influenced by walking time duration (Sakurai et al., 1997). Contrary to previous results, Ohta reported that training reduced not only recovery time for ABI but also the ABI fall observed after the walking period (Ohta et al., 2002). This seems consistent to what was observed in athletes performing maximal incremental exercise (Le Faucheur et al., 2006). The major limit of ABI, is that it provides no indication as to the level of hemodynamic impairment and is only a poor marker of the blood delivery (collateral vessels can normalize flow under low pressure). In theory, thigh pressure could differentiate proximal from distal hemodynamic recovery parameters (Flanigan et al., 1981). Nevertheless, although thigh pressure seems to be able to diagnose iliac stenosis after maximal heavy load exercise in athletes (Hirai and Schoop, 1984), it failed to diagnose aortoiliac stenosis in LEAD patients after exercise (Farris and Jamieson, 1975). Last, ABI will not be the optimal approach to the evaluation of buttock or thigh ischemia that might result from stenosis or occlusion of arterial branches that are not participating to the distal perfusion (i.e. profunda femoris or internal iliac artery). Many authors have proposed the use of near infrared spectrometry (NIRS) to estimate oxygen debt throughout exercise and recovery (Gardner et al., 2019; Baker et al., 2017; Koutsisaris, 2017; Komiyama et al., 2002; Andrade-Lima et al., 2018), although there is a debate on the influence of skin flow over the NIRS signal (Davis et al., 2006). Some authors reported that NIRS derived parameters correlate with pain rating or walking distance (Schorr et al., 2017; Gardner et al., 2009). A correlation was also observed between the oxygenated hemoglobin recovery time and the ABI recovery time after walking exercise. Although the recovery times measured by NIRS were shorter than the recovery time for the ABI (Kooijman et al., 1997; Watanabe et al., 2004). The period of recovery of NIRS derived parameters postexercise should be considered in perspective of the fact that a shorter lived but significant decrease is also observed in normal subjects (Seifalian et al., 2001), making the interpretation of which proportion of the time is related to ischemia an



**Fig. 2.** Typical examples of transcutaneous oximetry recordings and the corresponding radiological imaging. Upper panel is a patient with occlusion of the left common iliac artery (white arrow) with ischemia dominantly at the left thigh level (pink graph). Note that minimal DROP occurs almost 3 min after the end of the exercise period (grey area). Middle panel is a patient with severe right external iliac stenoses (white arrows), with ischemia dominantly on the left calf (red line) and left thigh (violet line). Note that the recovery time for the left thigh is longer than for left calf. Lower panel is a patient with a complete occlusion of the left, and sub-occlusion of the right, internal iliac arteries (White arrow). Note that a significant ischemia was observed in the left thigh (pink line) and left calf (yellow line) as a result of associated external iliac and femoral lesions but that the recovery time at the left (blue line) and right (green line) buttocks, largely exceeded the recovery time of distal ischemia. Colors for DROPs are the same on all figures: the black lines are the second chest electrodes. As shown its DROP value is almost flat confirming that chest changes were similar on the two chest probes.

interesting but unsolved issue. A recent study proposed an NIRS-guided training intensity maintaining a 15% reduction in skeletal muscle saturation to improve claudication without pain with attractive results (Murrow et al., 2019). This is a clever approach since simultaneous measurement of NIRS at the thigh and calf is possible. Nevertheless, on the one hand the physiological responses seem to differ at those two level (Quaresima et al., 2002), on the other hand to the best of our

knowledge post exercise multisite (proximo-distal) recording have never been reported in LEAD patients. Last, NIRS can be used in claudicating buttocks (Sugano et al., 2003), but seems to be disappointing at the buttock level possibly due to fat thickness (Bouye et al., 2005). Positron emission tomography (Depairon and Zicot, 1996), 31phosphorus magnetic resonance spectroscopy (Taylor et al., 1996; Pipinos et al., 2000; Kemp et al., 2001), magnetic resonance angiography (West et al., 2012):



**Fig. 3.** Distribution of the 50% and 90% recovery times (by intervals of 30 s) for all calf and non-calf (buttocks and thighs) localizations. Median values are 124 and 272 s respectively.

are potential candidate for research purposes but, to date, can hardly be used in routine.

Transcutaneous oxygen pressure is clearly of advantage to estimate calf and non-calf oxygen mismatch during exercise and recovery with the possibility to estimate regional perfusion impairment on buttocks, thighs, and calves simultaneously. Although a surface technique, it was shown accurate and reliable in the evaluation of RBFi (Henni et al., 2018). As expected, the recovery time was inferior to 10 min in most patients and did correlate with MWT and the severity of ischemia (as estimated by DROPm value). The relatively slow response of TcpO<sub>2</sub> in case of an abrupt change in the values to be recorded should be kept in mind. The 90% response to abrupt change was estimated to range 20 to 30 s and the observed recovery times probably overestimate true recovery time by the same delay. Whether TcpO<sub>2</sub> could be used to guide rehabilitation in patients with claudication as was done with NIRS is an exciting perspective for future investigations.

There are limitations to the present study. First, it is possible that our results in a 3.2 km/h and 10% grade treadmill test are not applicable to other testing procedures. We recently shown the changing walking

speed in patients unable to walk 1 min at this speed resulted in increased MWD but had no influence on DROPm, but the recovery time for DROP was not studied. Second, we did not record the time for pain dissipation and cannot correlate the estimation of hemodynamic recovery to symptoms in our patients. Third, a population bias is possible with patients referred to us for exercise TcpO<sub>2</sub> being frequently cases of atypical claudication or claudication of debatable vascular origin. Forth, the DROP provides only an estimation of the mismatch between oxygen delivery and oxygen consumption in the area of interest. Then, the normalization of DROP does not imply that perfusion has normalized, but only that oxygen mismatch has normalized. As a matter of fact, chest TcpO<sub>2</sub> was generally superior to chest values at rest at the end of the recovery period, confirming that physiological effect of exercise on arterial oxygen content are still measurable far after DROP has normalized. Fifth, patients were allowed to hold the treadmill bar during the recovery period, which may influence the time for recovery. This is true but we advocate that recovery in the standing position is closer to usual recovery position than the lying position required for ABI or radiological investigations. Sixth and last, the changes in TcpO<sub>2</sub> are highly reliable (Henni et al., 2018), the position of the probe on the limb is important and ischemia of the distal part of the thigh close to the knee without ischemia close to the groin is observed in case of superficial artery occlusion (Signolet et al., 2018). The same issue applies also to eventual foot ischemia although isolated foot ischemia without calf ischemia is a relatively rare observation (Henni et al., 2016). Whatever, due to the retrospective analysis of recording and the use of standard position of probes, it can be that we missed the most ischemic areas (feet, lower back).

## 1. Conclusion

This is the first study analyzing calf and non-calf (buttock and thigh) hemodynamic recovery after exercise in patients with claudication. The median half time recovery (50%RT) is 2 min, and almost all patients reach 90%RT in less than 10 min. Although recovery duration correlates significantly with the severity of RBFi of the same location, a wide discrepancy exists and when calf and non-calf localizations are considered. Non-calf recovery time exceeds calf recovery time in almost half of the patients. We suggest that non-calf ischemia should be measured when one aims at objectifying the biological effects of exercise or the effects of treatments on recovery from exercise. We also think that these observations might be of particular interest to guide the duration of stops in rehabilitation programs.

## Financial support

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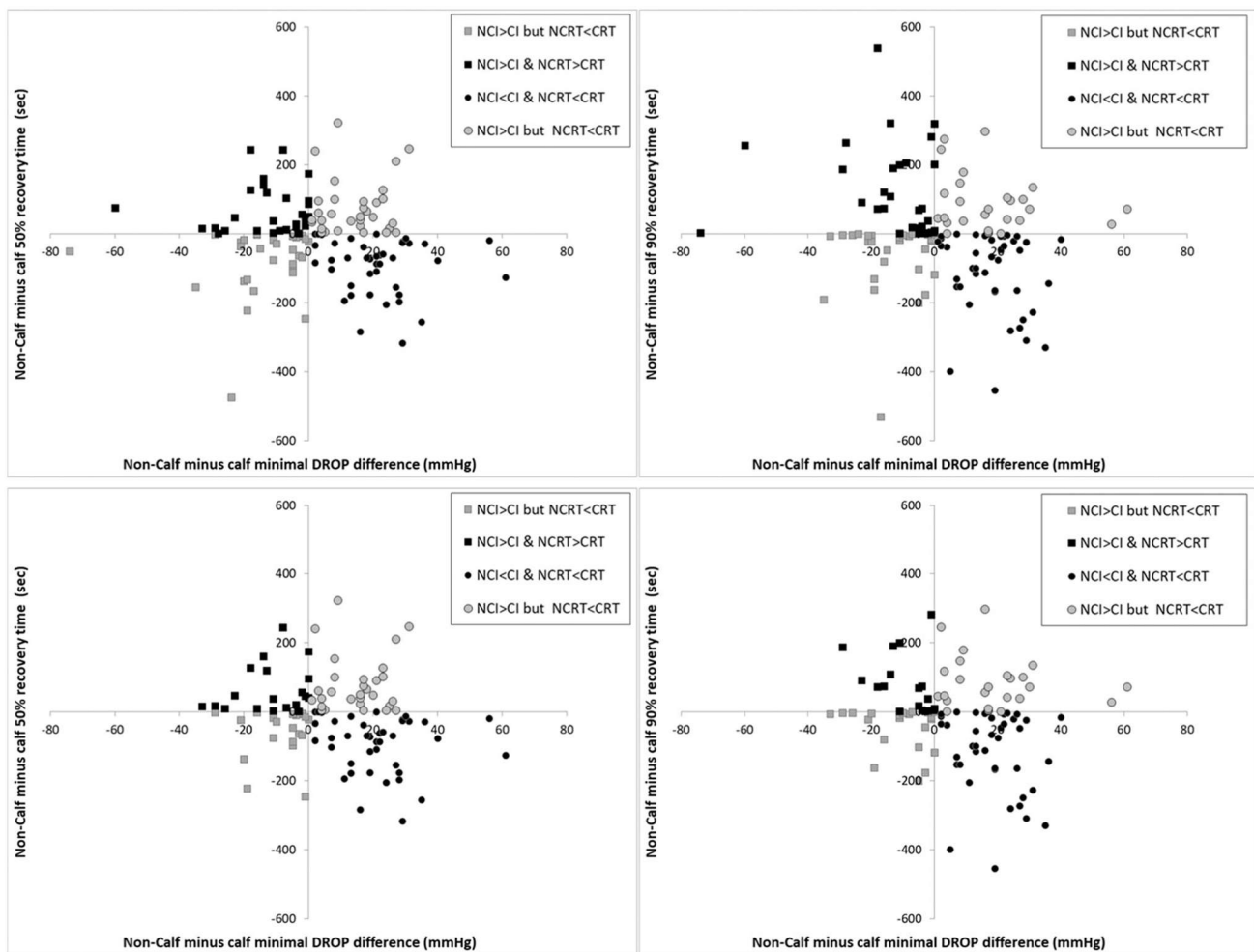
## CRediT authorship contribution statement

PA SH conceived and designed the study. PR JP, JH PA SH Participated to the recruitment of patients, MF, JH PR participated to the data analysis and interpretation. PA and SH prepared the manuscript draft, the other authors critically revised the manuscript. All authors approved the final version of the manuscript.

## Declaration of competing interest

PA has benefited the support of Radiometer, Perimed, Profusa and Medicap. None of these companies had access or interfered in the present project.





**Fig. 4.** Comparison of ischemia (DROP < -15 mmHg) at the calf (CI) and non-calf (NCI) area and of longest recovery time at the calves (CRT) and non-calves (NCRT) area, for the whole population (upper panels;  $N = 132$ ) and for patients with calf pain by history (lower panels;  $N = 108$ ). Results are presented for 50% and 90% recovery time.  $NCI > CI$  and  $NCI < CI$  means that non-calf ischemia is more severe (lower DROPm) and less severe (higher DROPm) than calf ischemia, respectively.  $NCRT > CRT$  and  $NCRT < CRT$  means that non-calf recovery time is longer and shorter than calf recovery time, respectively. Note that for all graphs this situation represents approximately half of the cases.

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## 2. Explorations des membres supérieurs à l'exercice dans le cadre du syndrome du défilé thoraco-brachial

### ***Microvascular response to the Roos test has excellent faisability and good reliability with suspected outlet syndrome***

#### Contexte :

Le SDTB est une des pathologies les plus controversées (29, 30). Il résulte d'une compression des vaisseaux et/ou nerfs entre le thorax et le membre supérieur. Le diagnostic repose sur la réalisation d'un examen clinique et d'explorations complémentaires (échodoppler, radiographie thoracique, TDM, IRM...) (31). Les explorations sont réalisées au cours de manœuvres dynamiques mettant en évidence cette compression. La TCPO2 permet l'enregistrement de l'altération ou d'une modification de la microcirculation de manière non-opérateur dépendant et peut-être utilisée lors de la réalisation de manœuvres dynamiques notamment des membres supérieurs.

Le but de cette étude est d'évaluer l'effet de la réalisation d'une manœuvre de ROOS sur la microcirculation des membres supérieurs en utilisation la TCPO2. L'hypothèse est que cette technique est faisable et peut permettre l'évaluation de la macro et de la microcirculation. L'objectif était également d'étudier la reproductibilité test-retest de la TCPO2 au cours d'une manœuvre de Roos chez les patients suspects de SDTB et chez des patients témoins. Enfin, le dernier objectif était d'apporter des résultats préliminaires dans la comparaison pré et post-opératoire.

#### Matériel et Méthodes :

42 patients ont bénéficié d'une TCPO2 durant la réalisation de deux manœuvres de ROOS consécutives. Le DROP minimal était enregistré pour chaque manœuvre à chaque bras. Réalisation d'une courbe ROC afin de déterminer les performances diagnostiques en fonction de la présence de symptômes durant le test. Comparaison des DROP minimaux sur les bras symptomatiques et asymptomatiques par test de Mann-Whitney. La reproductibilité test-retest est analysée par représentation de Bland-Altman.

#### Résultats :

Les symptômes rapportés par les patients n'étaient pas les mêmes que ceux décrits durant l'examen chez 1/3 des patients. Le DROP min était respectivement de -19 [-36 ; -7] et -8 [-16 ; -5] chez les patients symptomatiques (n=108) et asymptomatiques (n=60). Si l'on prend le diagnostic échodoppler de SDTB, la concordance avec la TCPO2 révélait une aire sous la courbe à 0.725 +/-0.058 avec un cut off optimal à -15mmHg. La sensibilité et la spécificité de la TCPO2 par rapport à l'écho doppler sont respectivement de 67% et 78%. Si l'on prend comme référence la présence de symptômes durant la réalisation des manœuvres, l'aire sous la courbe est de 0.698 +/- 0.04 avec un cut off à -10mmHg. La sensibilité et la spécificité de la TCPO2 par rapport à la survenue de symptômes cliniques sont respectivement de 62% et 66%. La reproductibilité test-retest du DROP minimum est bonne mais non parfaite, en partie à cause de la non-reproductibilité des manœuvres.

Conclusion : Cette étude, à notre connaissance, est la première s'intéressant à la TCPO2 dans le cadre du syndrome du défilé thoraco-brachial, lors de la réalisation de manœuvres dynamiques. La présence de

symptômes est significativement associée à la présence d'une ischémie. La TCPO2 permet un enregistrement simultané macro et microvasculaire. Il est probable qu'il faille répéter la manœuvre au moins deux fois lors des investigations diagnostiques. Les résultats préliminaires suggèrent que cette technique est sensible au changement post-opératoire.

Il apparaît que cette technique puisse s'intégrer dans une démarche diagnostique holistique chez ces patients suspects de SDTB.



# Microvascular Response to the Roos Test Has Excellent Feasibility and Good Reliability in Patients With Suspected Thoracic Outlet Syndrome

Samir Henni<sup>1,2</sup>, Jeanne Hersant<sup>1</sup>, Myriam Ammi<sup>3</sup>, Fatima-Ezzahra Mortaki<sup>4</sup>, Jean Picquet<sup>2,3</sup>, Mathieu Feuilloy<sup>5</sup> and Pierre Abraham<sup>2,4\*</sup>

<sup>1</sup> Vascular Medicine, University Hospital Center, Angers, France, <sup>2</sup> UMR INSERM 1083 – CNRS 6015, Mitovasc Institute, Angers, France, <sup>3</sup> Department of Cardiovascular and Thoracic Surgery, University Hospital Center, Angers, France, <sup>4</sup> Sports Medicine, University Hospital Center, Angers, France, <sup>5</sup> LALUM, UMR CNRS 6613, Groupe ESEO, Angers, France

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### \*Correspondence:

Pierre Abraham  
piabraham@chu-angers.fr

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**Background:** Exercise oximetry allows operator-independent recordings of microvascular blood flow impairments during exercise and can be used during upper arm provocative maneuvers.

**Objective:** To study the test-retest reliability of upper-limb oximetry during the Roos test in patients with suspected thoracic outlet syndrome (TOS).

**Materials and Methods:** Forty-two patients (28 men, 14 women; mean age: 40.8 years) were examined via transcutaneous oxygen pressure (TcPO<sub>2</sub>) recordings during two consecutive Roos tests in the standing position. The minimal decrease from rest of oxygen pressure (DROPmin) value was recorded after each maneuver was performed on both arms. The area under the receiver operating characteristic (ROC) curve defined the DROPmin diagnostic performance in the presence of symptoms during the tests. The Mann-Whitney *U*-test was used to compare the DROPmin in the symptomatic vs. asymptomatic arms. The test-retest reliability was analyzed with Bland-Altman representations. The results are presented as means ± standard deviations (SD) or medians [25–75 percentiles].

**Results:** The symptoms by history were different from the symptoms expressed during the Roos maneuvers in one-third of the patients. The DROPmin measurements were −19 [−36; −7] mmHg and −8 [−16; −5] mmHg in the symptomatic (*n* = 108) and asymptomatic (*n* = 60) arms, respectively. When TOS observed on ultrasound imaging was the endpoint, the area under the ROC curve (AUC) was 0.725 ± 0.058, with an optimal cutoff point of −15 mmHg. This value provided 67% sensitivity and 78% specificity for the presence TOS via ultrasound. When symptoms occurring during the test represented the endpoint, the AUC was 0.698 ± 0.04, with a cutoff point of −10 mmHg. This provided 62% sensitivity and 66% specificity for the presence of pain in the ipsilateral arm during the test. The test-retest reliability of DROPmin proved to be good but not perfect, partly because of unreliability of the provocation maneuvers.

**Conclusion:** To the best of our knowledge, this study is the first to investigate microvascular responses during the Roos maneuver in patients with suspected TOS. The presence of symptoms was significantly associated with ischemia. TcpO<sub>2</sub> facilitated the recording of both macrovascular and microvascular responses to the Roos test. The Roos maneuver should probably be performed at least twice in patients with suspected TOS.

**Keywords:** peripheral artery disease, exercise, provocative maneuvers, ischemia, microcirculation, oximetry

## INTRODUCTION

Thoracic outlet syndrome (TOS) is one of the most controversial disorders in medicine, with multiple recent editorials having been published on the subject (Ahmad and Murthy, 2018; Burt, 2018; Illig, 2018). TOS comprises a variety of symptoms and physical findings resulting from the external compression of vessels and/or nerves as they pass through multiple narrow spaces between the thorax and the upper limb (Jubbal et al., 2018; Kaplan et al., 2018). As described by Demondion et al. (2006), the diagnosis is based on clinical findings, but making this diagnosis is often difficult. The use of imaging (radiography, ultrasonography, computed tomographic angiography, or magnetic resonance imagery) is required to determine the nature and location of the underlying structures causing the compression (Ammi et al., 2017).

Many provocative maneuvers have been proposed to induce dynamic compression of the neural or vascular structures. A provocative test was proposed by Roos in 1966, which is referred to as the “Roos test” or the “elevated arm stress test” (EAST). Beyond the reproduction of symptoms induced by the Roos test, an evaluation of perfusion via Doppler, pulse palpation, and/or observation of hand pallor are generally performed to detect arterial compression. However, coldness and color changes could also result from sympathetic vasoconstriction during neurogenic TOS (Sanders et al., 2007). In evaluating vasoconstrictive responses to adrenergic stimulation, the study of skin micro-circulation during provocative maneuvers could be of major interest in the study of TOS, at least for research purposes. To the best of our knowledge, such microvascular investigations have never been reported.

We aimed to evaluate the effects of the Roos (EAST) test on upper arm microcirculation using transcutaneous oxygen pressure (TcpO<sub>2</sub>) measurements. We hypothesized that this technique would be feasible and could account for both macrovascular and microvascular impairments. We also aimed at estimating the reliability of the responses observed in both unaffected patients and patients referred for suspected TOS. Last, we aimed to identify the preliminary results of preoperative versus postoperative evaluations.

## MATERIALS AND METHODS

From March 2018 to September 2018, 42 patients were recruited into this prospective single-center study.

## Ethical Standards

The patients were fully informed about the study and its procedures; all patients signed a written consent document. This research and all its procedures were performed in compliance with the principles outlined in the Declaration of Helsinki. The study was promoted by the University Hospital in Angers, approved by our institutional Ethics Committee, and was registered in ClinicalTrials.gov under Ref: NCT03355274.

## Experimental Design

The study population comprised patients referred to the Department of Vascular Medicine for suspected TOS. All subjects were over 18 years of age and there was no maximum age limit set. Exclusion criteria were: pregnancy, any legal constraint, or current participation in another clinical trial. To date, one female patient was referred to us for a new evaluation after a prior surgery. Results from this observation are provided to illustrate the presence or absence of persistent ischemia in the surgically treated arm.

## Initial Assessment

At the point of study inclusion, we recorded patient demographics and conditions including: age, sex, presence of one or more cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, active smoking), history of chest or shoulder surgery, and any ongoing treatments. We also measured weight, height, systolic and diastolic blood pressures, and evaluated positional microvascular responses to the Roos test using transcutaneous oximetry (TcpO<sub>2</sub>) as described below. Results from ultrasound investigations performed prior to referral were encoded as “presence or absence of positive TO” on each side, according to the patient’s medical record. The technicians or physicians doing the TcpO<sub>2</sub> test were blinded to these data.

## Transcutaneous Oxygen Pressure Recordings

In brief, TcpO<sub>2</sub> is a useful technique that measures the local skin oxygen partial pressure using electrochemical probes heated to 44.5°C to improve local perfusion and oxygen transcutaneous diffusion. TcpO<sub>2</sub> changes, by calculating reductions in the rest of oxygen pressure (DROP) index, provide evidence of stimulation-induced regional blood flow impairments (Abraham et al., 2003, 2005; Bouye et al., 2004; Abraham, 2006; Hennin et al., 2018). DROP is calculated as the limb level changes minus the changes at a reference chest electrode. DROP allows for removal of error

due to unpredictable transcutaneous gradients (Abraham et al., 2003; Grouiller et al., 2006; Blake et al., 2018; Henni et al., 2018). In the present study, we positioned one probe 5–7 cm distal to the elbow joint at the proximal and internal portion of each forearm and one probe on the chest (parasternal) for reference. After a minimum of 15 min of heating, we started a 1-Hz recording with a 30-s reference period, after which patients performed two consecutive Roos tests. The second test was started after the DROP values returned to zero and after a minimum recovery period of 1 min following the end of the first test. Provocative maneuvers were conducted in the standing position with the patient's back against a wall. The patients were required to raise their arms to 90 degrees of abduction, with the arms fully externally rotated and the elbows at 90 degrees of flexion. Further, we asked the patients to try to touch the wall behind them with their elbows and wrists, but not their back, to ensure that the arms were flexed slightly behind the frontal plane, as shown in **Figure 1**. This "surrender" or "candlestick" position with opening and closing of both hands was sustained in all patients to the point of maximum pain, or for a minimum of 2 min in the absence of pain. Patients were repeatedly asked to report any symptoms (pain, fatigue, numbness, or tingling) experienced during the Roos test on each arm. The minimum value of DROP (DROPmin) during or in the minute following the end of each Roos maneuver was recorded for each arm. Inherently, DROP is a negative value that decreases with the increase in the severity of ischemia (Abraham et al., 2005) and is expressed in millimeters of mercury (mmHg).

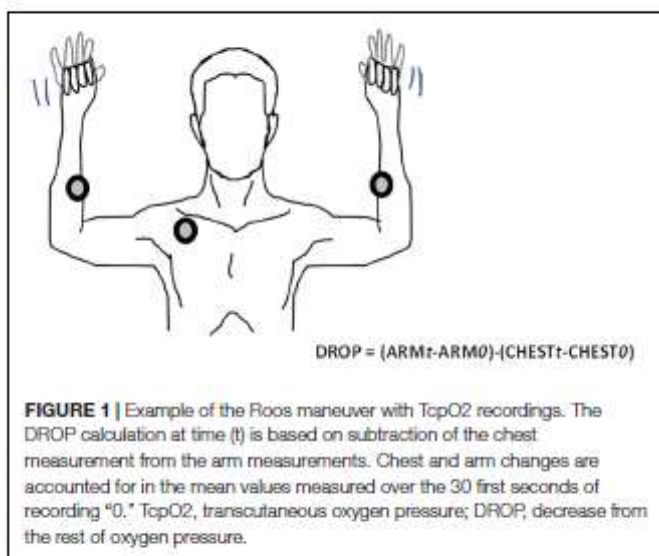
## Statistical Analysis

The data are presented as numbers (percentages), medians [25, 75 percentiles], or means  $\pm$  standard deviations (SD). A comparison of the DROPmin results between the symptomatic and asymptomatic arms was performed using the Wilcoxon rank test. A receiver operating characteristic (ROC) curve analysis comparing the DROPmin value to the presence/absence of

symptoms was used to define the optimal cutoff point for the DROPmin values in the prediction of symptom occurrence. All statistical analyses were performed using SPSS (IBM SPSS statistics V15.0, Chicago, IL, United States).  $P < 0.05$  was considered to be statistically significant. The area under the ROC curve (AUC) was used to determine whether DROP significantly predicted positive results on ultrasound imaging and/or the presence of symptoms during the Roos test. The optimal cutoff point was defined as the DROP value that resulted in the minimum distance to the 100% sensitivity / 100% specificity angle. The test-retest reliability of the DROP results observed for two consecutive Roos tests was analyzed using a Bland-Altman representation with logarithmic (10-log) transform in cases of heteroscedasticity, according to recommendations (Euser et al., 2008; Ludbrook, 2010). To create the 10-log transformation, DROPmin values were converted into absolute values (positive values). The absence of a decrease in DROP was encoded by  $-1$  mmHg and not zero. Last, the test-retest reliability of TcpO<sub>2</sub> was evaluated according to the similarity of symptoms between test 1 and test 2. Indeed, if discomfort or pain was present during one of the maneuvers, but absent during the other one, the TcpO<sub>2</sub> difference was expected to have resulted from unsatisfactory maneuver reproduction, with the presence of compression during one test and the absence of compression during the other.

## RESULTS

The recruited patients included 28 men and 14 women, aged  $40.8 \pm 12.2$  years old. The mean weight was  $70.3 \pm 16$  kg and mean height was  $164 \pm 7$  cm. Fifteen patients had one or more cardiovascular risk factors and 12 had a prior history of chest or shoulder surgery. Ongoing treatments included the use of lipid-lowering drugs ( $n = 2$ ) and sartans ( $n = 2$ ). Systolic and diastolic arm blood pressures were  $126 \pm 14$  and  $79 \pm 11$  mmHg, respectively. Among these patients, 15 reported unilateral symptoms on the right ( $n = 7$ ) or left ( $n = 8$ ) side and 27 reported bilateral symptoms. Among the patients reporting unilateral symptoms, 5 had previously undergone surgery for contralateral TOS. Among patients with unilateral symptoms, Roos maneuvers induced unilateral ( $n = 8$ ) or bilateral ( $n = 5$ ) pain. In two patients, the Roos maneuver did not reproduce the usual symptoms. Interestingly, among patients with unilateral symptoms, when the results were analyzed arm by arm, the symptoms were present in two consecutive tests in 8 patients, in neither of the tests in 5, and in one test only in 17 (in solely the first test in 8, and in solely the second test in 9). Of the 27 patients referred for bilateral symptoms, 2 had undergone previous unilateral ( $n = 1$ ) or bilateral ( $n = 1$ ) surgery for TOS. Among these patients, the Roos maneuvers induced unilateral ( $n = 6$ ) or bilateral ( $n = 20$ ) pain. In one patient, the Roos maneuvers did not reproduce the usual symptoms. Notably, when the 54 arms of the patients with bilateral symptoms were analyzed arm by arm, the symptoms were present during two consecutive tests in 31 patients, during neither test in 10, during solely the first test in 8, and during



solely the second test in 5. Of 42 patients, ultrasounds were positive for TOS on one or both sides in only 25 of them, as shown in **Table 1**.

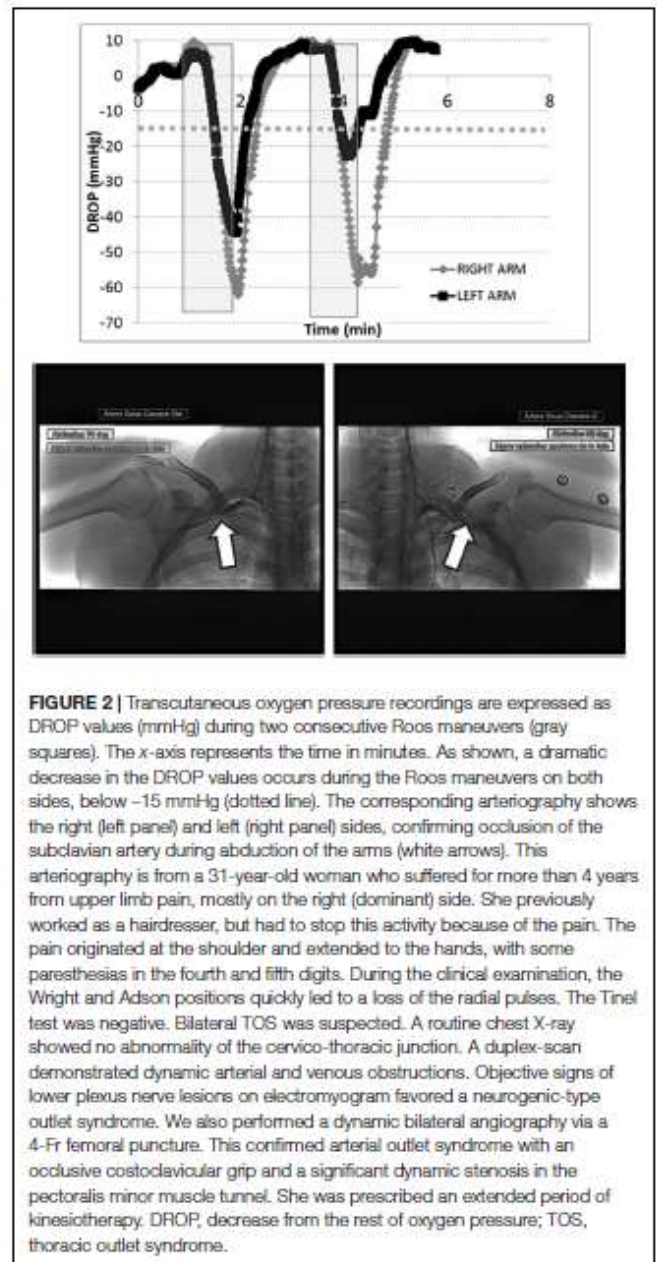
TcpO<sub>2</sub> showed excellent feasibility, with no technical failures or missing values. The chest TcpO<sub>2</sub> value at rest was 69 ± 10 mmHg. TcpO<sub>2</sub> at rest in the symptomatic (69 values) and asymptomatic (15 values) arms were 76 ± 12 and 74 ± 10 mmHg, respectively (*p* > 0.05). A typical example of a recording in a patient with TOS is presented in **Figure 2**. As shown, the Roos maneuvers were responsible for a sharp decrease in the right and left DROP values, although they were slightly decreased during the second maneuver on the left arm.

The lowest DROP<sub>min</sub> values of the two tests were as follows: -12 [-21, -7] mmHg in the arm with an absence of TOS findings on ultrasound imaging and -27 [-50, -14] mmHg in the arms with ultrasound evidence of TOS (*p* < 0.01). When TOS identified on ultrasound imaging was the endpoint, the AUC was 0.725 ± 0.058 (*p* < 0.001 from random choice), with an optimal cutoff point of -15 mmHg providing 67% sensitivity and 78% specificity for the presence of TOS on ultrasound.

On average, the DROP<sub>min</sub> values were as follows: -14 [-26, -6] mmHg for test 1 and -13 [-27, -7] mmHg for test 2 (*p* > 0.05) on the right side; -13 [-27, -7] mmHg for test 1 and -11 [-29, -6] mmHg for test 2 on the left side. On an arm-by-arm basis, among the 168 available values (42 patients, 2 arms, 2 tests), the DROP<sub>min</sub> values measured in the symptomatic (108 values) and asymptomatic (60 values) arms were -19 [-36, -7] mmHg and -8 [-16, -5] mmHg, respectively (*p* < 0.001). When the presence of symptoms during the test was the endpoint, the AUC was 0.698 ± 0.04 (*p* < 0.001 from random choice), with a cutoff point of -10 mmHg providing 62% sensitivity and 66% specificity for the presence of pain in the ipsilateral arm during the test.

For the entire test series, the average difference between the DROP<sub>min</sub> results of test 2 vs. test 1 on a Bland-Altman representation showed a clear heteroscedastic distribution with a mean difference of 1.2 mmHg. **Figure 3** shows the 10-log transformed data, confirming good agreement between the two tests (despite outlier values), with a mean difference close to zero and reasonable limits of agreements (LA).

Finally, the patient presented in **Figure 2** had a second test prior to surgery (**Figure 4**, upper panel), confirming the results of the first test, and then had surgery on the right (dominant) side by an axillary approach. She was referred 3 months after surgery with complete relief of symptoms in the right arm and normalization of the DROP<sub>min</sub> on the right side



**FIGURE 2 |** Transcutaneous oxygen pressure recordings are expressed as DROP values (mmHg) during two consecutive Roos maneuvers (gray squares). The x-axis represents the time in minutes. As shown, a dramatic decrease in the DROP values occurs during the Roos maneuvers on both sides, below -15 mmHg (dotted line). The corresponding arteriography shows the right (left panel) and left (right panel) sides, confirming occlusion of the subclavian artery during abduction of the arms (white arrows). This arteriography is from a 31-year-old woman who suffered for more than 4 years from upper limb pain, mostly on the right (dominant) side. She previously worked as a hairdresser, but had to stop this activity because of the pain. The pain originated at the shoulder and extended to the hands, with some paresthesias in the fourth and fifth digits. During the clinical examination, the Wright and Adson positions quickly led to a loss of the radial pulses. The Tinel test was negative. Bilateral TOS was suspected. A routine chest X-ray showed no abnormality of the cervico-thoracic junction. A duplex-scan demonstrated dynamic arterial and venous obstructions. Objective signs of lower plexus nerve lesions on electromyogram favored a neurogenic-type outlet syndrome. We also performed a dynamic bilateral angiography via a 4-Fr femoral puncture. This confirmed arterial outlet syndrome with an occlusive costoclavicular grip and a significant dynamic stenosis in the pectoralis minor muscle tunnel. She was prescribed an extended period of kinesiotherapy. DROP, decrease from the rest of oxygen pressure; TOS, thoracic outlet syndrome.

(**Figure 4**, lower panel). Because her left arm was only moderately symptomatic after surgery, she was unwilling to undergo a second operation.

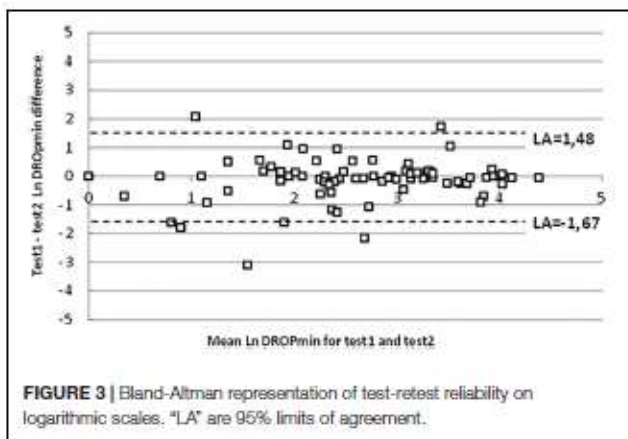
## DISCUSSION

To the best of our knowledge, this study is the first to investigate microvascular responses during the Roos test, one of the most largely used provocative maneuvers in the diagnosis of TOS. This study provides evidence that the technique is both feasible and reliable. Further, preliminary results suggest that it is sensitive to the changes observed after surgery.

**TABLE 1 |** Distribution of symptoms by history and results of ultrasound investigations in the studied population.

		Positive ultrasound results			
		None	Right	Left	Bilateral
Symptoms by history	Right	2	3	0	2
	Left	3	2	3	0
	Bilateral	12	2	4	9



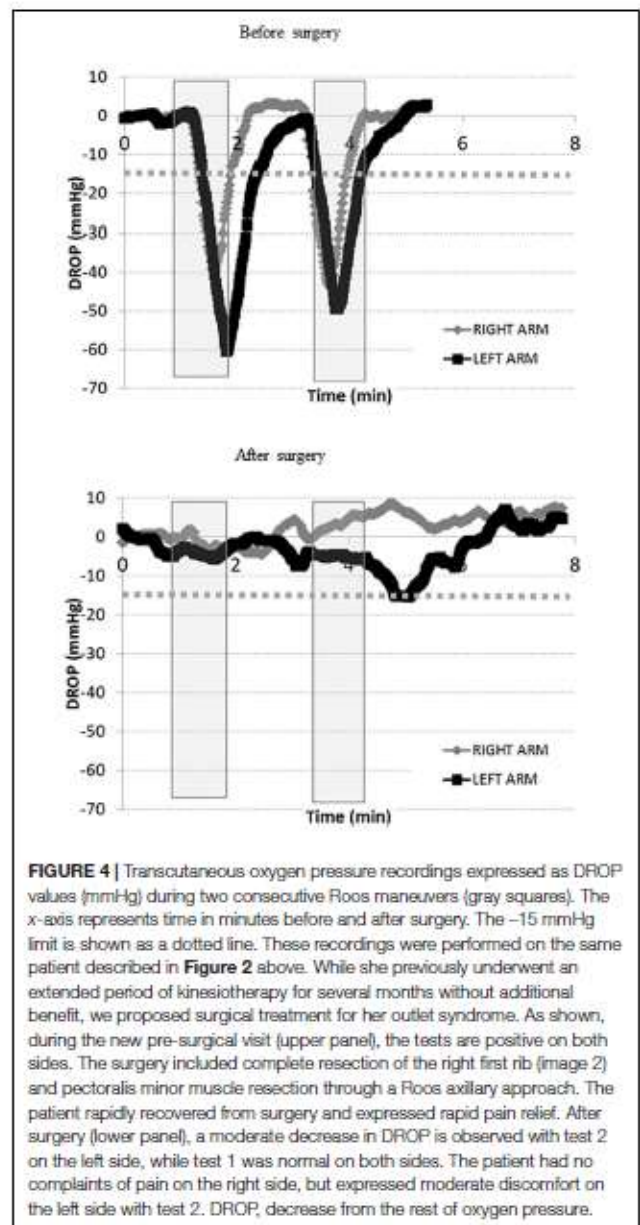


**FIGURE 3 |** Bland-Altman representation of test-retest reliability on logarithmic scales. "LA" are 95% limits of agreement.

Positive tests suggesting the presence of arterial, and/or venous, and /or nerve compressions are frequently observed in the general population. Using photo-plethysmography (PPG) in 130 apparently unaffected individuals, arterial obstructions were identified in 78 of them (60%) (Gergoudis and Barnes, 1980). Abnormal ultrasound or arterial PPG findings on the EAST and Upper Limb Tension Test (ULTT) were observed in 69% of 64 high-performance string instrument musicians, in contrast to 15% of 22 control subjects (Adam et al., 2018). Arterial flow anomalies on Doppler ultrasound and PPG were identified in 13% of 100 limbs from 50 normal volunteers (Chen et al., 2014). In 98 dissections of the thoracic outlet from 50 unselected cadavers, Juvonen et al. (1995) observed 63% with abnormal anatomy and 10% (5/50) had bilaterally normal anatomy. Thus, most neurovascular compressions remain asymptomatic and the specificity of tests will never reach 100% if symptoms are used as gold-standard endpoints.

There are conflicting results about the respective prevalences of arterial (ATOS), venous (VTOS), and neurogenic (NTOS) types of TOS and "combined" / "disputed" types (Ferrante and Ferrante, 2017; Peek et al., 2018). Relative ATOS, VTOS, and NTOS prevalences seem to partially rely on how each form is defined. Restricting arterial TOS to embolic events and venous TOS to Paget-Schroetter thromboembolic complications, as proposed by Sanders et al. (2007), leads to the consideration that over 95% of all TOS are neurogenic and less than 1% are arterial. Other series have reported more balanced results, using less restrictive definitions for ATOS and VTOS with results ranging from 48.7 to 74% of NTOS, 22 to 44% VTOS, and 4 to 25% ATOS (Ann Freischlag, 2018; Henry et al., 2018; Likes et al., 2014). Finally, whatever the definitions used and the exact proportions of each TOS type, the diagnosis of compression has generally been based on non-invasive clinical signs and vascular investigations.

Clinical provocative tests are considered to be of limited sensitivity and specificity (Warrens and Heaton, 1987; Gillard et al., 2001), probably partially resulting from a high rate of positive results in apparently asymptomatic patients, as previously discussed (Nord et al., 2008); however, it may also possibly result from a low test-retest reliability of the provocative



**FIGURE 4 |** Transcutaneous oxygen pressure recordings expressed as DROp values (mmHg) during two consecutive Roos maneuvers (gray squares). The x-axis represents time in minutes before and after surgery. The -15 mmHg limit is shown as a dotted line. These recordings were performed on the same patient described in Figure 2 above. While she previously underwent an extended period of kinesiotherapy for several months without additional benefit, we proposed surgical treatment for her outlet syndrome. As shown, during the new pre-surgical visit (upper panel), the tests are positive on both sides. The surgery included complete resection of the right first rib (image 2) and pectoralis minor muscle resection through a Roos axillary approach. The patient rapidly recovered from surgery and expressed rapid pain relief. After surgery (lower panel), a moderate decrease in DROp is observed with test 2 on the left side, while test 1 was normal on both sides. The patient had no complaints of pain on the right side, but expressed moderate discomfort on the left side with test 2. DROp, decrease from the rest of oxygen pressure.

maneuvers (Warrens and Heaton, 1987; Nord et al., 2008). No single non-invasive technique seems to be optimal for diagnosing TOS. One of the most widely used and useful tests for diagnosing TOS is ultrasonography. Unfortunately, preoperative duplex ultrasounds are only 41% sensitive for the diagnosis of NTO (Orlando et al., 2016). Ultrasonography only has a sensitivity of 87% and specificity of 88%, with risks of false-positive and false-negative results (Gillard et al., 2001). False-positive tests are assumed to result from signal losses or, when compared to the presence of symptoms by history, from the possibility of compression in asymptomatic – assumed healthy – individuals. False-negative tests could result either from non-adapted maneuvers, insufficient practitioner experience, or

inadequate technical recording. Magnetic resonance imaging (MRI) sensitivity, specificity, and positive and negative predictive values have been reported to be 41, 33, 89, and 4%, respectively (Singh et al., 2014). Whatever the technique, assuming that coldness and color changes would not be caused by ischemia resulting from subclavian artery obstruction, but from an overactive sympathetic nervous system (Sanders et al., 2007), Doppler ultrasonography would not adequately detect neurally induced cutaneous vasoconstriction. Whether or not pallor and coldness are always of neural origin, the specific benefit of TcpO<sub>2</sub> is that it can monitor both macro- and microvascular responses according to TcpO<sub>2</sub> decreases at arm level. These responses reflect cutaneous flow changes from the eventual occlusion of proximal vessels and the eventual reduction in skin blood flow secondary to sympathetic nervous system-induced vasoconstriction. The specific interest in TcpO<sub>2</sub> is that it is expected to decrease in cases of arterial compression (Babilas et al., 2008), secondary to neurally induced vasoconstriction (Provenzano et al., 2008) and isolated venous occlusion (Ostergren et al., 1983; Geis et al., 2008).

To the best of our knowledge, no other research has investigated upper limb TcpO<sub>2</sub> during provocative tests to evaluate TOS. Transcutaneous oxygen pressure changes have been well-described at rest and during exercise (Abraham et al., 2003). During exercise, this measurement was shown to be both accurate and reliable in the evaluation of exercise-induced ischemia (Abraham et al., 2003, 2005; Bouye et al., 2004; Abraham, 2006; Henni et al., 2018). Although absolute TcpO<sub>2</sub> has shown fair reliability (Rooke and Osmundson, 1989; Daviet et al., 2004), the calculation of the DROP index improved reliability in test-retest recordings (Bouye et al., 2004). In the present study, TcpO<sub>2</sub> facilitated the measurement of regional blood flow impairments, regardless of the underlying mechanism, and showed satisfactory reliability. Importantly, the  $-15$  mmHg cutoff point, using ultrasound results as a reference, is similar to the one identified from exercise TcpO<sub>2</sub> measurements (Abraham et al., 2003; Grouiller et al., 2006; Audonnet et al., 2017; Henni et al., 2018). Determining the cutoff point is important because limb elevation physiologically decreases TcpO<sub>2</sub> as hydrostatic pressure decreases (Dooley et al., 1997; Shah et al., 2008).

The present study had some limitations. First, we did not monitor the positions of the patients using three-dimensional cameras or accelerometers. This would be useful for excluding the  $\sim 15\%$  inconsistent test-retest results that relied on an imperfect reproducibility of carefully performed provocative maneuvers. Our opinion is that although provocative maneuvers were very carefully supervised, even non-measurable minor changes in position and intensity of shoulder muscle contractions could result in variable compressive effects. Similarly, we believe that the inconsistent test-retest results were not due to the technique itself, because TcpO<sub>2</sub> changes during exercise-induced ischemia are highly reliable and operator-independent (Henni et al., 2018).

Second, we could not confirm the presence or absence of arterial compression using contrast-enhanced imaging in many of the patients. One reason for this was that most patients with positive tests were referred to physical therapy or declined surgery. Radiological imaging in such patients

is not indicated. Further, admitting that pallor and coldness did not systematically result from arterial compression, but rather resulted from neurovascular vasoconstriction during nerve compression, indicated that contrast-enhanced imaging techniques should no longer be considered gold-standard techniques. This would be a limitation if our main goal was to evaluate the diagnostic performance of the TcpO<sub>2</sub> technique compared to a gold standard. However, this was not our goal. We only intended to test the feasibility and reliability of the technique. Nevertheless, the postoperative results in one of our patients confirmed that DROPmin values improve after surgery.

Third, we only tested the Roos maneuver, although other tests have been proposed to facilitate the diagnosis of TOS. Our choice was deliberate here, and relates to the fact that the Roos maneuver is generally reported as the one that provides a greater number of positive results (Rayan and Jensen, 1995; Nord et al., 2008). Future studies should evaluate the TcpO<sub>2</sub> response to other tests.

Finally, TcpO<sub>2</sub> is not considered a routine tool because of the cost of the device and the length of time required to reach stable values, specifically at arm level (Gorska et al., 2015; Chiang et al., 2018). Nevertheless, the diagnosis of TOS should be based on a holistic approach that includes the patient's history, clinical examination, and minimally invasive investigations. TcpO<sub>2</sub> could provide additional non-invasive evidence of abnormal microvascular responses to provocative tests (at least for the Roos test) before radiological imaging is chosen in cases of inefficient physiotherapy.

## CONCLUSION

In conclusion, to the best of our knowledge, this study is the first to examine microvascular responses during the Roos maneuver in patients with suspected TOS. However, additional studies with a larger number of patients are needed to evaluate the performance of TcpO<sub>2</sub> with respect to making the diagnosis of TOS. These studies should compare the test results to a gold standard, analyze the test-retest reproducibility, evaluate the responses to other provocative maneuvers, and estimate its sensitivity to the treatment of neural and/or vascular compression of the outlet. The Roos maneuver should probably be performed at least twice in patients with suspected TOS because of the moderate test-retest reliability of symptoms induced by the Roos test, even during carefully supervised maneuvers. TcpO<sub>2</sub> appears to be a promising non-operator-dependent investigative tool that allows for the simultaneous analysis of both arms during dynamic maneuvers in the standing position and investigations of the microvascular response to the Roos test. This might contribute to a holistic approach toward patients with suspected TOS.

## AUTHOR CONTRIBUTIONS

SH, JH, MA, F-EM, JP, and PA participated in patient recruitment, data acquisition, data analysis, and patient treatment. SH and PA participated in the preparation of the

study and provided technical and administrative support for the project. JH, JP, and PA supervised the project. SH, JH, JP, and PA wrote the manuscript. MA and F-EM reviewed and critically revised the draft. All authors approved the final version of the manuscript.

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## ***Comparison of transcutaneous oximetry with symptoms and arteriography in thoracic outlet symptoms***

### Contexte :

Le syndrome du défilé thoraco-brachial (SDTB) est une maladie rare, résultant d'une compression du paquet vasculo-nerveux dans le défilé thoraco-brachial. Il existe plusieurs sous-types de SDTB : neurologique, artériel et veineux. En considérant que les SDTB artériel et veineux ne surviennent que s'il existe des complications, la proportion de SDTB neurologique est de 90% (32, 33). Le diagnostic se compose d'un examen clinique avec reproduction des symptômes lors de manœuvres dynamiques mais également d'examen paraclinique. L'artériographie constitue le gold standard et permet une visualisation précise des anomalies structurelles, des différentes zones de compression. Il s'agit cependant d'une méthode invasive réservée à l'évaluation pré-opératoire. L'écho doppler est l'examen non invasif de première intention pour le diagnostic de SDTB, mais ses paramètres de sensibilité et spécificité restent limités (34).

Il a été démontré par l'article exposé ci-dessus que la dégradation du flux sanguin chez les patients présentant un SDTB pouvait être estimée par la réalisation d'une TCPO2 (35). Mais il n'existe pas de données de TCPO2 sur les sujets sains dans ce contexte. Des examens non-invasifs sont nécessaires pour étayer le diagnostic du SDTB.

L'objectif de cette étude était d'analyser la valeur diagnostique de la TCPO2 en comparaison aux données de l'artériographie dans le SDTB

### Matériel et Méthodes :

Il s'agit d'une étude prospective ayant inclus 76 patients et 40 volontaires asymptomatiques. Chez les patients symptomatiques les artériographies étaient considérées comme positives à partir de 75% de sténose. Il a été réalisé une courbe ROC évaluant la capacité de la TCPO2 à discriminer les patients des témoins durant la réalisation de manœuvres dynamiques afin de prédire la présence de résultats positifs en artériographie.

### Résultat :

Les DROP médians des contrôles et patients respectivement étaient : -14 [-8/-22] mmHg et -22 [-12/-42] ( $p < 0,02$ ). L'aire sous la courbe retrouve une bonne capacité de prédiction de la présence d'une compression en artériographie par la TCPO2 (AUC 0,694).

### Conclusion :

Le cut-off de TCPO2 observé est similaire à ce qui est retrouvé au niveau des membres inférieurs. La TCPO2 en combinaison à la réalisation d'un écho-doppler fait mieux en termes de prédiction des résultats positifs de l'artériographie que l'échodoppler seul.

La TCPO2 constitue un outil supplémentaire offrant des mesures objectives utiles dans la démarche diagnostique complexe du SDTB. Elle permet d'améliorer la sélection des patients devant bénéficier d'une prise en charge chirurgicale, elle-même difficile avec un risque de complications non négligeable.

# Comparison of transcutaneous oximetry with symptoms and arteriography in thoracic outlet syndrome

Pierre Abraham<sup>a,b,\*</sup>, Jeanne Hersant<sup>c</sup>, Pierre Ramondou<sup>c</sup>, Francine Thouveny<sup>d</sup>,  
Mathieu Feuilloy<sup>a</sup>, Jean Picquet<sup>b</sup> and Samir Henni<sup>a</sup>  
<sup>a</sup>Exercise investigation and Sports Medicine, University Hospital, Angers, France  
<sup>b</sup>UMR CNRS 6015, INSERM 1228, Medical School, University of Angers, France  
<sup>c</sup>Vascular Medicine, University Hospital, Angers, France  
<sup>d</sup>Vascular Radiology, University Hospital, Angers, France  
<sup>e</sup>LAUM, UMR CNRS 6613, Groupe ESEO, Angers, France  
<sup>f</sup>Thoracic and Vascular Surgery, University Hospital, Angers, France

## Abstract.

**BACKGROUND:** Non-invasive tests are still required to improve the holistic diagnostic approach of thoracic outlet syndrome (TOS).

**OBJECTIVES:** We aimed to analyze the diagnostic accuracy of the decrease from rest oxygen pressure (DROP) index of transcutaneous oximetry (TcPO<sub>2</sub>) in TOS.

**METHODS:** Seventy-six patients and 40 asymptomatic volunteers (Controls) were enrolled. In TOS-suspected patients, the arteriograms were investigated for the presence of  $\geq 75\%$  stenosis. The area under receiver operating characteristics curve (AUC) analysis tested the ability of forearm TcPO<sub>2</sub> during provocative maneuvers to discriminate Patients from controls and, to predict a positive arteriographic findings in the 44 TOS-suspected patients that had an arteriography.

**RESULTS:** The media [25/75° centile] DROP values of controls and patients were -14 [-8/-22] mmHg and -22 [-12/-42] mmHg, respectively (p for Mann-Whitney<0.02). AUC analysis showed a significant ability of TcPO<sub>2</sub> to predict the presence of subclavian arterial compression on arteriography (AUC, 0.694).

**CONCLUSIONS:** Although time consuming, TcPO<sub>2</sub> is independent of the observer expertise and could be useful in TOS-suspected patients to select the patients that should undergo arteriography.

Keywords: Ischemia, subclavian artery, thoracic outlet syndrome; transcutaneous oxygen pressure, diagnosis, diagnostic accuracy

## Glossary of Abbreviations

TOS	Thoracic outlet syndrome
TOS-s	Suspected thoracic outlet syndrome
TcPO <sub>2</sub>	Transcutaneous oxygen pressure
pO <sub>2</sub>	Partial pressure for oxygen
DROP	Decrease from rest of oxygen pressure

\*Corresponding author: P. Abraham, Laboratory of Physiology, University Hospital, Angers France. UMR INSERM 1083; CNRS6015, University of Angers, France. Tel.:+33 (0) 241 36 40 93; E-mail: E-mail: Pierre.abraham@univ-angers.fr.

RBFI	Regional blood flow impairment
EAST	The elevated arm stress test (EAST)
ROC	Receiver operating characteristic (ROC)
AUC	The area under the receiver operating characteristic curve
PPV	Positive predictive value
NPV	Negative predictive values
CI	95% confidence intervals
DOR	The diagnostic odds ratio

## 1. Introduction

Thoracic outlet syndrome (TOS) refers to a wide variety of symptoms attributable to compression of the neurovascular bundle in the thoracic outlet region of the upper extremity. TOS is classified a rare disease in France [1], while, paradoxically, compression of the neurovascular bundle during arm mobilization is a frequent observation in apparently healthy individuals [2–4]. In the United States, the Genetic and Rare Diseases Information Center underlines that while TOS as a group are not rare, individual subtypes are [5].

It is generally accepted that there is a distinction between neurogenic TOS resulting from brachial plexus compression, venous TOS resulting from subclavian vein compression, and arterial TOS resulting from subclavian artery compression. Considering that venous and arterial TOS appear only when complications occur (i.e., arterial embolism or venous thrombosis), neurogenic TOS accounts for more than 90% of all TOS cases, with some disputed cases [6, 7]. Nevertheless, lacking the ability to routinely estimate the effect of arm position on the brachial plexus, the classical diagnostic approach to TOS consists of reproducing pain during arm maneuvers and estimating the effect of these maneuvers on the artery to confirm bundle compression.

Arteriography is considered a key diagnostic test for TOS (and the gold standard for arterial TOS) as it provides information about the exact location and nature of the anatomic compression on the artery. However, arteriography is an invasive technique and as such is reserved for patients that are scheduled for surgery. As a result, ultrasound imaging (echo-Doppler) is the standard tool for the primary diagnosis of TOS. The performance of ultrasound imaging in the diagnosis of TOS remains contentious [8, 9], and TOS still represents a diagnostic challenge to the physician. In TOS, compression or occlusion of the artery during arm maneuvers results in pain with pallor of the hand due to ischemia. Pallor in neurogenic TOS could result either from simultaneous artery compression, or from cutaneous adrenergic vasoconstriction. Therefore, measurement of microvascular cutaneous circulation is of specific interest in diagnosing not only arterial but also neurogenic TOS.

Recent evidence has shown that forearm cutaneous blood flow impairment can be estimated by recording transcutaneous (Tc) oxygen pressure (pO<sub>2</sub>) in patients suspected of having TOS [10]. Nevertheless, TcpO<sub>2</sub> responses in healthy subjects have not been reported, and no comparisons of TcpO<sub>2</sub> against the gold-standard, arteriography have been performed. Furthermore, the added value of TcpO<sub>2</sub>, a microcirculatory technique, compared to ultrasound imaging alone in TOS diagnosis has not been evaluated.

We have undertaken the present study to determine the diagnostic performance and eventual added value of TcpO<sub>2</sub> for predicting a positive arteriography in patients with suspected TOS.

## 2. Materials and methods

This prospective study (Systematic Transcutaneous Oximetry Use in Thoracic outlet evaluation: “STOUT”) was performed at the Vascular Medicine department of the University Hospital in Angers, France. The study was approved by the Ethics Committee and French authorities, was registered at ClinicalTrials.gov (NCT 03355274), and conformed to the Declaration of Helsinki.

Patients were recruited between March 2018 and March 2019 from the vascular medicine, vascular radiology, and cardio-thoracic and vascular surgery departments if they had suspected TOS (TOS-s) and met the following criteria: 1) age of 18 years or older, 2) able to understand the purpose of the study, 3) fluent in French, and 4) complaining of stable upper limb disability for at least 3 months. Since we aimed to compare symptomatic and asymptomatic arms, we recruited both patients with TOS-s and healthy individuals, considering that few TOS-s patients would have asymptomatic arms and that few apparently healthy individuals would experience symptoms during the positional tests. Since another goal of the study was to compare the results of TcpO<sub>2</sub> to arteriography and because patients managed by the vascular medicine and surgery departments underwent arteriography only if surgery was scheduled, recruitment of patients was carried on until at least 40 TOS-s patients underwent arteriography. This was performed by weekly communication of the names of all patients that underwent upper limb arteriography for TOS-s by the radiology service to the research technician.

Healthy, asymptomatic volunteers (controls,  $n = 40$ ) were recruited by on-campus oral advertisements from March 2018 to December 2018. To be eligible, individuals had to: 1) have no acute or chronic upper limb pain or discomfort; 2) report no history of peripheral artery disease, except for hypertension; and 3) not be receiving analgesics.

All individuals provided written consent after a detailed explanation of the study design.

### 2.1. Patient characteristics and symptom history

A medical history assessment and physical examination were performed in all participants. We recorded the age; height; body weight; sex; systolic and diastolic arterial pressures; dominant arm; ongoing treatments; previous upper extremity trauma or surgery; previous cervical, shoulder, or chest trauma or surgery; and cardiovascular risk factors (active smoking, diabetes mellitus, and dyslipidemia). All patients completed a questionnaire to ascertain symptom history comprising the primary complaint (pain, weakness, fatigue and paresthesia) for each upper limb and the side of the most painful upper limb for TOS-s patients.

### 2.2. Ultrasound imaging

Doppler ultrasonography was performed systematically in healthy controls and in TOS-s patients with no recent investigations. When performed in TOS-s patients, only the results from this most recent investigation were made available to the referring physician and recorded in the patient’s medical file.

For all participants, ultrasound imaging results were classified as positive or negative for the presence of arterial compression based on the conclusion of the physician that performed the examination. The reports rarely mentioned the results for each specific maneuver.

### 2.3. TcpO<sub>2</sub> measurements

The TcpO<sub>2</sub> tests were performed with the operator blinded to the results of any previous ultrasound and arteriography investigations. TcpO<sub>2</sub> was recorded by a Radiometer TCM400 system (Radiometer, Copenhagen, Denmark) unit including three E5250 electrodes. Calibration was performed twice before



101 each session, as recommended by the manufacturer. Each electrode heated the underlying tissue to  
102 44.5°C in order to maximize local vasodilation and gas diffusion through the skin [11]. The system  
103 uses the polarographic method that consists of a silver anode and a platinum cathode, which generate  
104 a current proportional to the oxygen molecules that diffuse through the skin. Due to the diffusion  
105 gradient, TcpO<sub>2</sub> is lower than the underlying tissue's pO<sub>2</sub>. The gradient is unpredictable but constant  
106 for a defined probe position, once local heating is attained. The PCM400 was connected to a computer  
107 that recorded data on a 1 Hz basis and automatically calculated the decrease from rest of oxygen pressure  
108 (DROP) index. DROP accounts for changes in limb PO<sub>2</sub> values resulting from regional blood flow  
109 impairment (RBFi) in comparison to the changes in a reference area with assumed normal perfusion  
110 (the chest) during various provocative maneuvers. DROP is calculated as the difference in limb PO<sub>2</sub>  
111 change and chest PO<sub>2</sub> change and expressed in millimeters of mercury. It is 0 mmHg in the absence  
112 of RBFi, with decreases proportional to the severity of RBFi [12, 13].

113 Fixation rings were applied to the skin on the anterior aspect of both forearms, avoiding superficial  
114 vessels and body hair, and on the chest using double side adhesive. Few drops of contact liquid (Ref:  
115 943760) were instilled inside the fixation rings (Ref: 904891) and electrodes were screwed to the ring  
116 to avoid trapping of air bubbles. TcpO<sub>2</sub> was considered stable after a minimal heating period of 15  
117 minutes.

118 After explanation of the procedure, TcpO<sub>2</sub> measurements were performed with the participants  
119 standing with no view of the measured values. Recording during at least one minute resting period  
120 was performed before the start of upper limb stress tests (see below). Confirmation that DROP values  
121 were returned to baseline was required before a new test was started. The DROP results were neither  
122 communicated to the patients nor to the managing physicians.

#### 123 2.4. Upper limb stress tests

124 The elevated arm stress test (EAST) with opening and closing the hands on a regular basis was  
125 performed twice, followed by two Adson's tests with the head turned once to the right and once to the  
126 left. During the tests, patients were required to report any primary complaints (pain, weakness, fatigue  
127 and paresthesia) in both upper limbs, and the side of the most upper limb pain in symptomatic patients  
128 with bilateral symptoms.

#### 129 2.5. Arteriography

130 At the end of the enrollment period, we retrieved the arteriography results, provided that it was per-  
131 formed within 6 months of the TcpO<sub>2</sub> recording. The results were analyzed with the investigators  
132 blinded to the results of the other investigations (i.e., ultrasound imaging and TcpO<sub>2</sub>). Provoca-  
133 tive maneuvers during arteriography systematically included abduction with external rotation of the  
134 arm mimicking the EAST (assumed to specifically detect costo-clavicular compressions), as well as  
135 maneuvers mimicking Adson's tests (assumed to preferentially detect pectoral compression). These  
136 maneuvers were performed in the lying position and are referred to as Adson-type and EAST-type to  
137 differentiate them from maneuvers performed in the standing position during TcpO<sub>2</sub> recordings. Arte-  
138 riograms were classified positive in the presence of a stenosis (>75%) or occlusion of the subclavian  
139 artery. Each upper limb was classified separately.

#### 140 2.6. Data analysis

141 Based on clinical results, due to the possibility of not reproducing usual symptoms in TOS-s patients  
142 or inducing symptoms during the tests in apparently healthy controls, an analysis was performed on a

143 limb-by-limb basis based not only on the symptoms reported by history, but also on symptoms observed  
144 during the tests. Each upper limb was classified as either: symptomatic according to patient history,  
145 symptomatic during the test, symptomatic both according to patient history and during the tests.

146 For all analyses, the TcpO2 results used for each upper-limb were those with the lowest DROP values  
147 observed during the two consecutive EAST and/or Adson's tests. In one TOS patient only the EAST  
148 was available, its results were used for the analysis. Analysis of arteriography findings was performed  
149 on a limb-by-limb basis.

## 150 2.7. Statistical analysis

151 Descriptive statistics were summarized as mean  $\pm$  standard deviation or median [25/75<sup>o</sup> centiles].  
152 Comparisons between groups were made with Student's t test for patient's characteristics and ques-  
153 tionnaire scores or the Mann-Whitney U test for DROP values for quantitative variables and with the  $\chi$   
154 test or Fisher's test for qualitative variables. The area under the receiver operating characteristic (ROC)  
155 curve (AUC) was used to estimate the diagnostic performance of TcpO2 for symptoms and positive  
156 arteriography on a limb-by-limb basis. When the AUC was significantly different from random choice  
157 (area = 0.5), we determined the optimal cutoff point as the value minimizing the distance of the curve  
158 to the 100% sensitivity/100% specificity angle.

159 Regardless of the results of this study's ROC analysis, we used -15 mmHg as the cutoff point for  
160 abnormal TcpO2 based on our previous studies on the upper limb as well as experience with the lower  
161 limbs [10, 12, 14]. We tested the clinical value of performing Tcpo2 in addition to ultrasonography  
162 for predicting a positive arteriogram by calculating the positive (PPV) and negative (NPV) predictive  
163 values and their 95% confidence intervals (CI). The diagnostic odds ratio (DOR) of ultrasound alone  
164 or in combination with TcpO2 was calculated as the single indicator of diagnostic test performance  
165 [15]. We calculated the Z-score for DOR results from the contingency table to compare the DOR of  
166 ultrasound alone to other approaches.

167 All statistical tests were two sided, and  $p$  values  $< 0.05$  indicated statistical significance. The statistical  
168 analyses were performed using the Statistical Package for Social Sciences software for Windows (IBM  
169 Corp., Armonk, NY).

## 170 3. Results

### 171 3.1. Study population

172 Seventy-nine patients and 40 healthy volunteers were enrolled in the study. Three patients were  
173 excluded because of failure of TcpO2 recording (inability to stand up for the test  $n = 2$ , cutaneous  
174 allergic reaction to medical tapes  $n = 1$ ). There were significant differences in sex, age, weight, height,  
175 arterial pressures, and the prevalence of active smoking between the TOS and control groups while  
176 the other demographic characteristics were similar (Table 1). A history of unilateral symptoms was  
177 found in 26 TOS-s patients, 14 (18.4%) of which complained of symptoms on their right side, and  
178 all but one were right-handed. Twelve (15.8%) patients complained of symptoms on their left side, of  
179 which only two were left-handed. Bilateral symptoms were reported in 50 (65.8%) TOS-s patients. In  
180 these patients, the most painful upper limb was the right in all 20 right-handed patients, and the left  
181 in 27 right-handed and 3 left-handed patients. Thus, on history, there were 126 symptomatic and 26  
182 asymptomatic extremities in the TOS-s group and 80 asymptomatic extremities in the control group.  
183 Among the controls, 28 had a normal ultrasound investigation, 2 were positive on the left, and 3 were  
184 positive on the right. Seven volunteers were positive for bilateral arterial compression. Twenty-five

Table 1  
 Characteristics of the patients with suspected thoracic outlet syndrome (TOS-s) and healthy participants (controls)

	Controls ( <i>n</i> = 40)	TOS-s ( <i>n</i> = 76)	<i>P</i> value
Age (years)	28.3 ± 12.8	39.4 ± 11.3	0.000
Sex (male)	12 (30.0)	25 (32.9)	0.835
Height (cm)	170 ± 10	166 ± 8	0.012
Weight (kg)	62.1 ± 11.9	70.0 ± 16.1	0.007
Body mass index (kg/m <sup>2</sup> )	21.4 ± 2.8	25.5 ± 5.3	0.000
Systolic blood pressure (mmHg)	118 ± 10	125 ± 14	0.005
Diastolic blood pressure (mmHg)	74 ± 9	80 ± 11	0.005
Diabetes mellitus	0 (0.0)	2 (2.6)	0.544
Active smoking	3 (7.5)	25 (32.9)	0.003
Left-handed	4 (10.0)	6 (7.9)	0.735
Arm and forearm trauma or surgery	8 (20.0)	16 (21.1)	1.000
Cervical, chest, or shoulder trauma or surgery	0 (0.0)	20 (26.3)	0.000
Current treatment	12 (30.0)	19 (25.0)	0.660
• Cholesterol-lowering	1 (2.5)	4 (5.3)	0.658
• Antihypertensive	1 (2.5)	7 (9.2)	0.260
• Antiplatelet	1 (2.5)	1 (1.3)	1.000
• Oral contraception	10 (25.0)	9 (11.8)	0.111

185 TOS-s patients had a normal ultrasound investigation on both sides, 12 were positive on the left, 11  
 186 were positive on the right, and 28 had positive bilateral findings. As a result, 107 of a total of 232 upper  
 187 limbs were positive.

### 188 3.2. *Tcpo2* results

189 The common symptoms observed during the EASTs and Adson's tests are summarized in Table 2.  
 190 Symptoms were observed in 155 of a total of 232 upper-limbs during at least one of the two tests. A  
 191 typical example of *TcpO2* results in a patient with TOS is shown in Fig. 1. The average DROP values  
 192 found in the arms of controls and TOS-s patients were -13 [-8/-23] mmHg (*n* = 80) and -21 [-11/-41]  
 193 mmHg (*n* = 152), respectively (*p* < 0.01). In 2 TOS-s patients, only 1 EAST was performed because of  
 194 pain. For technical reasons and fatigue while standing, 1 patient did undergo the. The average DROP  
 195 in controls (-5 [-3/-7] mmHg; *n* = 80) was not significantly different from that in TOS-s patients (-4  
 196 [0/-7] mmHg; *n* = 150; *p* = 0.307).

### 197 3.3. *Ability of TcpO2 to detect symptoms*

198 As shown in Table 3, the *TcpO2* observed during the Adson's test was significantly predictive of the  
 199 presence of symptoms during the test, albeit with a small AUC, but not predictive of symptoms during  
 200 other tests or on history evaluation. In contrast, the *TcpO2* observed during the EAST could predict  
 201 symptoms during the EAST as well as during other tests and on patient history evaluation. The ROC  
 202 analysis revealed an optimal cut-off for predicting the presence of a history of symptoms or symptoms  
 during testing maneuvers of ≤ -21 mmHg.

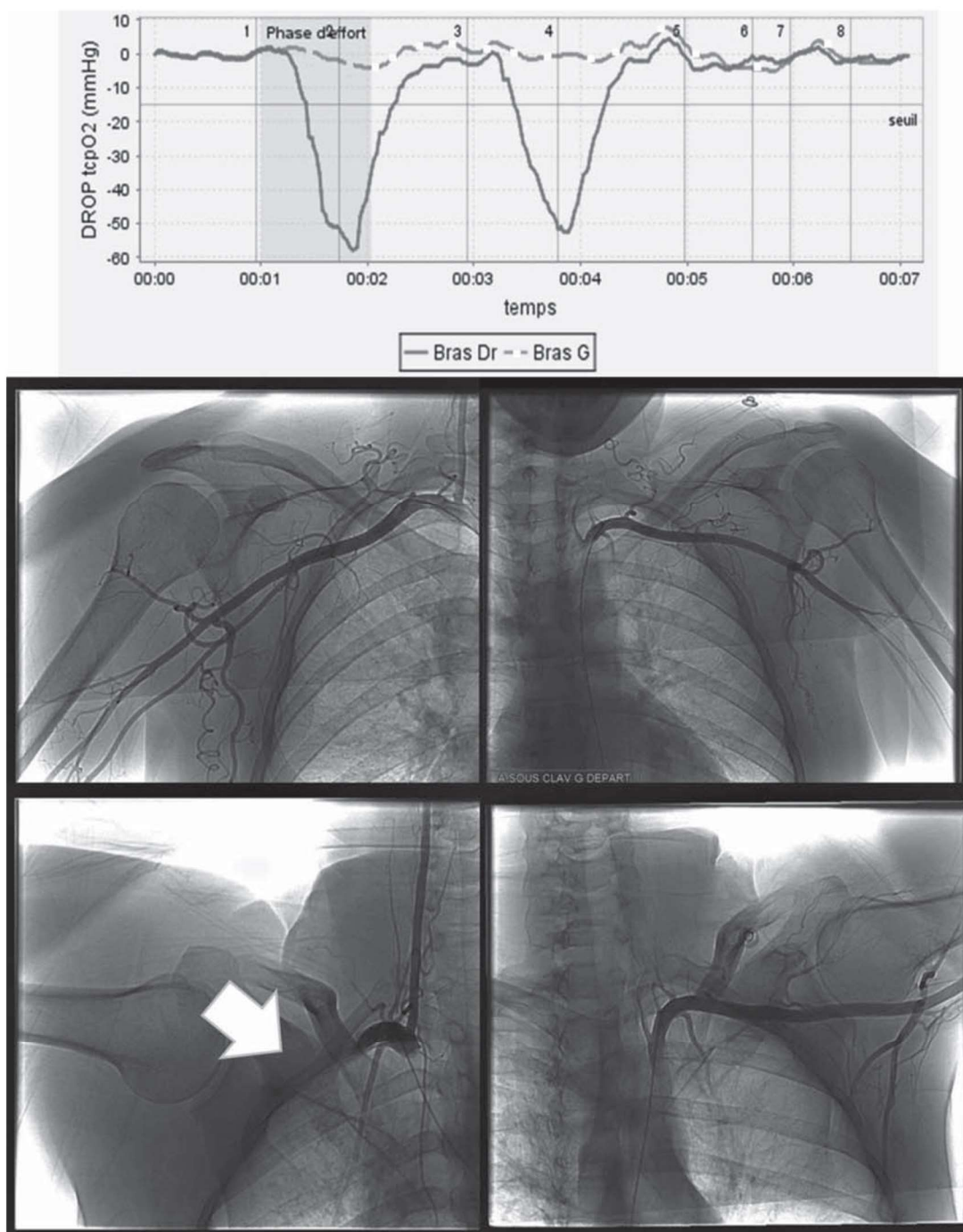


Fig. 1. Example of a 43-year-old female patient with almost permanent bilateral upper limb symptoms suspected of having thoracic outlet syndrome because of positional worsening. A duplex-scan showed dynamic arterial and venous obstructions, whereas both arteriography and transcutaneous oximetry showed strictly unilateral right arterial compression. The upper panel is the transcutaneous oxygen pressure (TcpO<sub>2</sub>) recordings during two consecutive elevated arm stress tests (starting at event markers 1 and 3 and ending at 2 and 4) followed by the first Adson's tests with the head on the right (from 5 to 6) and on the left (from 7 to 8) sides. TcpO<sub>2</sub> values in the Y axis are expressed as decrease from rest of oxygen pressure (DROp) values (mmHg). The X-axis represents the time in minutes, and "Bras Dr" and "Bras G" are the right and left arms respectively. The lower panel is the corresponding arteriographic findings in the neutral (upper images) for the right (left column) and left (right column) arms, confirming the presence of a severe right occlusion and absence of left apparent compression during arm abductions (lower images). Electromyography was considered almost normal and symptoms of the left shoulder were finally considered to be of an osteo-articular origin rather than due to a thoracic outlet syndrome.

Table 2  
Symptoms, ultrasound and TcpO2 findings during provocative maneuvers

	Controls (n = 40)	TOS-s (n = 76)	P
Positive ultrasound imaging on the right side	10 (25.0)	39 (51.3)	0.010
Positive ultrasound imaging on the left side	9 (22.5)	40 (52.6)	0.003
Symptoms during the EASTs on the right side	20 (50.0)	55 (72.4)	0.024
Symptoms during the EASTs on the left side	19 (47.5)	61 (80.3)	0.001
Symptoms during the Adson's tests on the right side	7 (17.5)	37 (49.3)*	0.001
Symptoms during the Adson's tests on the left side	7 (17.5)	41 (54.7)*	0.001
DROP during the EASTs on the right side (mmHg)	-15 [-8/-23]	-19 [-12/-35]	0.048
DROP during the EASTs on the left side (mmHg)	-12 [-8/-24]	-22 [-11/-41]	0.035
DROP during the Adson's tests on the right side (mmHg)	-6 [-3/-7]	-4 [0/-7]*	0.019
DROP during the Adson's tests on the left side (mmHg)	-5 [-3/-7]	-4 [0/-7]*	0.108
DROP in the most symptomatic upper limb, 1 test (mmHg)	-12 [-7/-22]	-21 [-10/-41]	0.029
DROP in the most symptomatic upper limb, 2 tests (mmHg)	-14 [-8/-22]	-22 [-12/-42]	0.013

\*Adson's tests were not performed in one of the TOS patients. DROP, the decrease from rest of oxygen pressure; TcpO2, transcutaneous oxygen pressure.

Table 3  
AUC analysis of TcpO2's diagnostic performance for symptoms

Symptoms			AUC±SD	P	DROP cutoff (mmHg)	Sensitivity	Specificity
+	-						
----- Symptoms by history -----							
124	106*	Adson's test	0.435 ± 0.038	0.088	x	x	x
126	106	EAST test	0.628 ± 0.036	0.001	-21	54	70.8
126	106	Both tests	0.626 ± 0.036	0.001	-20	57.1	65.1
----- Symptoms at performed tests -----							
92	138*	Adson's test	0.581 ± 0.039	0.038	-5	58.7	55.8
155	77	EAST test	0.704 ± 0.035	0.001	-20	55.5	77.9
----- Symptoms by history AND at any of the two tests -----							
115	115*	Adson's test	0.448 ± 0.038	0.174	x	x	x
117	115	EAST test	0.638 ± 0.036	0.001	-21	56.4	71.3
117	115	Both tests	0.640 ± 0.036	0.001	-21	58.1	68.7

Symptoms+ / Symptom - refer to the presence/absence of symptoms during the tests. Note that cut-off value and diagnostic performances were not calculated when the AUC was not different from a random choice: (AUC of 0.500). AUC, area under the receiver operating characteristic curve; TcpO2, transcutaneous oxygen pressure; EAST, elevated arm stress test. \*Adson's tests were not performed in one of the TOS patients.

### 3.4. Diagnostic performance of TcpO2 for positive arteriography

Of the 76 TOS-s patients, 44 underwent an arteriography. Analysis of the arteriography images found stenosis in 43 of 88 upper limbs during the Adson-type tests and 70 of the 88 upper limbs during the EAST-type tests. As a result, stenosis during one or both of the tests was found in 73 of the 88 upper limbs. The DROP values observed during the Adson's tests failed to predict the presence of ipsilateral stenosis on arteriography; the AUC was  $0.598 \pm 0.061$  ( $p = 0.117$ ) and  $0.439 \pm 0.073$  ( $p = 0.429$ ) for the Adson-type and EAST-type tests, respectively. Similarly, the DROP observed during the EAST

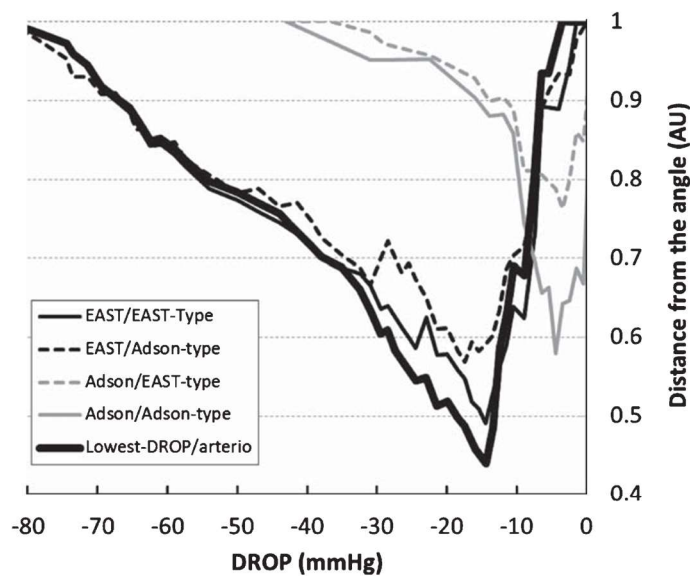


Fig. 2. Receiver operating characteristics (ROC) results showing the distance from the 100% sensitivity-100% specificity angle as a function of the DROP value observed during the tests. Note that areas under the ROC curve were significant only when the DROP results of the EAST tests were compared to the presence of a stenosis on arteriography during EAST-type maneuvers (thin black line), or when the lowest DROP observed during any of the clinical provocative maneuver was compared to the presence of a stenosis at any of the provocative tests performed during arteriography (thick black line).

failed to predict the presence of a stenosis during the Adson-type test (AUC,  $0.612 \pm 0.060$ ;  $p = 0.069$ ) but was significantly predictive during the EAST-type test (AUC,  $0.675 \pm 0.068$ ;  $p < 0.05$ ). Finally, the AUC for the lowest DROP observed during the EAST and Adson's tests was  $0.694 \pm 0.069$  ( $p < 0.02$ ). The optimal cut-off value for predicting a positive arteriogram was  $\leq -15$  mmHg as shown in Fig. 2.

Figure 3 shows the distribution of positive results for ultrasound imaging, arteriography, and TcpO<sub>2</sub> (using the pre-defined cut-off limit of 15 mmHg). For ultrasound alone, the sensitivity, specificity, PPV, and NPV for predicting a positive arteriogram were 63.0% (95% CI: 50.9-74.3), 33.3% (95% CI: 11.8-61.6), 82.1% (95% CI: 75.6-87.3), and 15.6% (95% CI: 7.9-28.7), respectively. The DOR of ultrasound with arteriography used as the gold-standard was 0.9 (95% CI: 0.3-2.8). For TcpO<sub>2</sub> alone, the sensitivity, specificity, PPV and NPV were 68.5% (95% CI: 56.6-78.8), 66.7% (95% CI: 38.4-81.2%), 90.9 (95% CI: 82.8-95.4), and 30.3 % (95% CI: 21.0-41.6), respectively. The DOR of TcpO<sub>2</sub> was 4.4 (95% CI: 1.3 vs. 14.2),  $p = 0.055$  from ultrasound.

Positive findings on both ultrasound imaging and TcpO<sub>2</sub> measurement showed a sensitivity, specificity, PPV, and NPV of 49.3% (95% CI: 37.2-61.4), 86.7% (95% CI: 59.5-98.3), 94.6% (95% CI: 82.5-98.5), and 26.5% (95% CI: 21.1-32.8), respectively, with a DOR of 6.0 (95% CI: 1.3-28.4),  $p = 0.105$  from ultrasound alone.

#### 4. Discussion

This is the first study comparing upper extremity dynamic TcpO<sub>2</sub> recordings in healthy volunteers and TOS-s patients and validating TcpO<sub>2</sub> against upper limb arteriography. The TcpO<sub>2</sub> cut-off observed in the present upper-limb study was incidentally identical to that in our previous studies at the lower limb level. We also showed that TcpO<sub>2</sub> in combination with ultrasonography trended to increase the prediction of a positive arteriogram as compared to ultrasonography alone.

Although TOS has been well-recognized for years, its diagnosis, classification, and optimal treatment remain a subject of debate [16, 17]. The most common symptoms are arm, shoulder, or supraclavicular

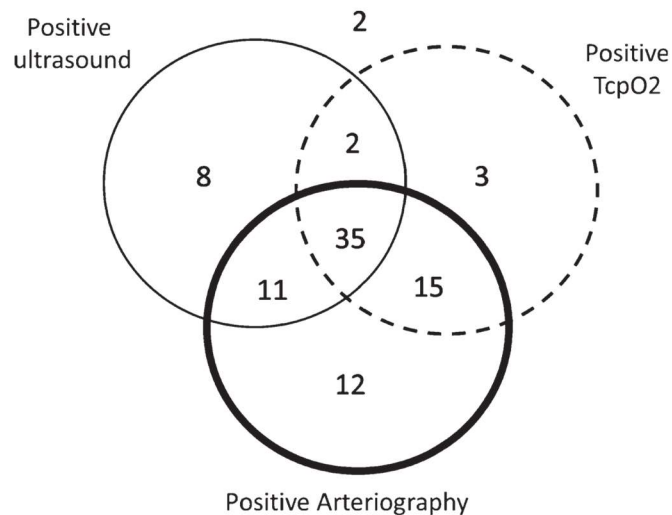


Fig. 3. Distribution of positive results (inside each circle) on ultrasound imaging (thin line circle: arterial compression), arteriography (Thick line circle: presence of > 75% stenosis), and TcpO2 (dash line circle: decrease from rest of oxygen pressure below the pre-defined cut-off limit of -15 mmHg) among the 88 upper limbs (44 patients underwent arteriography). Note that the left arm of the patient presented in Fig. 1 is among the 8 cases of isolated positive ultrasound results while the right arm is among the 35 results where all tests were consistent. TcpO2, transcutaneous oxygen pressure. Note that two tests were totally negative for all measurements.

234 pain; weakness; fatigue; and paresthesia in one or both of the upper extremities [18, 19]. The symptoms  
 235 mainly occur with arm elevation and/or abduction and are relieved once the arm is in the neutral position.  
 236 The occurrence of symptoms with simultaneous proof of arterial compression points to the diagnosis of  
 237 TOS. Compression can be detected with the observation of an arterial bruit at auscultation, a decrease  
 238 or abolition of pulse plethysmography, or positive ultrasound imaging or Doppler. Nevertheless, the  
 239 presence of arterial compression is not specific since arterial compression can remain completely  
 240 asymptomatic and can be found in apparently healthy individuals [3, 20]. The rate of false-positive  
 241 ultrasound results seems to be reduced when considering the presence of symptoms during the tests  
 242 rather than the sole history of symptom alone [21]. When TOS with typical symptoms is found, physical  
 243 therapy for at least 3 to 6 months is generally considered to be the primary treatment, although its  
 244 efficacy is unclear [22]. Surgery has shown excellent results despite some non-negligible risks [23],  
 245 resulting in TOS being considered one of the most frequent source of litigations and lawsuits in  
 246 thoracic surgery [24]. TOS can easily be misdiagnosed and many differential diagnoses need to be  
 247 considered. Finally, diagnostic and treatment decisions are generally based on a holistic approach using  
 248 different investigations including conventional radiography (searching for a long transverse process  
 249 of the seventh cervical vertebra, a cervical rib, an anomalous first rib, and fractures of the clavicle or  
 250 first rib), ultrasound or pulse plethysmography, and electromyography, as well as assessment of pain  
 251 characteristics, reliability of symptoms, and typical positional characteristics.

252 We believe that TcpO2 can provide additional clinically relevant information, has the added advantage  
 253 of being a non-invasive technique, allows for the simultaneous recording of both upper limbs,  
 254 and is not dependent on the physician's technical expertise. It directly measures overall impairment  
 255 of skin microcirculation, which could be advantageous. Many authors suggest that hand pallor results  
 256 from adrenergic vasoconstriction [7], although this explanation is inconsistent with the fact that foot  
 257 pallor is extremely rare during sciatica, another form of acute neural compression [25]. We believe  
 258 that pallor in patients with symptoms suggestive of neural compression results from the simultaneous  
 259 compression of the brachial plexus and subclavian artery [26]. Whether or not pallor arises from  
 260 arterial compression or adrenergic vasoconstriction, measuring skin microcirculation rather than arm

261 blood velocity (or pulsatility) is advantageous, since muscle adrenergic vasoconstriction is blunted by  
262 functional sympatholysis during forearm exercise [27, 28]. Unfortunately, although DORs trended to  
263 increase, the difference was not significant versus ultrasound alone likely due to insufficient number  
264 of cases.

265 However, TcpO2 measurement is a time-consuming technique, and unpredictable transcutaneous  
266 gradients are an issue. The DROP index is inherently independent from the PO2 transcutaneous gradient  
267 and accounts for eventual changes in systemic pO2 that can result from hyperventilation in response  
268 to pain. It is of interest that the -15 mmHg cut-off with respect to arteriography in the present study  
269 is similar to that found in a previous study validating exercise-induced ischemia against arteriography  
270 in patients with lower limb claudication [12, 14]. It is also noteworthy that the present study's DROP  
271 value for symptoms (-21 mmHg) is lower than the cut-off for a positive arteriography. Although the  
272 groups studied are different (significantly larger for the symptoms analysis), this is probably because  
273 compression found at arteriography may remain asymptomatic. We assume that a certain level of  
274 ischemia is required to induce symptoms, even in the presence of significant arterial compression.

275 Several reasons may underlie the discrepancies between arteriography and TcpO2. The effect of  
276 subclavian venous compression on forearm TcpO2 is unknown. Some authors found an increase,  
277 whereas others observed a decrease in calf TcpO2 during venous stasis [29, 30]. It cannot be excluded  
278 that "false-positive" TcpO2 results occurred as consequence of venous compression that remained  
279 undetected by arteriography, resulting in imperfect TcpO2 specificity. When arteriography is used as a  
280 gold-standard, positive TcpO2 results in patients with neurogenic TOS are logical despite no apparent  
281 arteriographic compression, particularly if the adrenergic vasoconstriction concept is true. Follow-up  
282 of surgically treated patients considered to have neurogenic TOS with negative arteriography is needed  
283 to define whether the decrease in TcpO2 disappears after surgery.

284 The thoracic outlet involves 3 narrow anatomic spaces: the scalene triangle, the costo-clavicular  
285 space, and the pectoralis minor space [31]. Many different maneuvers have been proposed to induce a  
286 vascular compression at these various levels. The fact that we used only the EAST and Adson's test may  
287 have resulted in "false-negative" TcpO2 results. Nevertheless, these two tests reportedly have the best  
288 sensitivity of all available provocative tests. Collateral circulation in the case of stenosis or occlusion  
289 of the subclavian artery may also normalize arm perfusion resulting in "false negative" results. Both  
290 situations may be resulting in an imperfect TcpO2 sensitivity.

291 The limitations of this study include the fact that none of the controls and not all TOS-s patients  
292 underwent arteriography. Routine arteriography was considered to be not acceptable for ethical and  
293 safety reasons, even in TOS-s patients. The decision to perform an arteriography was left to the  
294 discretion of the referring physician. In most cases, arteriography was performed only in the patients  
295 that were considered positive for TOS and eligible for surgery after failure of physical therapy to  
296 improve their symptoms. The fact that patients were referred from varying physicians and were subject  
297 to potentially heterogeneous medical decisions, even when showing a similar presentation, may have  
298 also interfered with the results. Another limitation is the time delay between ultrasonography, TcpO2,  
299 and arteriography. This might be one of the reasons underlying the inter-test discrepancies. Another  
300 possibility to explain discordant results, is the fact that arteriography was performed in the supine  
301 position while TcpO2 measurements were made with the patients standing. The effect of the body's  
302 position on vascular responses remains unknown.

303 As a conclusion: TcpO2 is useful in TOS-suspected patients and could help improve the selection  
304 of patients that should undergo arteriography. The technique allows recordable and objective mea-  
305 surements of forearm ischemia during forearm maneuvers which can be of interest in a disease for  
306 which diagnosis remains difficult and surgical treatment is a potential source of litigations and lawsuits.  
307 Whether TcpO2 can predict the outcome after surgery for patients with TOS remains to be determined.



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314 **Conflicts of interest**

315 None declared.

316 **Funding**

317 None declared.

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### 3. Exploration de repos et prédiction de la morbi mortalité des patients en ischémie de repos

#### *Sinusoidal changes in transcutaneous oxygen pressure suggesting Cheyne-Stokes respiration are frequent and of poor diagnosis among patients with suspected critical limb ischemia*

##### Contexte :

La TCPO2 est utilisée chez les patients présentant une ischémie critique. Les variations sinusoïdales de TCPO2 sont retrouvées chez les patients présentant un Cheyne Stokes (CS) avec évolution par phase crescendo/decrecendo suivie d'une apnée transitoire. Il est bien démontré que la prévalence des CS est importante chez les patients présentant une insuffisance cardiaque et sa présence augmente le risque de mortalité (36). Il existe peu de données sur la prévalence du CS chez les patients en ischémie critique. De plus les patients présentant une ischémie critique ont un risque de mortalité important indépendamment de la possibilité de revascularisation (37).

La TCPO2 est largement étudiée comme outil diagnostique de cette ischémie critique (niveau ou risque d'amputation, potentiel de cicatrisation). Elle a également été utilisée chez les patients présentant une insuffisance cardiaque et chez ces patients l'enregistrement de mouvements sinusoïdaux suggérerait une dyspnée de Cheyne Stokes (38). Cependant, la prévalence de ce phénomène chez les patients souffrant d'ischémie critique chronique n'a jamais été établie.

Le but de cette étude est de déterminer les caractéristiques de changement de TCPO2 de repos chez les patients suspects d'ischémie critique, d'observer si cela est effectivement enregistré au niveau thoracique mais également sur les sondes fixées aux membres inférieurs, définir les caractéristiques de courbes évoquant la présence d'un Cheyne Stokes, d'évaluer la prévalence dans notre population et d'étudier l'impact sur le devenir du patient.

##### Matériel et Méthodes :

Analyse rétrospective de 300 courbes thoraciques afin de déterminer la présence ou l'absence de Cheynes Stokes par analyse visuelle. Il a d'abord été déterminé l'erreur acceptable dans la régularité des pics par analyse des courbes ROC chez les patients présentant un Cheynes Stokes typique à la TCPO2 mais un profil non sinusoïdal. Puis il a été défini un minimum de 5 pics, une déviation standard de TCPO2 de  $> 1,25\text{mmHG}$ , une erreur de la régularité des pics en cross corrélation de  $< 10\%$ , une longueur de cycle de 30 à 100 secondes. Réalisation d'une comparaison du devenir des patients en fonction de la présence ou non d'un profil CS par modèle de Cox.

##### Résultat :

43 patients présentaient les 4 critères au niveau thoracique mais seulement 23 les présentaient également au niveau des membres inférieurs. Au cours du suivi, la présence d'un profil de courbe CS était significativement associée à un risque de mortalité augmenté (HR 2.69 [95%CI: 1.37-5;30];  $p < 0,05$ )

Il s'agit de la première étude rapportant les profils sinusoïdaux chez les patients suspects d'ischémie critique.

Conclusion :

Les profils Cheyne Stokes sont fréquents et impactent le devenir des patients présentant une ischémie critique de membres inférieurs.

Ces anomalies d'oxymétrie viennent aggraver les phénomènes de perfusion ce qui grève fortement le pronostic vital et va par conséquent pondérer la prise en charge thérapeutique, notamment chirurgicale, même si cela nécessite des études plus approfondies.



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## Sinusoidal changes in transcutaneous oxygen pressure, suggesting Cheyne-Stokes respiration, are frequent and of poor prognosis among patients with suspected critical limb ischemia

Jeanne Hersant<sup>a</sup>, Pierre Ramondou<sup>a,b</sup>, Wojciech Trzepizur<sup>c</sup>, Frederic Gagnadoux<sup>c</sup>,  
Jean Picquet<sup>d</sup>, Pierre Abraham<sup>a,b,e,\*</sup>, Samir Henni<sup>a,b</sup>

<sup>a</sup> Vascular Medicine, University Hospital, Angers, France

<sup>b</sup> UMR INSERM 1083 CNRS6015, University of Angers, France

<sup>c</sup> Pneumology, University Hospital, Angers, France

<sup>d</sup> Vascular and Thoracic Surgery University Hospital, Angers, France

<sup>e</sup> Sports Medicine, University Hospital, Angers, France

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## ABSTRACT

**Background and aims:** Transcutaneous oxygen pressure (TepO<sub>2</sub>) is used in patients with suspected critical limb ischemia (CLI). Sinusoidal changes (SC-) in TepO<sub>2</sub> are found in patients with Cheyne-Stokes respiration (CSR). We aimed to determine the characteristics of TepO<sub>2</sub> changes at rest in patients with suspected CLI, define the objective criteria for SC ~ TepO<sub>2</sub> patterns (SC+), and estimate the prevalence of SC+ in our population and its impact on the outcome.

**Methods:** We retrospectively analyzed 300 chest TepO<sub>2</sub> recordings performed in a 16-month period. We determined the presence/absence of SC ~ TepO<sub>2</sub> by visual analysis. We determined the acceptable error in the regularity of peaks of the cross-correlation with ROC curve analysis, among patients with typical SC ~ TepO<sub>2</sub> and non-sinusoidal patterns. Then, we defined SC+ as a minimum of five peaks, a standard deviation of TepO<sub>2</sub> > 1.25 mmHg, an error in regularity of peaks of the cross-correlation < 10%, and a cycle length between 30 and 100 s. In patients included until October 2019, we compared the outcome as a function of SC+ or SC- with Cox models.

**Results:** Mathematical detection of SC+ found that 43 patients (14.3%) fulfilled all four defined criteria at the chest level, but only 23 did so at the limb level. In the follow-up of 207 patients, the presence of SC ~ TepO<sub>2</sub> at the chest significantly increased the risk of mortality: hazard ratio: 2.69 [95%CI: 1.37–5.30];  $p < 0.005$ .

**Conclusions:** SC ~ TepO<sub>2</sub> is frequent, and is associated with a poor outcome in patients with suspected CLI.

## 1. Introduction

Cheyne-Stokes respiration (CSR) is considered to be rare in the general population and is characterized by regular cycles of crescendo and decrescendo changes in breathing amplitude, followed by periods of transient apnea. The prevalence of CSR is high in patients with heart failure, and its presence increases the mortality of affected patients [1, 2]. To the best of our knowledge, little is known about the prevalence of CSR in patients with lower extremity arterial disease. Patients with critical limb ischemia [3], or “chronic limb-threatening ischemia” [4] (CLI), have a high risk of morbidity and mortality [5,6], independently of the possibility of vascularization of the affected limb [7,8], or of the

type of revascularization [9]. Transcutaneous oxygen pressure (TepO<sub>2</sub>) is largely used as a diagnostic tool for CLI, to classify the risk of amputation in CLI patients, or to estimate the probability of healing of lower limb ulcers suspected to be of vascular origin [10–15]. TepO<sub>2</sub> has also been used for the evaluation of treatment of CSR in heart failure patients [16]. In these patients, CSR resulted in the presence of sinusoidal changes (SC-) in the TepO<sub>2</sub> values [16]. Amazingly, despite the worldwide use of TepO<sub>2</sub> in patients referred for TepO<sub>2</sub> measurements for suspected CLI, the prevalence of SC ~ TepO<sub>2</sub>, assumed to result from CSR in such patients, has never been reported.

We hypothesized that in patients with suspected CLI, the computer recording of TepO<sub>2</sub> could allow an estimation of the SC ~ TepO<sub>2</sub>

\* Corresponding author. Vascular Medicine, University Hospital, Angers, France.  
E-mail address: [piabraham@chu-angers.fr](mailto:piabraham@chu-angers.fr) (P. Abraham).

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prevalence. First, we analyzed the characteristics of  $TcpO_2$  changes at rest in patients with suspected CLI and verified whether or not SC ~  $TcpO_2$  patterns were observed at both limb and chest levels. Second, we proposed objective criteria for the presence (SC+) or absence (SC-) of SC patterns in  $TcpO_2$  recordings. Third, we estimated the prevalence of SC + (assumed to result from CSR) in our population, using these objective criteria. Finally, we compared the incidence of mortality in patients with SC + versus SC-.

## 1. Materials and methods

### 1.1. Population

The referral population was all the patients referred to the Vascular Medicine service of the University Hospital in Angers for  $TcpO_2$  investigations at rest because of suspicion of CLI (resting pain, or wound). Almost all patients were Caucasian; race and ethnicity were not recorded. During their medical visit, we systematically recorded the indication of the test, age, height, body weight, sex, systolic and diastolic pressure, history of diabetes mellitus, cardiac or respiratory insufficiency. For patients of the “New Oxymetry Variability Indices in Critical limb ischemia (NOVICE)” protocol, patient files were re-analyzed to record the information available at the date of the  $TcpO_2$  visit focusing on the presence/absence of lower extremity arterial disease (LEAD), and ongoing treatments. Ongoing treatment was simplified as categories focusing on: beta-blockers, antiplatelet or anticoagulant drugs, sartan or renine-angiotensine inhibitors or diuretic, cholesterol lowering drugs, psychotropic drugs, and pain killers. The presence of LEAD was based on the presence of either: an abnormal ultrasound imaging (occlusion or significant stenosis at rest of an arterial trunk, or a history for revascularization), an ankle brachial index  $\leq 0.90$  (non-measurable or non-compressible ankle pressures were considered not contributive for the presence of stenosis or occlusions of distal arteries), or a toe brachial index  $\leq 0.70$ .

### 1.2. Ethical considerations

The ethics committee has approved the “Critical Ischemia and TRAnscutaneous oximetry (CITRA)” study for the retrospective analysis of patients with suspected CLI referred for  $TcpO_2$  recordings, searching for sinusoidal changes in the recordings, under reference 2019-44. It was registered in Clinicaltrials.gov: NCT04369781. At admission, patients were aware that their medical file could be used for research purposes, and of their right to deny the use of the medical file at any time. As an analysis of our routine practice, according to the French Law, individual written consent was not required from the patients. If patients deny the use of their files for research purposes, this decision was recorded in the patient’s administrative file. Exclusion criteria for “CITRA” were missing or corrupted chest or limb  $TcpO_2$  recording,  $TcpO_2$  recordings  $< 5$  min. The NOVICE follow-up study aimed at determining the outcome of patients referred for suspected CLI (Clinicaltrials.gov: NCT04209998). This required second specific information to patients of CITRA. The exclusion criterion for NOVICE was a rebuttal of follow-up since the visit to our laboratory. Both studies conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The corresponding author has full access to all the data in the study and takes responsibility for its integrity and data analysis. Data is accessible upon reasonable request from the author or promoter.

### 1.3. Transcutaneous oximetry

As it has been performed per routine and for decades in our department,  $TcpO_2$  (TINA TCM400, Radiometer, Copenhagen, Denmark) was measured on the limb and at chest level while the patients rested in an air-conditioned room at a temperature of  $2 \pm 2$  °C. Calibration was performed twice before each session, as recommended

by the manufacturer. Each electrode temperature was set to 44.5 °C to heat the underlying tissue and maximize local vasodilation and gas diffusion through the skin [17]. The electrodes were screwed in fixation rings below the right clavicular prominence and at the dorsal aspect of the foot, or as distal as possible in case of amputation. In patients with known right subclavian artery occlusion or a history of right thoracotomy, the chest probe was placed on the left side. The probe at the chest accounts for systemic  $pO_2$  changes during eventual provocative maneuvers [18]. A minimal pretest heating period of 15 min was required to allow local heating of the skin. On our routine, patients were resting alone in the room, and a timer was used to recall the nurse in charge of the test to retrieve the values appearing on the screen of the TCM400 apparatus after this pretest heating period, while the patient was in the recumbent position. Whether or not all patients remained awakened was not determined. Sensitization maneuvers (such as leg elevation or leg lowering), pending on values observed at rest, were performed. All recordings were stopped after a minimum of 5 min after the end of the sensitization procedures with the patient returned to the resting recumbent position.

### 1.4. Recording of $TcpO_2$

Since mid-November 2018, a custom-made program has become available to allow real-time recording of  $TcpO_2$  tests performed in our service [19]. Since then, the TCM400 was connected to a computer that allowed recording data on a 1 Hz basis. The program was to be used on a routine basis to allow post-procedure quality control by the physician in charge of test interpretation. For most patients, the recording was started at the beginning of the test and was stopped once all procedures were completed. After the investigation, anonymized data were saved as text file spreadsheets for offline analysis.

### 1.5. Calculation of number of subjects

Based on the prevalence of CSR in patients with cardiovascular (cardiac) diseases [1], we estimated that the prevalence of CSR (and then of SC +) in our population could be as high as 15%. The minimum number of observations to have a confidence level of 95% and that the real value was within  $\pm 5\%$  of the expected value was 196. Based on the laboratory’s past activity and progressive use of the program by our nurses, we calculated that a period of 16 months was required to reach the required number of tests. We then analyzed the  $TcpO_2$  recordings performed in our laboratory between 15 November 2018 and 15 March 2020. For patients referred multiple times, only the first recording was kept for analysis.

### 1.6. Data collection and visual analysis

For all included patients, we retrieved medical files and  $TcpO_2$  recordings performed. Then,  $TcpO_2$  recordings were analyzed on an Excel spreadsheet, and graphs of chest and limb recording against time were visually analyzed. The visual analysis of the chest recording was classified as “typically sinusoidal,” “possible”, or “non-sinusoidal” patterns. The “possible” classification was based mainly on the observation of transient sinusoidal pattern, while the rest of the recording showed no apparent sinusoidal pattern, sinusoidal patterns of moderate amplitude, or relatively unstable rhythmicity of the changes. Then, observers selected a period of interest focusing on the suspected area of a minimum of 5 min to be analyzed mathematically. Note that this period could be different at the chest and limb levels to optimize the detection at each probe position.

### 1.7. Analysis of data

Variables in chart reviews, results of  $TcpO_2$  analyses, and follow-up search results were anonymized and assembled in a database using an

Excel spreadsheet.

From the TcpO<sub>2</sub> recordings:

- 1 We counted the number of consecutive peaks in the selected period.
- 2 We estimated the standard deviation of the TcpO<sub>2</sub> values over the period of interest.
- 3 We estimated the length of each cycle from the autocorrelation analysis of the data.
- 4 We analyzed the regularity of the peaks of the autocorrelation analysis, as a way of confirming that the initial signal was sinusoidal. Indeed, in case of SC changes, the ratio of time for the occurrence of the second (T<sub>2<sup>nd</sup></sub>) and third (T<sub>3<sup>rd</sup></sub>) peaks to the time of occurrence of the first peak (T<sub>1<sup>st</sup></sub>) on the cross-correlation analysis should be 2 and 3, respectively, confirming that the second and third peaks are harmonics of the first peak [20]. Then, we determined the time for the peaks for the first, second, and third peaks, and calculated the (T<sub>2<sup>nd</sup></sub>/T<sub>1<sup>st</sup></sub>) and (T<sub>3<sup>rd</sup></sub>/T<sub>1<sup>st</sup></sub>) time of peak ratios. Last, we calculated the absolute relative errors of these ratios from their theoretical values using the following formulas: %D<sub>2/1</sub> = ((T<sub>2<sup>nd</sup></sub>/T<sub>1<sup>st</sup></sub>) - 2)/2 · 100 and %D<sub>3/1</sub> = ((T<sub>3<sup>rd</sup></sub>/T<sub>1<sup>st</sup></sub>) - 3)/3 · 100. When both %D<sub>2/1</sub> and %D<sub>3/1</sub> were available, we used the higher of the two ratios (H%D) to determine the optimal H%D to be used to determine the presence of a sinusoidal pattern. Using the H%D, we aimed to determine the acceptable H%D to discriminate non-sinusoidal from sinusoidal results. We then excluded "possible" results and used the ROC analyses. In ROC analysis, the optimal cutoff point was to minimize the distance of the curve to the 100/100% sensitivity/specificity angle. Fig. 1 illustrates the different steps of the recordings and analyses.

### 1.1. Determination of the prevalence of SC+

To determine the presence (SC<sub>+</sub>) or absence (SC<sub>-</sub>) of SC ~ TcpO<sub>2</sub> on objective criteria, we applied the following criteria to our results on chest (Chest-SC) and limb (Limb-SC):

- 1 Number of consecutive peaks in the selected period ≥ 5.
- 2 A minimal SD value ≤ 2.25 mmHg. This arbitrary value correspondsto a minimum amplitude of sinusoids of 3.5 mmHg while excluding random changes of less than 8 mmHg approximately.
- 3 A cycle of autocorrelation between >30 s and <100 s.
- 4 H%D inferior to the cutoff point determined from the ROC analysis.

### 1.2. Determination of outcome

Follow-up time for patients included in "CITRA" until October 2019 (n = 211), and not denying the "NOVICE" study, was considered as the interval between the date of TcpO<sub>2</sub> recording until the occurrence of death or until the subject was censored (lost to follow-up after a minimum period of 3 months monitoring and a maximum of one year or until March of 2020 without death). This last point aimed to avoid the integration of the COVID-19 epidemic period that occurred in April in the Loire valley. For the follow-up, the outcome was determined on office follow-up and from the hospital patient file. If office follow-up visits were not available, alternate data sources included medical records from other hospital departments, the local electronic medical database, and telephone interviews of the referring physician.

### 1.3. Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and "R" (R-foundations for statistical computing,

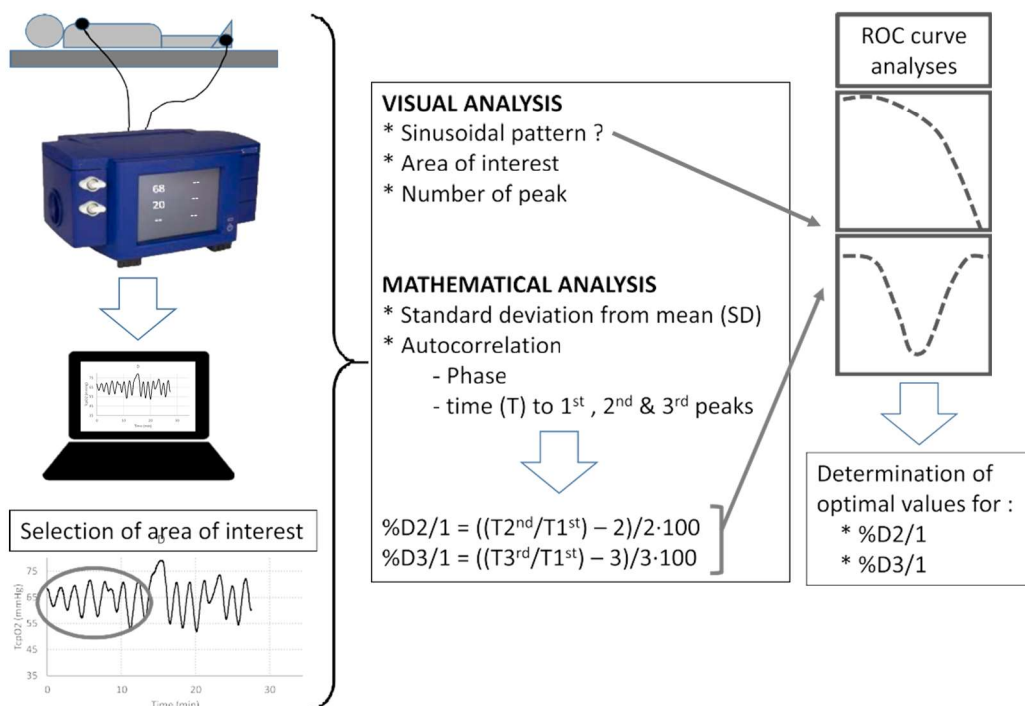


Fig. 1. Schematic representation of the CITRA protocol.

Vienna, Austria). Considering the normality of the continuous variable, either *t*-test or the Wilcoxon signed ranks test were performed, and results were expressed as mean  $\pm$  SD or median with 25/75<sup>o</sup> centiles. Proportions are reported with 95% confidence intervals when appropriate. Categorical variables expressed as percentages were compared using the Fisher exact test. Survival analysis was represented using Kaplan–Meier method. Univariate analysis models were performed with a log-rank test to detect differences in overall survival. Thereafter, multivariate analysis were performed to account for potential confounders of the CSR to mortality relationship eventually found in the univariate models taking into account: Age <75 or  $\geq$ 75 years old, the presence or absence of cardiac insufficiency, respiratory insufficiency, LEAD, diabetes mellitus, ongoing treatments with the previously defined drug categories. Models validity were evaluated by analysis of the Schoenfield’s residuals. Two models were performed: one for chest-SC, and one for limb-SC. Last, comparison of these two models was performed using the partial likelihood ratio test for mis-specified nonnested semi-parametric Cox model [21]. For both the univariate and multivariate models, hazard ratios are reported with 95% confidence intervals [95%CI]. For all statistical tests, a two-tailed probability level of  $p < 0.05$  was used to indicate statistical significance. Non-significant results are reported as N.S.

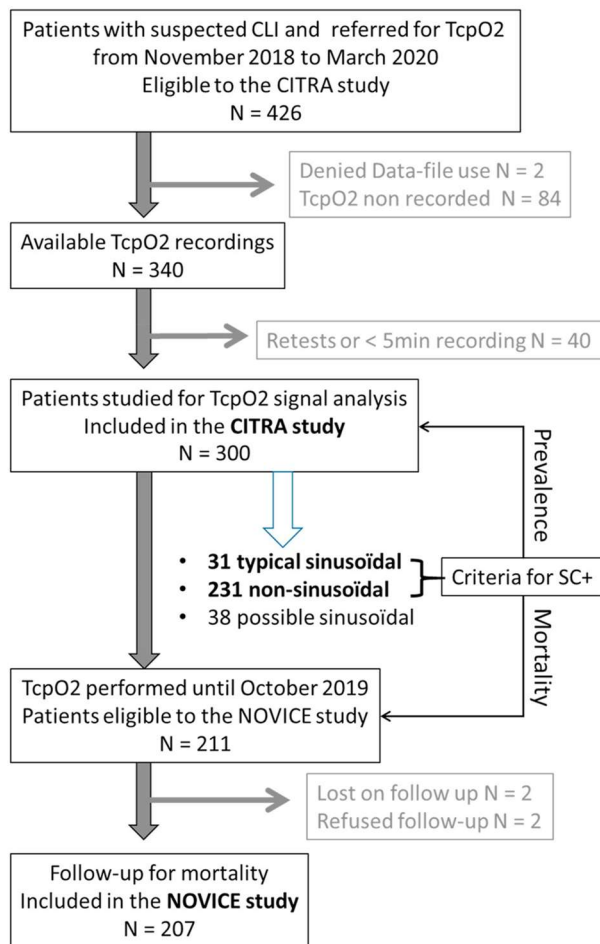


Fig. 2. Flowchart of the study.

## 1. RESULTS

As shown in Fig. 2, throughout the “CITRA” study period of analysis, 426 patients were referred to our laboratory. Note that most of the 84 tests that were not recorded on a computer in the first three months of program availability were due to the progressive learning of program used by nurses and computer issues. Since May 2019, an average of 92% of the TcpO<sub>2</sub> performed have been electronically recorded. We finally had 300 recordings from different patients (197 males/103 females), aged 76.0  $\pm$  12.1 years, BMI 27.5  $\pm$  6.4 kg/m<sup>2</sup>. The absolute chest TcpO<sub>2</sub> was on the average 55.9  $\pm$  13.9 mmHg, and limb TcpO<sub>2</sub> was 28.3  $\pm$  19.9 mmHg.

On the visual analysis of each recording, 31 (10.3%; 95CI: 7.1–14.3%) of the chest recordings were encoded “typically sinusoidal,” and 38 (12.7%; 95CI: 9.13–17.0) recordings were encoded “possible.” The remaining 231 recordings were encoded as non-sinusoidal. Examples of “typical” and “possible” sinusoidal chest patterns and their simultaneous limb recordings are presented in Fig. 3.

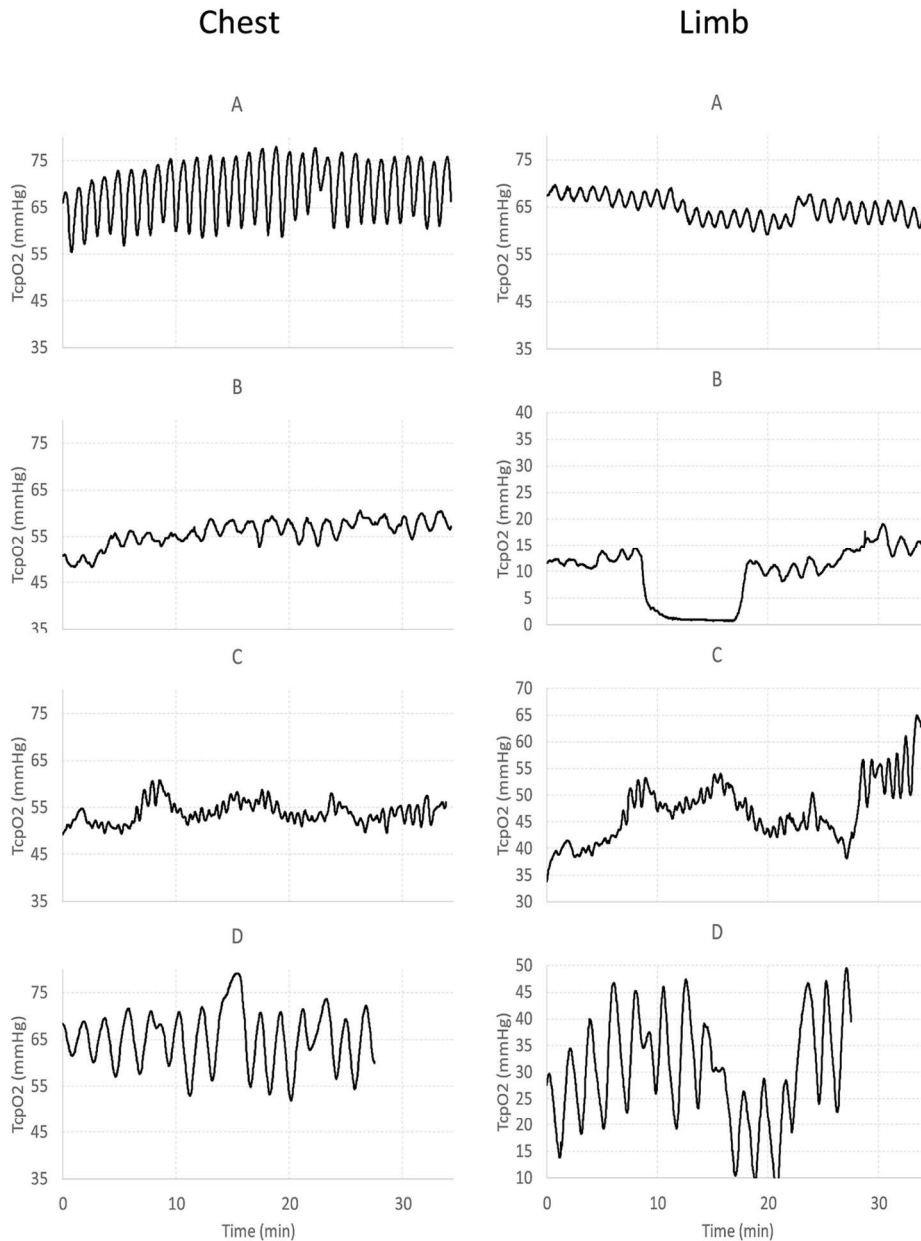
Fig. 4 illustrates the selection of the area of interest in a patient with a typical sinusoidal pattern of the chest recording. Note that in patients who were visually classified as having a non-sinusoidal pattern, we tried to focus on an area of eventual TcpO<sub>2</sub> instability. On the selected 5-min areas of interest, at the chest level, in 92 patients, no transient TcpO<sub>2</sub> peaks were found in the recording. For the other 208 observations, the visual analysis identified one to 25 peaks with a median number of 5 [3–8]. The variability of absolute chest TcpO<sub>2</sub> recordings found in the 300 recordings was 1.93 (1.28–2.95) mmHg. At the limb level, in 134 patients, no transient peaks were found in the recording. For the other 166 observations, the visual analysis identified from one to 25 peaks with a median number of four [2–6]. The variability of absolute limb TcpO<sub>2</sub> recordings found in the 300 recordings was 1.85 (1.18–2.91) mmHg.

From the cross-correlation analysis, the presence of a first, second, and third peak was found in only 254, 226, and 188 recordings, respectively, at the chest level, and in 215, 173, and 132 recordings, respectively, at the limb level. When present, the delay for the occurrence of the first peak of the cross-correlation analysis (phase of the sinusoid in case of the sinusoidal pattern) was 110 (62–211) s (n = 254) at the chest and 158 (84–253) s (n = 216) at the limb levels, respectively. When both %D<sub>2/1</sub> and %D<sub>3/1</sub> were available in the cross-correlation analysis, %HD (highest of the %D<sub>2/1</sub> and %D<sub>3/1</sub> ratios) was  $\leq$ 5% in 43 cases,  $\leq$ 10% in 52 cases, and  $\leq$ 15% in 69 of the 188 chest results. At the limb level, results were  $\leq$ 5% in 23 cases,  $\leq$ 10% in 42 cases, and 15%  $\leq$  in 54 of the 132 limb results. After exclusion of “possible” visual results, the ROC curve analysis determined that %HD 19% provided the best cutoff point to discriminate sinusoidal patterns from non-sinusoidal patterns at both the chest and limb levels. This cutoff had a sensitivity of 90.3% and a specificity of 76.2% at the chest level and a sensitivity of 73.9% and specificity of 80.2% at the limb level and with areas of 0.904 0.028 ( $p < 0.001$ ) and of 0.817 0.053 ( $p < 0.001$ ) for chest and limb ROC surfaces, respectively. Then, we applied H%D < 10% as the last criterion for the objective determination of SC ~ TcpO<sub>2</sub> prevalence in the CITRA, and analysis of mortality in the NOVICE studies.

Using the four predefined criteria (including H%D < 10%) on the areas of interest, we found 43 patients who fulfilled all four criteria at chest level, this resulted in a prevalence of 14.3% (95%CI: 10.4%–18.3%) of SC in our population. When considering the limb results, only 23 patients fulfilled all four criteria, which resulted in an apparent prevalence of only 7.7% (95%CI: 4.7%–10.7%), based on limb results. Table 1 reports the characteristics of patients with (SC+) or without SC ~ TcpO<sub>2</sub> (SC-) based on chest TcpO<sub>2</sub> mathematical analysis.

Characteristics of the sub-group of 207 patients that accepted the NOVICE follow-up are reported in Table 1. Note that the difference in systolic pressure observed for the CITRA population was not found in the CITRA subgroup. During the follow-up period, 43 (20.8%) patients died,





**Fig. 3.** Four typical examples (patients A to D) of sinusoidal patterns with various amplitude and various cycle lengths. In patient B, limb elevation results in TcpO<sub>2</sub> being almost zero and with no visible sinusoids, whereas the sinusoidal pattern persisted during limb elevation in patient D. Note that the time scale is similar for all recordings and that the range of all TcpO<sub>2</sub> scales is 40 mmHg to facilitate the comparison of the different amplitudes of sinusoids.

with the shortest delay being 6 days after TcpO<sub>2</sub> recording. The presence of SC+, based on objective criteria applied to limb results, found no significant difference in mortality between limb-SC+ and limb-SC- patients: hazard ratio: 1.35 [95%CI: 0.46-3.99];  $p = 0.559$ . As shown in Fig. 5, the presence of SC ~ TcpO<sub>2</sub> based on objective criteria applied to chest recordings (Chest-SC<sub>+</sub>) was associated with a significant increase in mortality over the follow-up period: Hazard ratio: 2.69 [95%CI: 1.37-5.30];  $p = 0.003$ .

Results for the multivariate analysis are reported in Table 2 and confirm that chest-SC is still significantly associated with mortality after adjustment for possible confounders. Of interest is to note that the hazard ratio for chest SC ~ TcpO<sub>2</sub> observed after adjustment for age is

almost similar to the one resulting from the univariate analysis. Also of interest is to note that if limb-TcpO<sub>2</sub> is used, age  $\geq 75$  years is the only factor associated with mortality. Last, comparison of CoX models for chest-SC and limb-SC confirms that chest-TcpO<sub>2</sub> is preferable to limb-TcpO<sub>2</sub> analysis, with a significant difference between these two measurements in their association with mortality:  $p = 0.0258$ .

## 1. Discussion

Our study is the first to report sinusoidal oscillatory patterns of TcpO<sub>2</sub> recordings in patients with suspected CLI and their relationship to mortality.

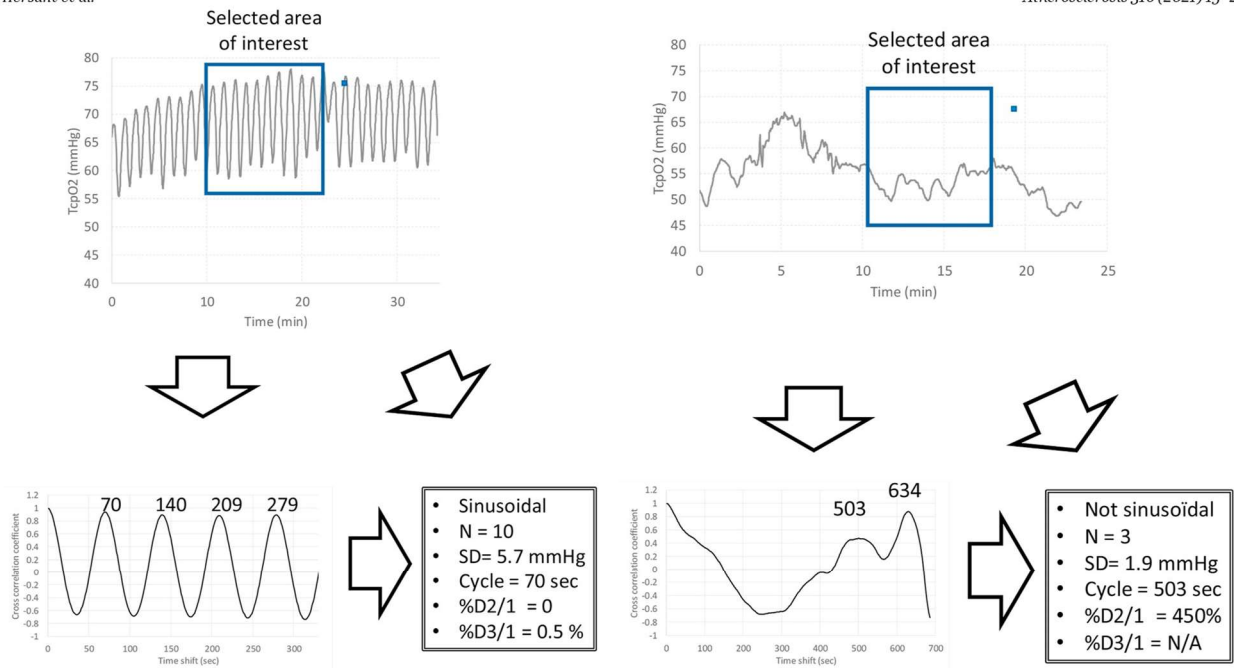


Fig. 4. Two examples of recordings with (left panel) or without (right panel) sinusoidal changes. After selection of an area of interest, lower panels are the respective results for each of the studied criteria and cross-correlation analyses.

Table 1  
Characteristics of the patients fulfilling (SC+) or not fulfilling (SC-) mathematical analysis of the recordings.

	CITRA group			NOVICE sub-group		
	Chest SC+ (n = 43)	Chest SC- (n = 257)	p value	Chest SC+ (n = 27)	Chest SC- (n = 180)	p value
<b>Characteristics</b>						
Age (years)	79.5 ± 12.7	75.4 ± 12.0	0.053	80.3 ± 12.1	75.6 ± 12.0	0.060
Male sex	30 (69.8%)	167 (65.0%)	0.541	20 (74.1%)	117 (65.0%)	0.392
Height (cm)	167 ± 10	167 ± 10	0.652	170 ± 12	168 ± 17	0.508
Weight (kg)	79.4 ± 26.3	77.4 ± 20.3	0.641	79.6 ± 27.1	76.4 ± 20.2	0.489
BMI (kg/m <sup>2</sup> )	27.8 ± 7.4	27.6 ± 6.3	0.855	27.2 ± 7.8	26.9 ± 6.8	0.844
<b>Ongoing treatments</b>						
Beta blockers	15 (34.9%)	80 (31.1%)	0.624	9 (33.3%)	60 (33.3%)	1.000
Antiplatelet or anticoagulant	26 (60.5%)	183 (71.2%)	0.156	16 (59.3%)	135 (75.0%)	0.086
RAA inhibitors or diuretics	24 (55.8%)	155 (60.3%)	0.578	16 (59.3%)	111 (61.7%)	0.811
Cholesterol lowering drugs	16 (37.2%)	119 (46.3%)	0.268	10 (37.0%)	90 (50.0%)	0.209
Psychotropic agents	12 (27.9%)	81 (31.5%)	0.635	10 (37.0%)	63 (35.0%)	0.836
Pain killers	20 (46.5%)	108 (42.0%)	0.582	12 (44.4%)	83 (46.1%)	0.871
<b>Arm arterial blood pressure</b>						
Systolic pressure (mmHg)	123 ± 20	135 ± 23	0.001	129 ± 20	134 ± 23	0.326
Diastolic pressure (mmHg)	72 ± 17	74 ± 15	0.309	76 ± 18	76 ± 15	0.833
<b>Positive tests for lower extremity artery disease</b>						
Positive ultrasound	38 (88.4%)	241 (93.8%)	0.199	23 (85.2%)	177 (98.3%)	0.001
Ankle/brachial index ≤ 0.90	21 (48.8%)	111 (43.2%)	0.490	14 (51.9%)	76 (42.2%)	0.347
Toe/brachial index ≤ 0.70	13 (30.2%)	71 (27.6%)	0.725	7 (25.9%)	48 (26.7%)	0.768
Any of the three above	40 (93.0%)	246 (95.7%)	0.438	27 (100%)	177 (98.3%)	-
<b>Symptoms at referral</b>						
Rest pain without wound	5 (11.6%)	42 (16.3%)	0.431	2 (7.4%)	23 (12.8%)	0.425
Wounds	38 (88.4%)	215 (83.7%)	0.431	25 (92.6%)	157 (87.2%)	0.425
<b>History of</b>						
Diabetes mellitus	15 (34.8%)	125 (48.6%)	0.094	9 (33.3%)	90 (50.0%)	0.147
Respiratory insufficiency	7 (16.3%)	29 (11.3%)	0.351	4 (14.9%)	21 (11.7%)	0.750
Cardiac insufficiency	15 (34.8%)	76 (29.6%)	0.482	8 (29.6%)	62 (34.4%)	0.670
<b>Transcutaneous oxygen pressure at:</b>						
Chest level (mmHg)	56.1 ± 10.3	55.9 ± 14.4	0.929	56.2 ± 10.4	56.4 ± 14.2	0.939
Limb level (mmHg)	24.1 ± 21.1	29.0 ± 19.6	0.159	23.6 ± 19.4	27.9 ± 19.7	0.292

Results are mean ± standard deviation or number of observations and proportions within the group. BMI is defined as the body mass index. AP is for arm pressure; RAA is for renin-angiotensin-aldosterone system. Positive ultrasound is occlusion or significant stenosis at rest of an arterial trunk, or a history of revascularization.

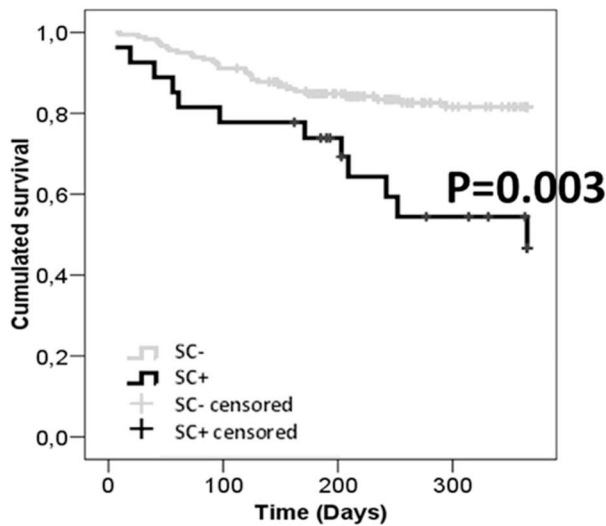


Fig. 5. Survival rate of patients included in the NOVICE study: SC+ and SC- refer to patients who fulfill or do not fulfill the criteria for the presence of sinusoidal changes in the chest transcutaneous oxygen pressure values.

TcpO<sub>2</sub> is a cornerstone for the investigation of patients with suspected CLI. TcpO<sub>2</sub> requires local heating of the skin to allow stable maximal local vasodilation, which decreases the tissue to surface transcutaneous gradient. Microvascular studies have shown that stable maximal vasodilation is attained after 10 or 15 min of local heating [22, 23]. Therefore, in clinical routine and in addition to the duration of the calibration process, time is required after probe positioning before measurements can be recorded, making TcpO<sub>2</sub> a time-consuming approach. Arsenault et al. studied the association between the risk of lower limb amputation healing failure leading to amputation revision and a TcpO<sub>2</sub> level below cutoffs of 10–40 mmHg. The relative risk of lower limb amputation healing failure for patients with a TcpO<sub>2</sub> value

below a cutoff appears to decrease with increasing cutoff values, while no single cutoff appeared optimal [24]. This is not surprising due to the unpredictable transcutaneous gradient. Indeed, a moderately low absolute limb TcpO<sub>2</sub> value can either result from a low tissue pO<sub>2</sub> associated with a low transcutaneous gradient, or from a normal tissue pO<sub>2</sub>, but is associated with a high transcutaneous gradient. Despite this uncertainty in absolute values, relative changes in chest TcpO<sub>2</sub> have repeatedly shown a good correlation with changes in tissue or arterial pO<sub>2</sub>[25,26].

TcpO<sub>2</sub> has been previously used to study the changes in CSR cycles under treatment [16]. In heart failure patients, the measurement site to detect oxygen saturation changes in CSR does not seem to matter [27]. In our patients, SC ~ TcpO<sub>2</sub> observed at the chest level may not be visible at the limb level (specifically in case of low limb absolute value), underlying the interest of the use of a chest probe in CLI-suspected patients. It is important to note that the oscillations that we searched have a reasonably low temporal frequency. Clark-type electrodes are reported to provide a 90% response to an abrupt change in the value to be recorded, ranging from 20 to 25 s [28]. TcpO<sub>2</sub> changes are comparable with photoelectric probes but seem to be slower with paramagnetic probes [29,30]. Therefore, it is uncertain whether the present results with Clark-type electrodes could be observed with all TcpO<sub>2</sub> technologies.

Cheyne-Stokes respiration (CSR), sometimes referred to as Hunter-Cheyne-Stokes breathing, is a type of breathing disorder characterized by cyclical episodes of apnea, followed by increasing then decreasing ventilation amplitude, resulting in sinusoidal changes in arterial pO<sub>2</sub>. Although visual analysis can detect the SC ~ TcpO<sub>2</sub> changes, we used the autocorrelation to confirm with objective criteria that the second and third peaks were harmonic values of the first peak, which characterizes a sinusoidal pattern. Beyond CSR, there are multiple types of abnormal respirations that potentially lead to permanent or transient hypoxemia at rest, including sleep obstructive apnea syndrome, chronic hypoventilation, Kussmaul respiration, sighing respiration, Biot respiration, apneustic breathing, and central neurogenic hypoventilation [31]. CSR is different from most abnormal respirations, and also from obstructive sleep apnea syndrome. The ventilation cycle length in

Table 2

Results of the multivariate analysis of chest (upper panel) and limb (lower panel) recordings for the detection of sinusoidal changes in transcutaneous oxygen pressure (SC ~ TcpO<sub>2</sub>) adjusted for possible confounders.

	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	p
Chest SC- TcpO <sub>2</sub>	2.40	1.19	4.83	0.014
Age ≥75 years old	2.45	1.13	5.31	0.023
Use of beta-blockers	1.75	0.93	3.28	0.083
Respiratory insufficiency	1.61	0.85	3.02	0.142
Lower extremity artery disease	1.34	0.14	12.79	0.800
Pain killers	1.22	0.63	2.35	0.559
Diabetes mellitus	1.21	0.59	2.46	0.605
Cardiac insufficiency	1.19	0.61	2.30	0.615
Use of diuretics or RAA inhibitors	1.04	0.52	2.10	0.906
Use of cholesterol lowering drugs	1.01	0.50	2.07	0.969
Psychotropic drugs	0.98	0.50	1.91	0.959
Use of anti-platelet or anticoagulant drugs	0.68	0.37	1.27	0.231
	Hazard ratio	Lower limit of 95% CI.	Upper limit of 95% CI.	p
Limb SC- TcpO <sub>2</sub>	1.20	0.35	4.12	0.777
Age ≥75 years old	2.49	1.19	5.19	0.015
Use of beta-blockers	1.78	0.94	3.37	0.078
Respiratory insufficiency	1.76	0.90	3.41	0.097
Diabetes mellitus	1.15	0.60	2.20	0.677
Pain killers	1.15	0.62	2.17	0.655
Lower extremity artery disease	1.11	0.15	8.43	0.918
Use of diuretics or RAA inhibitors	1.08	0.56	2.11	0.813
Cardiac insufficiency	1.08	0.56	2.09	0.825
Psychotropic drugs	1.02	0.53	1.96	0.946
Use of cholesterol lowering drugs	0.91	0.47	1.75	0.777
Use of anti-platelet or anticoagulant drugs	0.65	0.34	1.24	0.186

RAA stands for renine-angiotensin-aldosterone system. 95% CI is the 95% confidence interval in the determination of the hazard ratio.

patients with CSR is typically 40 s or more (generally 40–90 s) in CSR; thus, the interval 35–100 s was used in our study. Of note, patients can show CSR either during wakefulness or sleep or both [32]. In practice, while attention is generally paid to temperature conditions of the measurement room when performing TcpO<sub>2</sub> recordings, it might be that a calm and quiet room is needed to allow patients with suspected CLI to fall asleep during the recording to unmask CSR not only during wakefulness, but also during sleep. Further, we likely underestimated the true prevalence of SC ~ TcpO<sub>2</sub> because the room where we performed our measurements is very active and rather noisy, and we probably missed sinusoidal changes only occurring while patients were sleeping.

The American Academy of Sleep Medicine (AASM) requires the presence of five or more central apneas or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over a minimum of 2 h of monitoring to define CSR. Our short-term recording (far less than 2 h) with most patients remaining awakened, may miss some patients with SC and do not allow us to fulfill the definition of CSR, but we observed in all cases more than five consecutive cycles of ascending and descending sinusoidal pO<sub>2</sub> changes (one of our 4 criteria for a positive test). The use of standard deviation (SD) of the TcpO<sub>2</sub> signal as a fourth criterion is based on the fact that for strictly sinusoidal signals, the ratio of the peak-to-peak amplitude of changes to SD is  $2\sqrt{2}$  (~2.83), while this ratio ranges from 6 to 8 in the case of random, square, or other non-sinusoidal changes [20]. As a consequence, defining a minimal SD value is important to confirm that reasonably ample TcpO<sub>2</sub> oscillations occurred while simultaneously excluding random changes of mild to moderate amplitudes.

CSR has received considerable attention in the last decade due to its association with cardiovascular diseases. The prevalence of CSR in the general population is rare but could be as high as 20% in patients with stroke or heart failure, two major causes of mortality and morbidity [1]. Amazingly, CSR prevalence in patients with lower limb arterial disease and specifically CLI was unknown. However, TcpO<sub>2</sub> is largely used in patients with severe lower limb peripheral artery disease and was previously proposed as a technique that can be used to diagnose CSR [16]. The present results suggest that CSR, assumed to induce SC ~ TcpO<sub>2</sub> changes, could be an underestimated frequent condition in CLI. We recorded the values with a custom-made program to try to attain an objective definition of SC ~ TcpO<sub>2</sub> changes (rather than account for the sole visual analysis of changes). Nevertheless, the SC ~ pattern in TcpO<sub>2</sub> can be easily observed in everyone's routine provided that: 1) a chest probe is used, 2) screen selection used on the TcpO<sub>2</sub> device is the one showing the temporal recording with adapted graphical scale and not the sole instantaneous numerical values. Nevertheless, the objective determination might help select the patients on objective criteria to determine whether SC ~ TcpO<sub>2</sub> is a risk factor for mortality in patients with suspected CLI.

Peripheral artery disease, even asymptomatic, carries a high risk of mortality, and this risk increases with the clinical severity of the disease. For example, in a 10-month follow-up of 2173 symptomatic patients, the all-cause death rates per 100 person-years were 3.5 and 26.2 for claudication and CLI, respectively [33]. In CLI, some studies in small groups of patients (n 113) with favorable healing after revascularization report a 1-year death rate as low as 14% [34], but most of the larger studies reported rates of 29–49%, independent of whether revascularization was performed [7,8].

Within a group of patients with CLI, determining the risk of short-term and mid-term mortality is of paramount importance. Various risk factors recordable at admission are predictive risk factors of a post-hospital midterm or long-term mortality in CLI. Biological markers such as low albumin or anemia [35,36], clinical factors such as diabetes mellitus [37], renal failure requiring dialysis [38,39], sex [40], underweight [41], age >75 years [34], non-ambulatory status [34,35], or sarcopenia (HR, 3.22) [39] have been proposed. All these factors show hazard ratios ranging from 2.46 to 4.30 [34,39]. While ejection fraction <50% was found as a risk factor of the two-year mortality after

revascularization in patients with critical limb ischemia: (HR, 3.14;  $p = 0.02$ ) [35], the five-year mortality was indeed lower in thero-heart-failure group than in heart failure patients but did not differ on the basis of ejection fraction in heart failure patients [42–44]. Last, the chronic obstructive pulmonary disease is an independent predictor of 30 days, and 2 years of death [45], or 30 days major adverse cardiovascular events [37], in patients with CLI.

Limitations include the fact that we included patients with suspected rather than proven CLI. We believe that this is closer to the real world where patients referred for TcpO<sub>2</sub> have suspected, rather than already confirmed, CLI. Further, and as recently underlined, the definition of CLI remains largely debated, which would induce a possible bias if we aimed to select only confirmed CLI cases. Second, we do not have evidence on cardiac function in most of our patients, although patients were required to self-report the presence of cardiac disease. Whether the oscillations observed in our patients did rely on underlying cardiac dysfunctions is unknown but warrant future investigations. Third, we previously discussed the importance of comorbid conditions (e.g., sarcopenia, renal failure, and anemia) as risk factors for mortality in patients with CLI. We do not have these data for most of our patients. Comparison to other markers of mortality remains to be determined, with the advantage of SC ~ TcpO<sub>2</sub> being readily available. Fourth, oscillations in respiration in CSR are associated with oscillations in sympathetic nerve activation [46]. Although local heating abolishes local sympathetic tone, SC ~ TcpO<sub>2</sub> observed could result from cutaneous vasoconstriction-vasodilation episodes rather than from arterial pO<sub>2</sub> changes. We advocate that whether or not TcpO<sub>2</sub> changes reflect local vasomotor changes or changes in systemic arterial pO<sub>2</sub> is not an issue because both mechanisms are assumed to rely on the same underlying disease (i.e., CSR). Overall, although we assume that the observed TcpO<sub>2</sub> oscillations likely resulted from CSR, in the present retrospective analysis, no patient was referred for pulmonary polysomnographic investigations to confirm our hypothesis and validate whether patients with SC ~ TcpO<sub>2</sub> fulfilled all of the AASM criteria for CSR. Similarly, only in very few cases the observation of abnormal breathing during the test was available in the notes of the most expert nurses. In patients with suspected CLI, teaching nurses or technicians about CSR, and training them to detect and report abnormal respiration (among which CSR) is required.

In conclusion, the observation of abnormal breathing by a nurse performing TcpO<sub>2</sub> tests of patients with suspected CLI should be reported, but even if unreported, objective determination of SC ~ TcpO<sub>2</sub> is readily available to the physician supervising TcpO<sub>2</sub> results, provided that continuous recordings (and not only screen reading of instantaneous TcpO<sub>2</sub> values) are performed. Optimally, SC ~ TcpO<sub>2</sub> can be determined objectively based on mathematical criteria. The observation of these TcpO<sub>2</sub> oscillations at the chest level (assumed to rely on CSR) is associated with an increased mortality rate in patients referred for suspected CLI. Limb-TcpO<sub>2</sub> alone is insufficient to detect CSR, likely due to absolute low values. Whether the presence of SC ~ TcpO<sub>2</sub> should modify the decisions for treating patients is a challenging question for the future. These specific TcpO<sub>2</sub> changes convey original information and support the use of TcpO<sub>2</sub> in CLI-suspected patients.

#### Clinical trial registration number

<https://clinicaltrials.gov/NCT04209998&NCT04369781>.

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#### Author contributions

PA SH conceived and designed the study. PR JP, JH PA SH

participated to the recruitment, WT FG JH participated to the data analysis and interpretation. PA and SH prepared the manuscript draft, PR, WT, FG, JP, JH critically revised the manuscript. All authors approved the final version of the manuscript.

#### CRediT authorship contribution statement

**Jeanne Hersant:** Formal analysis, recruitment Data analysis and interpretation, critical revision. **Pierre Ramondou:** Formal analysis, recruitment Data analysis and interpretation, critical revision. **Wojciech Trzepizur:** Formal analysis, Data analysis and interpretation, critical revision. **Frederic Gagnadoux:** Formal analysis, Data analysis and interpretation, critical revision. **Jean Picquet:** recruitment, critical revision. **Pierre Abraham:** Conceptualization, Methodology, Writing – original draft, recruitment, draft preparation. **Samir Henni:** Conceptualization, Methodology, Writing – original draft, recruitment, draft preparation.

#### Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# DISCUSSION

## 1. Préambule

L'oxymétrie permet un enregistrement non-opérateur dépendant de modifications microcirculatoires.

Concernant les différentes études présentées au cours de ce travail, c'est la première fois qu'il a été rapporté :

- L'exploration de la récupération sur l'analyse des sondes hors mollet, en cuisses et en fesses
- L'analyse de son intérêt et sa validation dans une nouvelle pathologie : le SDTB
- L'analyse des courbes thoraciques sinusoïdales au cours d'oxymétrie transcutanée de repos dans un contexte d'ischémie critique et leurs liens avec la mortalité de ces patients.

Nous allons successivement rapporter les bénéfices et les limites du développement de ces nouvelles applications de l'oxymétrie transcutanée. Puis, nous exposerons les perspectives qui s'en dégagent.

## 2. Apports et limites de ces nouvelles applications

### 2.1. Exploration d'effort des membres inférieurs

Il est important de partir du constat que : même si la prévalence de claudication de mollet reste prépondérante, la prévalence de claudication de cuisse ou de fesses reste non négligeable et variable selon les études (26, 27). De plus, l'analyse de la récupération n'a été effectuée que sur les mollets. Ce critère est un point-clé dans la constitution des programmes de rééducation afin de connaître le temps de récupération optimal en fonction de l'exercice réalisé auparavant. De plus, il a déjà été démontré qu'il est difficile de se baser uniquement sur la dissipation clinique des symptômes, constamment moindre que la normalisation hémodynamique (18).

En outre, de nombreuses études ont été menées sur l'intérêt des IPSc dans ce contexte en fin d'exercice (39) mais peu se sont intéressées à la durée de chute des IPSc ou au temps de retour aux valeurs pré-exercices. C'est notamment en ça que la TCPO2 présente un apport.

Enfin, la TCPO2 permet de déterminer un « niveau » d'atteinte hémodynamique et prend en compte l'existence d'une collatéralité.

Concernant les limites de notre démarche dans l'exploration des membres inférieurs :

- Tout d'abord, il est utilisé un protocole standard (3,2km/h et 10% de pente) avec des résultats qui ne seraient peut-être pas extrapolables à d'autres systèmes d'évaluation. En effet, lors de la nécessité de modification du protocole il a été montré qu'il avait une influence sur le temps maximal de marche mais pas sur les DROP, malheureusement le temps de récupération n'avait pas été étudié.
- Il faudrait également trouver une corrélation entre la durée des symptômes cliniques et le temps de récupération hémodynamique, ce qui n'a pas été étudié
- De plus, la population incluse dans cette étude pouvait ne pas être représentative du fait de l'inclusion d'un nombre non négligeable de patients adressés pour claudication atypique et étant donc non représentatifs de l'ensemble de la population de patients claudicants.

- Enfin, les DROP n'apportent qu'une estimation de la différence d'oxygénation entre l'oxygène délivré et celui consommé. Du fait du positionnement protocolisé des électrodes, certaines zones d'ischémie ont pu être méconnues.

## 2.2. Exploration des membres supérieurs

Il s'agit des premières études s'intéressant à l'apport de la TCPO2 dans le SDTB et les résultats sont en faveur d'une analyse fiable et reproductible.

Ce raisonnement de développement de l'oxymétrie dans cette pathologie s'intègre dans un courant de pensée de discordance quant à la définition, la répartition (émergence de sous-types de SDTB « combinés » ou « disputed » (40)) et la prise en charge du SDTB (prise en charge chirurgicale considérée comme une de celle entraînant le plus de litige et de poursuite judiciaire (41)). En effet, concernant le diagnostic de SDTB, aucune exploration non invasive n'apparaît optimale. La plus utilisée est l'échodoppler qui procure une sensibilité et une spécificité respectivement de 87% et 88% (42) avec un risque non négligeable de faux positifs et faux négatifs. Quant à l'IRM, ses paramètres de sensibilité, spécificité, VPP et VPN sont respectivement de 41%, 33%, 89% et 4%.

D'un point de vue symptomatologique, l'appartenance des symptômes de pâleur et froideur à une atteinte plutôt artérielle ou nerveuse reste très débattue (33). En effet, ces derniers peuvent être la conséquence d'une compression artérielle ou d'une vasoconstriction adrénergique par compression sympathique. L'échodoppler ou l'artériographie méconnaîtrait cette atteinte alors que la TCPO2 permet une analyse macro et microcirculatoire et enregistre peu importe l'étiologie, une baisse des valeurs traduisant une ischémie locale. Cela constitue un réel apport de cette technique mais également une limite dans son étude de comparaison au gold standard avec une augmentation probable du nombre de faux positifs.

De plus, afin de valider notre méthode nous avons pu déterminer sur la première analyse un cut off de -15mmHG qui a pu être validé à nouveau sur la seconde analyse réalisée versus l'artériographie permettant de renforcer nos résultats.

Si l'on s'intéresse plus précisément aux limites de notre démarche d'analyse de l'oxymétrie dynamique des membres supérieurs :

- Tout d'abord, il n'a pas été réalisé d'analyse précise de l'angulation des membres supérieurs, ce qui permettrait d'éliminer les patients pour lesquels la mesure n'était pas reproductible.
- De plus, la confirmation de l'existence ou non d'un SDTB n'a pu être réalisée en comparaison à une imagerie avec injection de contraste intraveineux sur une majorité de patients car un nombre non négligeable de patients n'ont par la suite pas bénéficié de chirurgie mais uniquement d'une thérapeutique par kinésithérapie.



- En outre, il est important de noter que seule la manœuvre de Roos a été testée au cours des protocoles ce qui peut biaiser la sélection des patients. Cependant, il s'agit de celle ayant été déterminée comme apportant le plus de résultat positif (43).
- Enfin, la présence de collatérales artérielles peut normaliser l'examen par TCPO2. En effet, d'un point de vue fonctionnel il n'y aura pas d'ischémie du fait de phénomènes de suppléances mais anatomiquement sur l'artériographie il y aura une compression artérielle, ce qui crée des faux négatifs de la TCPO2.

### 2.3. Exploration de repos des membres inférieurs

Antérieurement, la TCPO2 de repos a été utilisée pour l'évaluation des patients présentant une respiration de Cheyne-Stokes (CS) sous traitement. Le CS est rare dans la population générale mais sa prévalence peut s'élever à plus de 20% chez les patients souffrant d'AVC ou de défaillance cardiaque, ce qui constitue deux causes majeures de mortalité et morbidité. La prévalence du CS chez les patients en ischémie critique reste inconnue. Beaucoup de critères ont déjà été proposés comme étant prédicteurs d'un risque de mortalité plus élevé chez les patients en ischémie critique : marqueurs biologiques (hypoalbuminémie, anémie), diabète, IRC avec dialyse, > 75 ans, BMI faible, statut non ambulatoire, la FEVG > 50% ou encore la sarcopénie.

Il semble assez instinctif de relier ces deux pathologies et l'observation de mouvements sinusoïdaux sur nos enregistrements thoraciques nous a amenés à développer ce sujet. Cela implique de réaliser un enregistrement des courbes thoraciques et non pas seulement la relève de la mesure de la sonde thoracique à un instant donné, ce qui est fréquemment observé.

Les limites de notre démarche concernant l'analyse des mouvements sinusoïdaux enregistrés sur les courbes thoraciques chez les patients en ischémie critique sont les suivantes :

- Les changements enregistrés le sont avec une électrode Clark et il est difficile de savoir dans quelle mesure cela est extrapolable aux autres techniques (électrode photo électrique ; électrode paramagnétique).
- Un algorithme a été réalisé afin de différencier un CS d'une autre respiration anormale (SAOS, hypoventilation chronique, dyspnée de Kussmaul, respiration de Biot) mais cela reste bien sûr discutable.
- La détection de ces CS peut être mise à mal si l'examen n'est pas réalisé dans une pièce calme, sans nuisance sonore.
- De plus, nous avons cité ci-dessus les facteurs ayant déjà été déterminés comme aggravant le pronostic des patients en ischémie critique, or ces derniers n'ont pas été relevés dans notre étude.
- Il est important de noter que l'oscillation respiratoire est associée à l'oscillation de l'activation nerveuse sympathique et la chaleur locale va abolir le tonus sympathique local. C'est pourquoi les mouvements sinusoïdaux pourraient correspondre à des épisodes de vasoconstriction/vasodilatation transcutanée plus qu'à des changements de pO2 artériel. Cela a été accepté car les deux mécanismes sont reliés à la même pathologie sous-jacente.
- Enfin, les patients n'ont pas bénéficié d'une polysomnographie afin de valider le diagnostic de CS.

## PERSPECTIVES

Premièrement, concernant l'exploration d'effort, la TCPO<sub>2</sub> pourrait s'imposer afin de guider la rééducation et notamment le temps nécessaire d'arrêt des patients avec claudication, comme cela a été le cas dans le cadre d'étude récente avec la NIRS (44).

Secondairement, l'analyse des courbes thoraciques de TCPO<sub>2</sub> chez les patients en ischémie critique pourrait modifier ou s'intégrer dans une démarche holistique de prise en charge et de décision thérapeutique ou non chez ces patients.

Enfin, et de manière plus développée concernant le SDTB, il paraît licite d'imaginer que la compression du paquet vasculo-nerveux soit dépendante de l'angle qui est réalisé en abduction du membre supérieur. Or dans la majorité des centres le bilan pré-opératoire comprend une imagerie en coupe de type angioRM ou angioscanner et non une artériographie dynamique. Dans ce type d'imagerie en coupe, le membre supérieur, par contrainte d'installation dans la machine est placé à 120-130° et non 90-110° comme il est habituellement décrit dans les manœuvres dynamiques notamment du chandelier. Un travail en cours dans notre centre vise à étudier les valeurs de TCPO<sub>2</sub> à 90° et 110° afin d'observer une modification (diminution ou augmentation) des DROPS entre ces deux angles. Pour une plus grande précision, une caméra filme le patient et analyse durant la manœuvre l'angle d'abduction et de rétropulsion du membre supérieur. Les premiers résultats tendent à montrer que moins de patients passent le seuil d'ischémie lors d'une abduction à 110° que pour un angle de 90° ce qui peut notamment être mis en lien avec la libération du paquet vasculaire à partir d'une valeur d'angle ce qui pourrait remettre en question la performance des imageries en coupe de type angioscanner ou angioRM. En outre, il paraît primordial à ce stade d'envisager une évaluation pré et post opératoire afin de valider de manière encore plus forte notre technique mais également d'ancrer cet examen dans la démarche de prise de décision et de prise en charge thérapeutique du patient.

Enfin, l'exploration de la microcirculation ne se résume pas qu'à l'oxymétrie transcutanée et des travaux sont en cours et dont certains déjà publiés afin d'analyser l'intérêt et la place de la photoplethysmographie dans le SDTB.

## **Conclusion**

Cette thèse permet à travers ces différents travaux de mettre en exergue d'autres applications de l'oxymétrie transcutanée dans l'exploration vasculaire.

Il s'agit de modalités au caractère original, permettant chacune d'améliorer la définition de la pathologie et de guider la prise en charge avec une meilleure sélection des patients devant bénéficier d'une prise en charge chirurgicale.

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## **LISTE DES ABBREVIATIONS**

AOMI : artériopathie oblitérante des membres inférieurs  
AUC : area under the curve  
AVC : accident vasculaire cérébral  
BMI : Body Mass Index  
CS : Cheyne-Stokes  
DO<sub>2</sub> : apport en oxygène  
DROP : decrease from rest of oxygen pressure  
FEVG : fraction d'éjection du ventricule gauche  
Hb : hémoglobine  
HR : hazard ratio  
IPSc : index de pression systolique de cheville  
IRC : insuffisance rénale chronique  
IRM : imagerie par résonance magnétique  
MWT : maximal walking time  
NIRS : near infrared spectroscopy  
PaO<sub>2</sub> : pression partielle en oxygène au niveau systémique  
PO<sub>2</sub> : pression transcutanée en oxygène  
Q : débit cardiaque  
ROC : receiver operating characteristic  
SaO<sub>2</sub> : saturation artérielle en oxygène  
SAOS : syndrome d'apnée obstructive du sommeil  
SDTB : syndrome du défilé thoraco-brachial  
TCPO<sub>2</sub> : transcutaneous oxygen pressures  
TDM : tomodensitométrie

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**Titre :** Oxymétrie transcutanée : état des lieux et nouvelles applications

**Mots clés :** oxymétrie transcutanée, ischémie, artériopathie, syndrome du défilé thoraco-brachial,

**Résumé :** L'oxymétrie transcutanée permet une analyse objective, non opérateur-dépendant de la présence d'une ischémie de repos ou d'effort. Ce travail vise à développer de nouvelles applications de l'oxymétrie transcutanée en se basant sur des explorations réalisées quotidiennement (TCPO<sub>2</sub> d'effort dans la claudication ou TCPO<sub>2</sub> de repos dans l'ischémie critique) mais également en l'appliquant à une nouvelle pathologie (syndrome du défilé thoraco-brachial). Successivement, il est rapporté l'intérêt de l'analyse du temps de récupération dans les localisations hors mollet chez les patients présentant un artériopathie au stade de claudication d'effort. Secondairement, l'applicabilité et la validation de l'oxymétrie transcutanée versus un gold standard (artériographie) dans le syndrome du défilé thoraco-brachial. Enfin, l'intérêt de l'analyse continue des courbes thoraciques lors de la réalisation d'une oxymétrie transcutanée de repos chez les patients présentant une ischémie critique, en rapportant la présence de mouvements sinusoïdaux, suggérant une respiration de Cheyne-Stockes et son impact en termes de morbi-mortalité. Ce travail a permis de développer des applications originales de l'oxymétrie transcutanée afin d'améliorer la prise en charge globale de ces patients.

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**Title:** Transcutaneous oxygen pressure: state of play and new applications

**Keywords:** transcutaneous oximetry; ischemia; arteriopathy, thoracic outlet syndrome

**Abstract:** Transcutaneous oximetry is an objective and non-operator dependent investigation assessing rest and exercise ischemia. This work aims to focus on new transcutaneous oximetry applications based on daily investigations (as exercise transcutaneous oximetry in peripheral arterial disease or rest transcutaneous oximetry in critical limb ischemia) but also new area of interest (thoracic outlet syndrome). Firstly, we reported non-calf hemodynamic recovery interest in patient with arterial limb claudication. Secondly, we studied the feasibility and reliability of transcutaneous oximetry in thoracic outlet syndrome and its validation versus gold standard (arteriography). Finally, we reported sinusoidal changes in transcutaneous oxygen pressure, suggesting Cheyne-Stockes respiration, appearing to be frequent and of poorer prognosis in critical limb ischemia patients. Transcutaneous oximetry allows original applications to improve global patient management with peripheral artery disease.