



# Physiopathologie et évaluation de la capacité de marche au cours de l'artériopathie oblitérante des membres inférieurs

Guillaume Mahé

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**Physiopathologie et évaluation de la capacité de marche  
au cours de l'artériopathie oblitérante des membres inférieurs.**

**THÈSE DE DOCTORAT**

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*La compréhension et la caractérisation d'une pathologie sont l'étape essentielle pour la prise en charge optimale d'un patient.*



A mes parents,  
A Marie,  
A Antoine,



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## RÉSUMÉ

Le système cardiovasculaire permet les apports notamment en oxygène et en glucose et l'élimination des déchets métaboliques nécessaires à la vie cellulaire. Une inadéquation entre les apports et les besoins engendre une ischémie. A l'effort, les besoins en oxygène et en glucose sont augmentés. Lorsque cette ischémie a lieu dans un territoire tissulaire des membres inférieurs, elle peut être à l'origine de douleurs survenant à la marche, limitant ainsi la capacité de marche des patients. Cette douleur est appelée la claudication intermittente. Cette évaluation de la capacité de marche est difficile en raison de la difficulté qu'ont les patients à évaluer leurs limitations à la marche. Différents outils de mesure ont été développés comme des questionnaires, des tests de laboratoire notamment sur tapis et des tests ambulatoires comme le géo-positionnement satellitaire (GPS). Les avantages et les inconvénients de ces outils de mesure sont présentés dans ce travail. Des outils de mesures objectifs doivent donc être développés afin de permettre une évaluation fonctionnelle plus précise mais aussi pour mieux caractériser les mécanismes physiopathologiques sous-jacents à ces limitations induites par l'ischémie. Les travaux de recherche réalisés ont porté sur : (1) le développement et l'amélioration d'outils de mesure de la capacité de marche (questionnaires, test sur tapis roulant) ; (2) l'évaluation des différentes localisations ischémiques à la marche et l'influence de l'hypoxémie d'effort. Les travaux menés ont permis de montrer les limites d'un questionnaire préalablement validé (Walking Impairment Questionnaire ; WIQ) et de développer un nouveau questionnaire d'évaluation de la capacité de marche plus court et tout aussi fiable. Par ailleurs, en utilisant une méthode d'évaluation ambulatoire de la capacité de marche, le GPS, le concept de variabilité de la capacité de marche à court terme a été mis en évidence. Cette variabilité à court terme pourrait être l'une des explications à cette difficulté d'évaluation de la capacité de marche. De plus, les durées optimales du test sur tapis à charge constante ont été précisées. Enfin, différentes localisations ischémiques ont été présentées au niveau des membres inférieurs et nous avons montré que certains patients avec une limitation de la capacité de marche ont une hypoxémie d'effort à la marche. Celle-ci

pourrait être la cause de leur limitation de leur capacité de marche. L'ensemble de ces travaux permettra de mieux évaluer la capacité de marche chez l'artériopathe à la fois pour le diagnostic mais aussi pour la prise en charge thérapeutique.

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## LISTE DES ABRÉVIATIONS

ACC/AHA : American College of Cardiology/ American Heart Association

Ag : Argent

AMPc : Adénosine-monophosphate cyclique

AOMI : Artériopathie oblitérante des membres inférieurs

Bpm : Battements par minute

Cl : Chlore

COX : Cyclo-oxygénase

DMM : Distance maximale de marche

DROP : Delta from rest of oxygen pressure

EACH-Q : Estimate ambulation capacity by history questionnaire

ECG : Électrocardiogramme

EDHF : Facteur hyperpolarisant dérivé de l'endothélium

GMPC : Guanosine-monophosphate cyclique

GPS : Géo-positionnement satellitaire

HDL : High density lipoprotein

H<sub>2</sub>O : Eau

Hz : Hertz

IC : Intervalle de confiance

IMC : Indice de masse corporelle

IPPB : Index de pression pénienne-bras

IPS : Index de pression systolique

Km : Kilomètre

LDL : Low density lipoprotein

min : Minute

ml : Millilitre

mmHg : Millimètre de mercure

NIRS : Near-InfraRed Spectroscopy

NO : Monoxyde d'azote

NOS : NO synthase

O<sub>2</sub> : Oxygène

OH<sup>-</sup> : Hydroxyde

OMS : Organisation mondiale de la santé

PAD : Peripheral arterial disease, terme anglo-saxon pour désigner l'AOMI

PADHOC : Peripheral arterial disease holter control

PGI<sub>2</sub> : Prostaglandines de type 2

ROC : Receiver Operating Characteristics

TcPO<sub>2</sub> : Mesure transcutanée de la pression partielle en oxygène

µm : Micromètre

WHO : World Health Organization, terme anglo-saxon pour désigner l'OMS

WIQ : Walking impairment questionnaire



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# 1 INTRODUCTION

## 1.1 L'appareil cardiovasculaire

L'appareil cardiovasculaire est constitué d'une « pompe », le cœur, d'un contenant, les vaisseaux sanguins et d'un contenu, le sang (Murray, 1964).

En effet, les échanges gazeux (oxygène et gaz carbonique) et les échanges de nutriments nécessaires à la vie entre les cellules et l'environnement se font par diffusion et ne sont possibles que sur une courte distance de l'ordre quelques micromètres. L'Homme étant un organisme pluricellulaire complexe, un réseau de distribution est nécessaire pour assurer ces échanges gazeux et de nutriments et ainsi permettre la viabilité de l'ensemble des tissus. Ce nécessaire réseau de distribution est d'ailleurs bien mis en évidence au cours de l'infarctus du myocarde. Lors de l'obstruction d'une artère coronaire gauche par exemple, une souffrance cellulaire (de certains myocytes) apparaît alors même que moins d'un centimètre en dessous, l'atrium et le ventricule gauche sont « remplis » de sang oxygéné et riche en nutriments. Le rôle essentiel de l'appareil cardiovasculaire est donc d'assurer une circulation sanguine rapide par convection à tous les tissus de l'organisme pour permettre les échanges gazeux et de nutriments avec les cellules et d'assurer une épuration des déchets métaboliques cellulaires (Levick, 2009).

Le bon fonctionnement de cet appareil dépend de la « qualité » des trois facteurs constituant cet appareil cardiovasculaire à savoir la pompe cardiaque, les vaisseaux et le sang. Tout dysfonctionnement de l'un de ces trois facteurs entraînera, à partir d'un certain stade, un dysfonctionnement de cet appareil cardiovasculaire et donc une souffrance tissulaire.

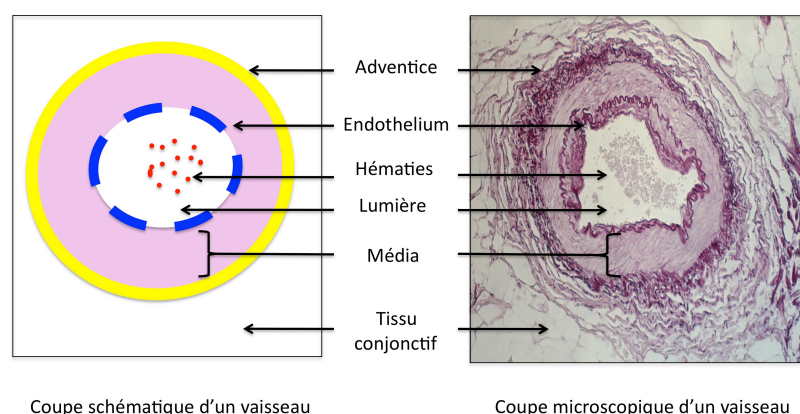
Le cœur est un muscle creux constitué par des cardiomyocytes<sup>1</sup>. Il a une activité contractile rythmique autonome. Cette contractilité, de l'ordre de 70 battements par minute chez l'Homme au repos, permet un apport sanguin pulsatile régulier dans les vaisseaux. Le cœur est en réalité constitué de deux pompes fonctionnant en parallèle :

---

<sup>1</sup> Cardiomyocytes : Cellules musculaires du cœur. Ce sont des cellules cylindriques mesurant de 10 à 20  $\mu\text{m}$  de large pour 50 à 100  $\mu\text{m}$  de long. Ces cellules ne possèdent qu'un seul noyau central.

une pompe droite, appelée cœur droit et une pompe gauche appelée cœur gauche. Chaque pompe est constituée d'un atrium et d'un ventricule placés en série. Le cœur droit, régime à basse pression (4 mmHg en télédiastole<sup>2</sup> à 25 mmHg en systole<sup>3</sup> chez l'adulte sain), assure la circulation pulmonaire. Il éjecte du sang désaturé en oxygène vers le système artériel pulmonaire, où les échanges alvéolo-capillaires permettent de saturer le sang en oxygène et d'évacuer le gaz carbonique. Le cœur gauche, régime à haute pression (9 mmHg en télédiastole à 120 mmHg en systole chez l'adulte sain) éjecte un sang saturé en oxygène dans la circulation systémique aussi appelée grande circulation pour alimenter tous les tissus de l'organisme. Le débit cardiaque varie en fonction de l'activité du sujet. Il est d'environ 5900ml/min au repos chez un homme sédentaire debout et passe à 24000ml/min pendant un exercice à consommation d'oxygène maximale. La distribution sanguine au tissu cardiaque est assurée par les artères coronaires.

Les vaisseaux sont le second élément important du système cardiovasculaire. La plupart des vaisseaux sont constitués de trois couches distinctes, qui sont de la lumière à la périphérie, la couche endothéliale ou intima, la couche musculaire ou média et la couche fibreuse ou adventice (figure 1). Chaque couche a sa propre fonction. Schématiquement, l'intima a un rôle d'échange, la média a un rôle d'amortissement (cf. infra avec l'effet Windkessel) (Belz, 1995; Frank, 1899) et l'adventice a un rôle structural (permet aux vaisseaux de ne pas augmenter de taille à l'infini). Ces trois couches sont présentes en proportion variable dans les artères et les veines.



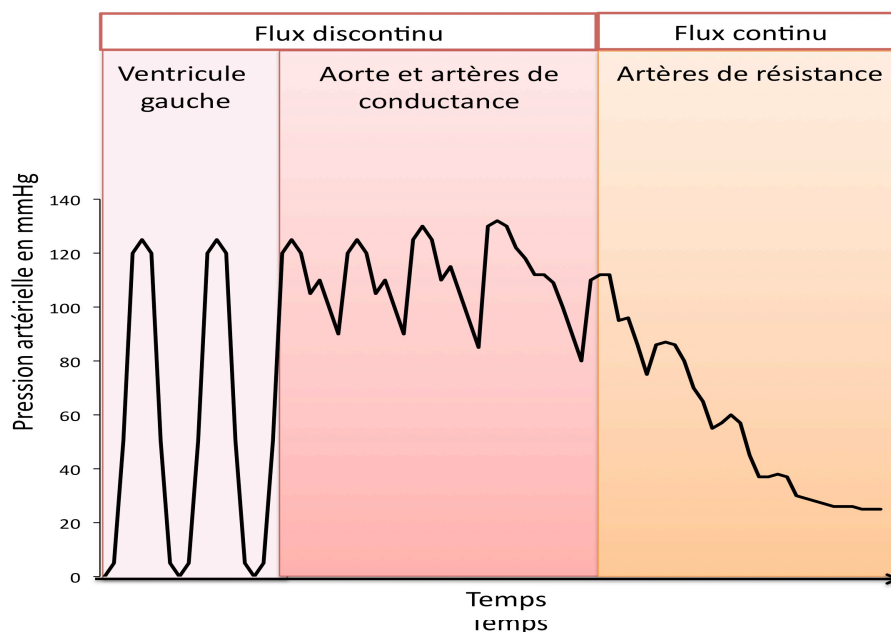
**Figure 1 : Coupes de vaisseaux**

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<sup>2</sup> Télédiastole : Fin de la relaxation cardiaque.

<sup>3</sup> Systole : Contraction cardiaque. Elle peut être soit auriculaire soit ventriculaire.

Les vaisseaux sanguins peuvent aussi être différenciés en fonction de leur rôle. Ainsi, les artères apportent du sang oxygéné aux organes (hormis les artères pulmonaires) et les veines apportent du sang désaturé en oxygène aux poumons (excepté les veines pulmonaires). Le système artériel peut se décomposer en macrocirculation et en microcirculation. La macrocirculation représente les artères de conductance, dont les rôles essentiels sont la conduction sanguine et la transformation d'un flux pulsatile en un flux continu (effet Windkessel, figure 2)(Frank, 1899).



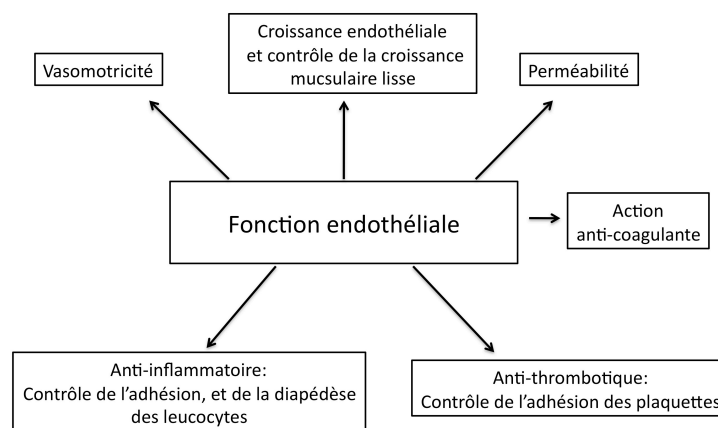
**Figure 2 : Effet Windkessel : transformation d'un flux discontinu en un flux continu dans le système vasculaire. Phénomène décrit par Dr O. Franck (Frank, 1899).**

La microcirculation représente les artères de résistance, dont le rôle essentiel est celui d'échange avec les tissus (nutrition et épuration des toxines) et de régulation de la résistance du système circulatoire. La microcirculation est présente dans tous les organes.

L'endothélium, couche monocellulaire, tapissant la paroi interne des vaisseaux est une surface non thrombogène d'interaction et d'échange avec le liquide plasmatique et les éléments figurés du sang (notamment les plaquettes). L'endothélium représente une surface d'échange très importante constituée d'environ  $1 \cdot 10^{13}$  cellules pour une



masse estimée à environ trois kilogrammes. L'endothélium possède une fonction spécifique définie par le terme de fonction endothéliale. Cette fonction endothéliale regroupe en fait plusieurs fonctions dont la finalité est la régulation des résistances périphériques pour faire face aux contraintes physiologiques, physiques ou environnementales. Cette fonction comprend la capacité de croissance de l'endothélium, la possibilité d'être perméable à certaines substances, la capacité de permettre l'adhésion ou la diapédèse (migration cellulaire à travers une couche cellulaire) et la vasomotricité (figure 3).



**Figure 3 : Rôle de la fonction endothéliale.**

La vasomotricité est modulée par divers stimuli chimiques ou mécaniques agissant sur l'endothélium. En fonction du stimulus, l'endothélium réagit par trois voies indépendantes connues à ce jour : (1) la voie du monoxyde d'azote (NO) via les NO-synthase de type III (NOS III) (Buus et al., 2000; Furchgott and Zawadzki, 1980), (2) la voie des prostaglandines (PGI<sub>2</sub>) via les cyclo-oxygénases (COX) (Durand et al., 2004) et (3) la voie du facteur hyperpolarisant dérivé de l'endothélium (EDHF) (Buus et al., 2000; Hoepfl et al., 2002). Ces trois molécules, le NO, les PGI<sub>2</sub> et l'EDHF diffusent alors au niveau des cellules musculaires lisses et permettent la relaxation via le guanosine-monophosphate cyclique (GMPc) pour le NO, via l'Adénosine-monophosphate cyclique (AMPc) pour les PGI<sub>2</sub> et via l'ouverture de canaux potassiques pour l'EDHF.

L'atteinte de cette fonction endothéliale constitue la dysfonction endothéliale. C'est un phénomène majeur dans la genèse de l'athérosclérose, qui est pourvoyeuse de pathologies vasculaires (Vanhoutte, 1997; Vanhoutte, 2009).

Le troisième composant important du système cardiovasculaire est le sang. Le sang est un fluide normalement constitué de 55% de plasma sanguin et de 45% d'éléments figurés représentés par les hématies, les leucocytes et les plaquettes. Le plasma sanguin représente la partie liquide du sang et est constitué de protéines, de nutriments, de déchets métaboliques, d'hormones et d'électrolytes inorganiques ( $\text{Na}^+$ ,  $\text{K}^+$ , ...). Le sang assure le transport des gaz notamment de l'oxygène par le biais de l'hémoglobine contenue dans les hématies et le transport des nutriments et des déchets métaboliques nécessaires à la viabilité cellulaire. En outre, il permet la défense de l'organisme par l'intermédiaire des leucocytes et la communication cellulaire par l'intermédiaire des hormones.

## **1.2 Physiologie vasculaire à l'effort**

### **1.2.1 Généralités**

L'effort est une activité physique qui peut être définie comme tout mouvement corporel dû à la contraction des muscles squelettiques et induisant une dépense énergétique supérieure à celle de repos. La dépense énergétique de repos correspond à la quantité d'énergie nécessaire au métabolisme basal au repos et en neutralité thermique. A l'effort, une augmentation des apports énergétiques aux cellules ainsi qu'une augmentation de l'élimination des déchets métaboliques cellulaires sont nécessaires pour assurer cette dépense énergétique supérieure.

L'activité physique met en jeu les muscles squelettiques, qui seront les effecteurs du mouvement, les muscles lisses principalement des vaisseaux et des voies aériennes, et le muscle cardiaque.

Les principales caractéristiques entre les muscles squelettiques<sup>4</sup> et les muscles lisses<sup>5</sup> sont présentées dans le tableau 1 :

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<sup>4</sup> Muscles squelettiques : Muscles insérés sur un os du squelette et qui permettent le maintien de la posture, le déplacement des segments osseux nécessaires aux mouvements du sujet et pour certains qui participent à l'homéostasie de l'organisme (muscles respiratoires) Mercier, J., et al., Muscles. In: E. Pradel, (Ed.), Physiologie humaine. Wolters Kluwer France, Rueil-Malmaison, 2009, pp. 17-34.

| Caractéristiques         | Muscle lisse             | Muscle strié              |
|--------------------------|--------------------------|---------------------------|
| Aspect microscopique     | Lisse                    | Strié                     |
| Noyau (x)                | Unique                   | Multiples                 |
| Diamètre des cellules    | 2-10 $\mu\text{m}$       | 10-100 $\mu\text{m}$      |
| Réticulum sarcoplasmique | Peu important            | Très important            |
| Contraction              | Hélicoïdale, lente       | Linéaire, rapide          |
| Innervation              | Système nerveux autonome | Système nerveux somatique |

**Tableau 1 : Différences entre le muscle lisse et le muscle strié, d'après Physiologie Humaine (Mercier et al., 2009).**

L'effort nécessite une adaptation du système cardiovasculaire du sujet. Trois types d'adaptations sont indispensables (Levick, 2009):

- Le flux sanguin pulmonaire doit augmenter afin d'améliorer les apports en oxygène et l'élimination du gaz carbonique ;
- Le flux sanguin dans les muscles actifs doit augmenter pour favoriser les apports en oxygène et en glucose aux cellules musculaires ;
- La pression artérielle doit être stabilisée, en dépit des adaptations (augmentation du débit cardiaque et diminution des résistances périphériques principalement dans les territoires musculaires actifs) pour permettre les adaptations des flux sanguins pulmonaire et musculaire.

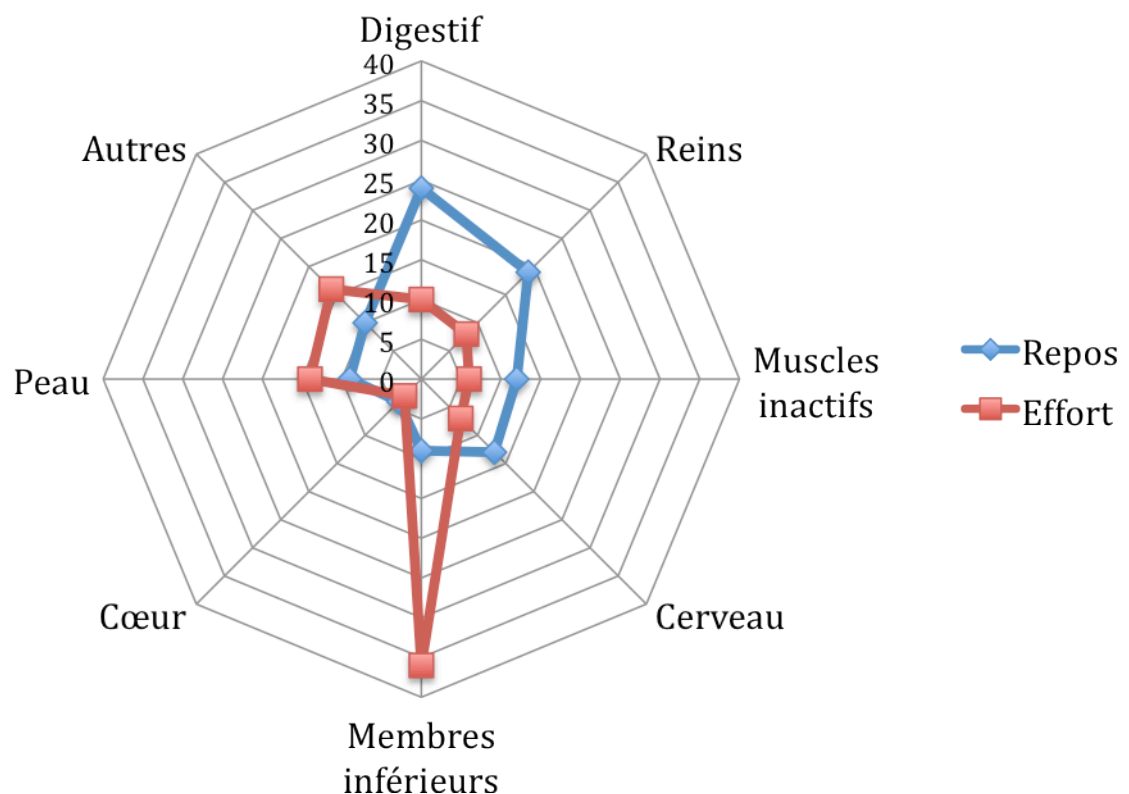
Le débit cardiaque et par conséquent le débit pulmonaire augmentent de façon linéaire avec l'augmentation de la consommation d'oxygène (Innes et al., 1988). Au cours de l'effort, certains territoires ont une augmentation des débits et d'autres une diminution (figure 4 et tableau 2).

Lors de l'effort, la circulation coronarienne augmente en fonction de la charge de travail cardiaque (Levick, 2009). La perfusion des muscles respiratoires augmente avec

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<sup>5</sup> Muscles lisses : Muscles présents dans toutes les parois des organes creux (vaisseaux, voies aériennes,...). Ils jouent un rôle essentiel de tonus et permettent le maintien de l'homéostasie de l'organisme. Ibid.

l'augmentation de la ventilation. Cette augmentation de perfusion peut représenter jusqu'à 16% du débit cardiaque à l'effort. La perfusion de la peau diminue en début d'exercice en raison d'une vasoconstriction transitoire puis une vasodilatation apparaît pour assurer la thermorégulation<sup>6</sup>, nécessaire au cours de l'effort. En revanche, une vasoconstriction survient dans les territoires non actifs comme le système digestif, le rein, et les muscles non actifs. Cette vasoconstriction au niveau des territoires non-actifs permet de conserver une pression artérielle systémique optimale. Le maintien d'une pression artérielle systémique suffisante est essentiel pour assurer la perfusion adéquate de tous les tissus périphériques au cours de l'effort.



**Figure 4 : Variations du pourcentage du débit cardiaque dans chaque territoire entre le repos (débit de 5,8 l/min) et l'effort (10,8 l/min) lors d'un exercice modéré des membres inférieurs, adapté de Wade OL et Bishop JM (Levick, 2009; Wade and Bishop, 1962)**

<sup>6</sup> Thermorégulation: Ensemble des phénomènes physiologiques permettant le contrôle de la température corporelle.

| Territoire         | Repos | Effort | Variations |
|--------------------|-------|--------|------------|
| Digestif           | 1,40  | 1,10   | ↘          |
| Reins              | 1,10  | 0,90   | ↘          |
| Muscles inactifs   | 0,70  | 0,60   | ↘          |
| Cerveau            | 0,75  | 0,75   | =          |
| Membres inférieurs | 0,50  | 3,90   | ↗          |
| Cœur               | 0,25  | 0,35   | ↗          |
| Peau               | 0,50  | 1,50   | ↗          |
| Autres             | 0,60  | 1,70   | ↗          |
| Poumons            | 5,80  | 10,80  | ↗          |

**Tableau 2 : Evolution des débits en l/min des différents territoires entre le repos et l'effort lors d'un exercice modéré des membres inférieurs adapté de Wade OL et Bishop JM (Levick, 2009; Wade and Bishop, 1962)**

### 1.2.2 Circulation musculaire à l'effort

A l'effort, le débit sanguin augmente dans les muscles actifs. Cette augmentation peut passer de 1 l/min (20% du débit cardiaque) chez un homme au repos à 19 l/min au cours d'un effort de forte intensité (> 80% du débit cardiaque maximal). Cinq phénomènes importants ont lieu conjointement :

#### 1) La chasse veineuse.

Lors de la contraction musculaire, les veines musculaires et profondes sont écrasées par les muscles actifs entraînant une chasse veineuse. Cette chasse veineuse engendre une augmentation de la différence de pression entre le réseau veineux et le réseau artériel conduisant ainsi à une augmentation du débit sanguin.

#### 2) L'hyperhémie métabolique ou l'hyperhémie fonctionnelle.

Elle se caractérise par une augmentation du débit sanguin au niveau des muscles actifs en raison du relargage de substances vasodilatatrices (ions potassium, ions hydrogènes, adénosine,...) par les cellules actives. Au niveau des vaisseaux résistifs

systémiques, cette augmentation de débit peut aussi être liée à l'hypoxémie<sup>7</sup>. Lorsque la pression partielle en O<sub>2</sub> est inférieure à 40 mmHg, les artérioles se dilatent

### 3) Le recrutement capillaire.

Il permet d'augmenter la surface d'échange avec les cellules en réduisant la distance pour la diffusion d'oxygène et de glucose pour les cellules (Levick, 2009).

### 4) La vasodilatation ascendante des petites artères nourricières.

Une artère nourricière est une artère provenant d'une artère de conductance et allant jusqu'aux artères terminales. Cette vasodilatation est médiée par les cellules endothéliales (Segal and Jacobs, 2001). Les substances vasodilatatrices induisant l'hyperhémie métabolique engendrent une hyperpolarisation locale des cellules endothéliales. Cette hyperpolarisation est transmise à la cellule endothéliale d'amont par l'intermédiaire des « gap junctions<sup>8</sup> » et aux myocytes vasculaires par les « gap junctions » myo-endothéliales entraînant ainsi une vasodilatation de toute l'artère nourricière d'amont (Levick, 2009).

### 5) La vasodilatation induite par le flux au niveau des artères de conductance.

Elle contribue aussi à l'augmentation des apports aux muscles actifs. Suite à l'hyperémie métabolique et à la vasodilatation ascendante, le flux augmente dans les artères de conductance en amont. Cette augmentation de flux entraîne une augmentation des forces de cisaillement (« shear-stress ») qui stimule la production de NO par les cellules endothéliales et contribue ainsi à la dilatation de l'artère (Levick, 2009).

L'ensemble de ces mécanismes contribue à l'adéquation entre les apports et les demandes énergétiques autorisant les efforts musculaires. Malheureusement, cette adéquation n'est pas toujours possible notamment dans le cadre de certaines pathologies artérielles.

## 1.3 Physio-pathologie vasculaire à l'effort en cas de sténose artérielle

La sténose artérielle correspond à une réduction plus ou moins importante du calibre d'une artère. Cette sténose provoque plusieurs modifications limitant les

<sup>7</sup> Hypoxémie : Baisse de la pression partielle en oxygène dans le sang artériel.

<sup>8</sup> Gap junctions : Ce sont des jonctions intercellulaires constituées de protéines et qui permettent aux cellules de communiquer.

adaptations à l'effort et entraînant ainsi une inadéquation entre les demandes énergétiques cellulaires et les apports. Tout d'abord, il existe une diminution du débit sanguin en aval, qui peut être plus ou moins compensée par les artères collatérales. Les lois de Darcy, Poiseuille et Bernouilli permettent de comprendre l'hémodynamique en conditions normales et pathologiques. La loi de Darcy nous apprend que, dans un état stable, le débit entre un point A et un point B est fonction de la conductance hydraulique et de la différence de pression entre ces deux points ( $\text{Pression(A)} - \text{Pression(B)}$ ). La conductance hydraulique est l'inverse de la résistance. La loi de Poiseuille définit la résistance. La résistance est inversement proportionnelle à la quatrième puissance du rayon du vaisseau et directement proportionnelle à la viscosité du sang et à la longueur du vaisseau considéré. La loi de Bernouilli nous précise qu'en fait, le débit entre le point A et le point B est linéairement proportionnel à la différence d'énergie mécanique du fluide entre ces deux points. Cette énergie mécanique du fluide est la somme de l'énergie de pression, de l'énergie potentielle et de l'énergie cinétique. Au niveau d'une sténose artérielle, la vitesse sanguine augmente et une partie de l'énergie totale du sang est convertie en énergie cinétique diminuant ainsi l'énergie de pression. En outre, le phénomène de vasodilatation ascendante peut être réduit si la sténose est située sur une artère nourricière. En effet, l'endothélium doit être intègre pour permettre cette vasodilatation (Segal and Jacobs, 2001). De plus, la dysfonction endothéliale à l'origine de la maladie athéromateuse est aussi à l'origine d'une moindre vasodilatation pouvant limiter l'hyperhémie métabolique et la vasodilatation induite par le flux au niveau des artères de conductance (Levick, 2009). Cette inadéquation entre les apports et les demandes cellulaires musculaires peut être à l'origine de douleur au niveau du groupe musculaire ischémié par l'intermédiaire de phénomènes complexes non établis à ce jour (Hirsch et al., 2006). Lorsque ce sont les groupes musculaires des membres inférieurs qui sont en ischémie, ceux-ci sont à l'origine de douleurs des membres inférieurs. Cette douleur, qui a la particularité d'apparaître lors d'un effort de marche et de s'estomper dans les dix minutes suivant l'arrêt de l'effort, est appelée la claudication intermittente. Cette douleur est à l'origine d'une limitation de la capacité de marche et elle est fréquemment rencontrée dans une maladie vasculaire périphérique appelée l'artériopathie oblitérante des membres inférieurs (ANNEXE 1).

## 1.4 Objectifs et plan du travail de thèse

Ce travail présente l'artériopathie oblitérante des membres inférieurs, qui est une atteinte des vaisseaux des membres inférieurs, en décrivant l'épidémiologie, les facteurs de risque et les moyens diagnostiques pour cette pathologie. Cette pathologie peut être soit asymptomatique soit symptomatique. La principale symptomatologie présentée par le patient est l'apparition de douleurs à la marche, qui limitent sa capacité de marche. Cette douleur est en grande partie liée à l'ischémie des groupes musculaires. Ce travail, en étudiant la capacité de marche des patients, va s'attacher à étudier de façon indirecte et directe l'ischémie des membres inférieurs. Nous aborderons les difficultés de l'évaluation de la capacité de marche en présentant les différents moyens possibles pour cette évaluation. En effet, cette évaluation de la capacité de marche et ainsi de l'ischémie peut se faire soit par l'interrogatoire, soit par des tests de laboratoire, soit par des tests ambulatoires. Chaque type d'évaluation présente des avantages et des inconvénients qu'il convient de connaître afin de les utiliser au mieux en fonction de leur intérêt pour le patient, pour le clinicien et pour le physiologiste. Après la mise en évidence de cette limitation de la capacité de marche, nous verrons que cette limitation de la capacité de marche peut être due à deux principales localisations ischémiques : l'ischémie distale, qui est la mieux connue et l'ischémie proximale, qui est moins connue et de diagnostic plus délicat. Cette distinction est importante car elle peut expliquer les différentes localisations douloureuses présentées par les patients et expliquer les éventuels errements diagnostiques. De plus ces lésions ischémiques engendreront des modifications physiopathologiques, fonction de la sévérité de la maladie, chez les patients. Cependant, nous montrerons que cette limitation de la capacité de marche peut aussi être associée à une diminution du contenu artériel en oxygène, qu'il ne faut pas méconnaître, à savoir l'hypoxémie d'effort. En outre, d'un point de vue clinique, cette évaluation de la capacité de marche apparaît importante pour trois raisons : elle est le reflet de la gravité de l'atteinte de la maladie, c'est un critère chirurgical et elle permet d'évaluer l'évolution sous traitement ou après une prise en charge spécialisée notamment par la réadaptation (Hirsch et al., 2006). Cette évaluation de la capacité de marche est ainsi un point clé de la prise en charge des patients présentant une artériopathie oblitérante des membres inférieurs.





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## 2 L'ARTÉRIOPATHIE OBLITÉRANTE DES MEMBRES INFÉRIEURS

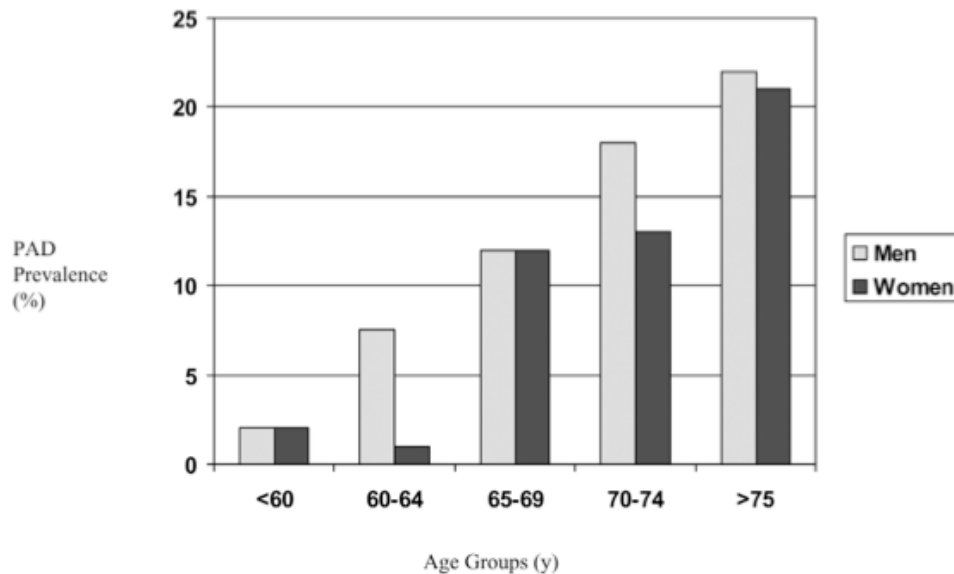
### 2.1 Définition et prévalence de l'artériopathie oblitérante des membres inférieurs (AOMI)

L'artériopathie oblitérante des membres inférieurs (AOMI) se caractérise par l'obstruction partielle ou complète des artères des membres inférieurs (Hirsch et al., 2001). La première description de la symptomatologie liée à l'AOMI a été réalisée chez le cheval par Jean-François Bouley, un vétérinaire, en 1831. Dans son rapport présenté à la tribune de l'Académie royale de médecine, J.F. Bouley décrit « la claudication intermittente des membres postérieurs, déterminée par l'oblitération des artères fémorales » (Bouley, 1831; Sugar, 1994). La première description chez l'Homme est attribuée à Barth en 1835 (Sugar, 1994) et les descriptions mécanistiques à Charcot en 1858. La diminution du calibre artériel rencontrée dans l'AOMI chez l'Homme est le plus souvent secondaire à la formation de plaques d'athérosclérose alors que dans la description de J.F. Bouley la claudication était liée à un parasite intestinal, *Strongylus vulgaris*. Ce parasite, en migrant dans les artères intestinales, entraîne une endartérite aortique qui se complique fréquemment d'accidents thrombo-emboliques (Becker, 2005). La définition initiale de l'AOMI se basait sur la présence de douleurs musculaires aux mollets apparaissant à la marche et soulagées par le repos (claudication intermittente) et/ ou sur l'absence d'un ou plusieurs pouls artériels aux membres inférieurs (Société française de médecine vasculaire et al., 2010). Actuellement, le critère diagnostique retenu est une mesure d'index de pression systolique de cheville de repos strictement inférieure à 0,90 (Hirsch et al., 2006).

La prévalence de cette pathologie varie selon le critère diagnostique. Le travail de Criqui et collaborateurs a mis en évidence ces variations de prévalence en étudiant une population californienne de 613 hommes et femmes (moyenne d'âge de 66ans) avec quatre outils de mesure différents (Criqui et al., 1985). En utilisant le questionnaire de Rose (Rose, 1962), questionnaire développé pour identifier la douleur spécifique de l'AOMI, la prévalence était de 2,2% chez l'homme et de 1,7 % chez la femme (Criqui et al., 1985). Cette prévalence passait à 20,3% chez l'homme et à 22,7% chez la femme en utilisant les anomalies de pouls fémoral ou tibial postérieur (Criqui et al., 1985). La prévalence était de 11,7% lorsque la mesure de l'index de pression systolique était utilisée (Criqui et al., 1985). D'autres études ont corroboré ces résultats d'une faible

prévalence avant l'âge de 50 ans et d'une augmentation de celle-ci après l'âge de 50 ans (figure5) (Boccalon et al., 2000; Diehm et al., 2004; Dormandy and Rutherford, 2000).

En définissant l'AOMI par un index de pression systolique de repos inférieur à 0,90, la prévalence en France est de 11% chez les sujets de plus de 40 ans (Boccalon et al., 2000).



**Figure 5 : Prévalence de l'artériopathie oblitérante des membres inférieurs (AOMI) diagnostiquée par la mesure de l'index de pression systolique en fonction de l'âge (Criqui et al., 1985). « PAD » signifie AOMI, « Men » signifie hommes, « Women » signifie femmes, « Age groups » signifie groupe d'âge et « y » signifie années.**

La prévalence de l'AOMI chez l'homme et la femme semble peu différente contrairement à celle de la maladie coronarienne (Fowkes et al., 1991; Kannel and McGee, 1985; Stoffers et al., 1996). Cette différence avec les autres maladies athéromateuses peut trouver son explication dans le fait que les valeurs d'index de pression systolique de repos de la femme sont physiologiquement plus faibles que chez l'homme pouvant ainsi conduire à une majoration de la prévalence chez la femme (Schank et al., 2006). En définitive, la prévalence de l'AOMI augmente avec l'âge chez les individus et avec l'exposition aux facteurs de risques de l'athérosclérose et ce, aussi bien aux USA qu'en Europe et qu'en Asie (Al Zahrani et al., 1997; Cheng et al., 1999; Gallotta et al., 1997).

## 2.2 Les facteurs de risque de l'artériopathie oblitérante des membres inférieurs

La cause majeure de l'AOMI est l'athérosclérose, qui est une maladie inflammatoire (Hansson, 2005; Ross, 1999). Elle est définie depuis 1957 par l'OMS comme « une association variable de remaniements de l'intima des artères, consistant en une accumulation locale de lipides, de complexes glucidiques, de sang, de produits sanguins, de tissus fibreux et de dépôts calciques, l'ensemble associé à des remaniements de la média ». Les facteurs de risque de l'athérosclérose sont bien établis et sont par conséquent ceux de l'AOMI (Hirsch et al., 2006). Les principaux facteurs de risque sont les facteurs de risque environnementaux représentés par le tabagisme, l'alimentation, l'inactivité physique mais aussi l'hypertension artérielle, le diabète, la dyslipidémie (Dormandy and Rutherford, 2000; WHO, 2007).

Le tabagisme augmente le risque de survenue d'AOMI de 2 à 6 fois selon les études (Fowkes et al., 1992; Kannel and McGee, 1985). De plus, cette augmentation du risque est dépendante de la dose journalière et de la durée de tabagisme (Powell et al., 1997; Price et al., 1999).

L'alimentation joue un rôle dans la survenue des maladies athéromateuses (WHO, 2007). Une alimentation riche en vitamine A, vitamine C, folates, vitamine B6, fibres, et acides gras poly-insaturés oméga 3 réduit la prévalence de l'AOMI, et améliore la distance de marche et l'index de pression systolique de cheville (Gardner et al., 2011a; Khandanpour et al., 2009; Lane et al., 2008; Maxwell et al., 2000; Merchant et al., 2003; Wilmlink et al., 2004). Une évaluation alimentaire avec des outils validés est intéressante pour limiter ce facteur de risque (Carsin and Mahe, 2010; Mahe et al., 2011a; Mahe et al., 2010d; WHO, 2007).

La pratique d'activité physique réduit le risque cardiovasculaire de façon inversement proportionnelle à l'intensité de cette activité physique (Hamer and Chida, 2008). Le risque de développer une AOMI est inversement lié à la pratique physique antérieure (Housley et al., 1993). L'AOMI évolue moins chez le patient ayant une activité physique régulière (Gardner et al., 2011b; Garg et al., 2009). L'incitation à une activité physique d'intensité modérée supérieure à 30 minutes pluri-hebdomadaires doit être réalisée chez l'artériopathe et le sujet sain (Graham et al., 2007; Hirsch et al., 2006; WHO, 2007).

L'hypertension artérielle augmente le risque de développer une AOMI mais son effet est moindre que sur la coronaropathie et l'accident vasculaire cérébral (Fowkes et al., 1992; Murabito et al., 1997). Le risque de claudication intermittente est lui augmenté de 2,5 à 4 fois chez l'homme et chez la femme hypertendus dans l'étude Framingham (Kannel and McGee, 1985).

Le diabète augmente le risque d'AOMI par 2 à 4 fois et est présent chez 12 à 20% des patients présentant une AOMI (Criqui et al., 1997; Hiatt et al., 1995; Meijer et al., 1998). Le risque de développer une AOMI est de plus proportionnel à la sévérité et à la durée du diabète (Beks et al., 1995).

L'augmentation du cholestérol total ou du « low density liprotein » (LDL) cholestérol ou la baisse du « high density liprotein » cholestérol (HDL) augmente le risque d'AOMI (Fowkes et al., 1992; Hiatt et al., 1995; Kannel and McGee, 1985).

En définitive, tous ces facteurs de risque participent à l'augmentation de la prévalence de l'AOMI. Ces facteurs sont à identifier chez les patients artériopathes afin d'optimiser leur prise en charge (WHO, 2007).

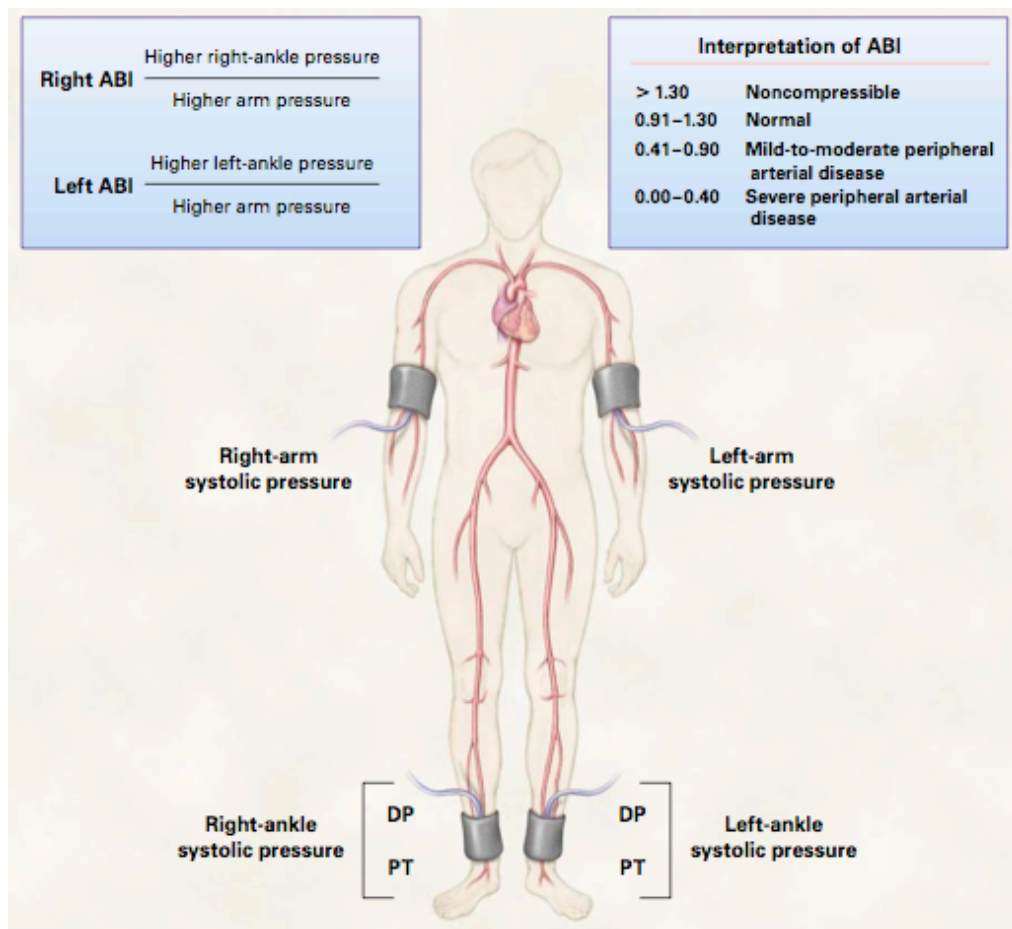
## **2.3 Les méthodes diagnostiques de l'artériopathie oblitérante des membres inférieurs**

L'interrogatoire et l'examen clinique ont une place importante lors du diagnostic d'AOMI (Hirsch et al., 2006). L'interrogatoire s'attarde à rechercher les différents facteurs de risque d'athérosclérose (cf. supra), à rechercher des antécédents de coronaropathie et d'accident vasculaire cérébral qui sont des pathologies fréquemment associées (Steg et al., 2007) et à caractériser les douleurs à la marche (Hirsch et al., 2006).

Lors de l'examen clinique, les pressions artérielles aux deux bras sont mesurées. L'auscultation des artères périphériques (notamment carotides, aorte, iliaques et fémorales) est effectuée ainsi que la palpation des pouls (artère tibiale postérieure, artère pédieuse et artère fibulaire). Des troubles trophiques cutanés sont recherchés.

A l'aide d'un appareil doppler et d'une sonde doppler (5 à 10 Mhz), les pressions des artères tibiales postérieures et pédieuses droites et gauches sont mesurées permettant de calculer les index de pression systolique (IPS) de cheville de repos pour chaque membre inférieur. D'après les recommandations actuelles, l'index de pression

systolique de repos est calculé en divisant la valeur la plus haute de la jambe divisée par la valeur la plus haute des pressions humérales (figure 6) (Grenon et al., 2009; Hiatt, 2001; Hirsch et al., 2006). Le résultat doit être exprimé avec 2 chiffres après la virgule (Hirsch et al., 2006). Cependant, en prenant la valeur la plus élevée de chaque jambe, Espinola-Klein et collaborateurs ont montré qu'une partie des patients à haut risque cardiovasculaire n'était pas prise en charge (10,8% de 831 patients). Ces auteurs ont alors suggéré d'utiliser la valeur la plus basse de chaque jambe et défini l'index de pression systolique de repos modifié (Espinola-Klein et al., 2008).



**Figure 6 : Méthode de mesure de l'index de pression systolique de cheville d'après Hiatt (Hiatt, 2001).**  
 « Right-arm systolic pressure » signifie pression artérielle systolique du bras droit, « left-arm pressure systolic pressure » signifie pression artérielle systolique du bras gauche. « Right-ankle systolic pressure » signifie pression artérielle systolique de cheville droite, « left-ankle systolic pressure » signifie pression artérielle systolique de cheville gauche. DP signifie artère pédieuse et PT signifie artère tibiale postérieure.  
 « Right ABI » signifie index de pression systolique (IPS) de cheville droit et « left ABI » signifie IPS de cheville gauche.

Prenant en considération ces données, nous avons suggéré d'utiliser la valeur la plus basse pour le dépistage de l'artériopathie oblitérante des membres inférieurs et

d'utiliser la valeur la plus haute pour le suivi de patients artériopathes (Mahe et al., 2010c).

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Ankle-brachial index and peripheral artery disease.

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## Accuracy of Financial Disclosures Reported by Physicians

**TO THE EDITOR:** Okike et al. (Oct. 8 issue)<sup>1</sup> found that the rate of conflict-of-interest disclosure reported by physicians who participated in the 2008 annual meeting of the American Academy of Orthopaedic Surgeons (AAOS) was 79% for directly related payments and 50% for indirectly related payments. I am writing to provide an update on the critical steps the AAOS has taken since the time this study was performed.

The AAOS has worked diligently for years and will continue to perfect, modify, and simplify the disclosure process that physicians use to identify their consulting and other arrangements with companies. Specifically, since 2008, we have made our mandatory disclosure process electronic; required disclosure of all potential conflicts and relationships, regardless of their relevance to the presentation; provided numerous educational programs and materials for our members that emphasize the importance of full disclosure and teach them how to fulfill this requirement; and formed a board project team to review our policies and recommend enhancements.

We believe that mandatory, complete disclosure and the appropriate management of conflicts of interest are essential. Our ongoing efforts to streamline the process and educate our members enable the physicians to focus on their real work — improving the quality of life for our patients with musculoskeletal conditions.

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Dr. Zuckerman reports receiving royalties from Exactech for design of a shoulder-replacement system. No other potential conflict of interest relevant to this letter was reported.

1. Okike K, Kocher MS, Wei EX, Mehlman CT, Bhandari M. Accuracy of conflict-of-interest disclosures reported by physicians. *N Engl J Med* 2009;361:1466-74.

**THE AUTHORS REPLY:** We thank Zuckerman for his response to our article. We agree that the AAOS has taken several important steps to improve the process for disclosing conflicts of interest since the time our study was conducted.

In addition to the steps taken by the AAOS, several recent changes regarding conflict of interest and its disclosure have been made by medical journals,<sup>1</sup> healthcare organizations,<sup>2</sup> universities,<sup>3</sup> pharmaceutical companies,<sup>4</sup> and state governments.<sup>5</sup>

We are optimistic that these changes will serve to promote full disclosure of conflicts of interest by all investigators; such disclosure is a minimum requirement for managing financial conflicts of interest in biomedical research.

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Since publication of their article, the authors report no further potential conflict of interest.

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3. New Johns Hopkins Medicine policies tighten rules on industry interactions. Press release of Johns Hopkins Medicine, Baltimore, April 8, 2009. (Accessed January 14, 2010, at [http://www.hopkinsmedicine.org/Press\\_releases/2009/04\\_07\\_09.html](http://www.hopkinsmedicine.org/Press_releases/2009/04_07_09.html).)

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## Ankle–Brachial Index and Peripheral Arterial Disease

**TO THE EDITOR:** Grenon et al. (Nov. 5 issue) have presented a validated method of calculating the ankle–brachial index that is currently used in the evaluation of patients with peripheral arterial

disease.<sup>1,2</sup> The highest systolic pressure in the dorsalis pedis or posterior tibial artery divided by the highest arm pressure determines the validated ankle–brachial index calculation.<sup>1,3</sup> However,



## CORRESPONDENCE

we would suggest that the decision to use this formula may depend on whether a physician wants to screen a patient for peripheral artery disease or wants to pursue follow-up for patients in whom the disease has already been diagnosed. Indeed, Espinola-Klein et al. found that when screening patients for the disease, using the highest artery pressure in the leg to calculate the index caused a group of patients at high risk for cardiovascular events to be overlooked (10.8% of 831 patients).<sup>4</sup> The authors suggest the use of a modified method for calculating the ankle-brachial index in which the lowest pressure in the leg artery is used instead of the highest. Using this modified method, they found that rates of cardiovascular events were comparable for patients with a validated ankle-brachial index of less than 0.90 and those with a modified ankle-brachial index of less than 0.90 (28.4% vs. 25.0%).<sup>4</sup> In conclusion, for follow-up of patients with peripheral arterial disease, taking the highest leg artery pressure seems best, whereas the lowest leg artery pressure might be recommended when screening patients for peripheral arterial disease.

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No potential conflict of interest relevant to this letter was reported.

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4. Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. *Circulation* 2008;118:961-7.

**TO THE EDITOR:** Grenon et al. emphasized the importance of calculating the ankle-brachial index in patients with peripheral arterial disease. The measurement method that they describe, which makes use of a Doppler probe and sphygmomanometer, is recommended as the reference method. However, the authors failed to mention the main limitation of this technique, which is its variability within and between observers.<sup>1,2</sup> We recently reported that this variability leads to marked center effects in multicenter studies, despite extensive staff training.<sup>3</sup> The center effect represented about 20% of the whole variability when the ankle-brachial index was considered as a continuous end point and about 10% of the whole variability when it was considered as a binary end point, whereas no center effect was observed for other clinical variables. Therefore, the statement by Grenon et al. that measurement of the ankle-brachial index with the use of Doppler probe and sphygmomanometer "can be used with versatility in the physician's office" is probably too optimistic, since the variability we describe is reason to limit its routine use. An alternative that could be put forward to standardize measurement of the ankle-brachial index in primary care is the use of a semiautomated device, which would require little observer training and seems subject to less variability.<sup>3</sup>

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**THE AUTHORS REPLY:** The standard method of reporting ankle-brachial indexes has always been to compare the highest systolic pressures from

the ankle and the arm.<sup>1</sup> Previous reports aimed at assessing the prognosis for patients with reduced ankle-brachial indexes have described different methods of calculation. One method takes the higher of the pressures for the dorsalis pedis and posterior tibial arteries in each leg, calculates the ankle-brachial index with the use of each measure, then uses the lowest of the two indexes calculated to predict prognosis.<sup>2</sup> Another method uses the mean of the pressures in the dorsalis pedis and posterior tibial arteries in each leg,<sup>3</sup> and still others suggest that for situations in which the pressures in the two pedal arteries are different, the lower value may be of benefit as well.<sup>4,5</sup> We agree with these observations.

However, the purpose of the video is to show the average practitioner a simple way of calculating the ankle-brachial index. The calculation used in the video is inaccurate about 10% of the time, which reflects the operator-dependent nature of even this simple procedure. With this in mind, if an average practitioner finds a difference in ankle-brachial indexes because of pressure differences in the two pedal arteries, it is more likely that

the lower result is a false positive, as there may be some difficulty in relocating the Doppler signal when flow is restored. Hence, the higher ankle-brachial index would still be the more accurate and useful result.

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Since publication of their article, the authors report no further potential conflict of interest.

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## Transfusion of RhD-Positive Blood in “Asia Type” DEL Recipients

**TO THE EDITOR:** The RhD status of transfusion recipients and donors is routinely matched for red-cell transfusion. This worldwide practice is due to the potent immunogenicity of RhD. In East Asians, the frequency of RhD-negative status is only about 0.3%, which sharply limits the supply of RhD-negative blood. However, approximately 30% of RhD-negative persons carry an RhD variant, termed “Asia type” DEL.<sup>1</sup>

Beginning in 2008, my colleagues and I organized a collaborative group of 10 laboratories, located in 10 cities in northern, central, and southern China. This group retrospectively evaluated 104 RhD-negative pregnant women with anti-D alloantibodies from 2005 through 2007. We also tracked 199 consecutive RhD-negative pregnant women with a history of gestations or parturitions in 2008. Women who delivered an RhD-negative infant or received Rh immune globulin were excluded from the study. We distinguished Asia type

DEL through Rh C, c, E, and phenotypes and DNA-based polymerase-chain-reaction assays or RHD sequencing.<sup>2,3</sup> In our retrospective study, we expected a DEL frequency of 0.30 among 104 pregnant women with documented anti-D alloimmunization. However, none of the 104 women expressed the DEL variant. In the second group, of the 199 RhD-negative women who were prospectively investigated for anti-D alloimmunization, 44 (22.1%) expressed the DEL variant. None of the carriers of this variant had anti-D antibodies, whereas such antibodies were detected in 38 of 155 truly RhD-negative women (24.5%) (relative risk of anti-D alloimmunization, 29.3).

The Asian type DEL displays the complete repertoire of RhD antigen epitopes.<sup>4</sup> Our study supports the biochemical observations that the DEL variants express normal RhD and pose virtually no risk of forming anti-RhD antibodies. We suggest that persons in East Asian populations who

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La mesure recommandée d'IPS a été validée comparée à l'artériographie des membres inférieurs (Hirsch et al., 2006). Suite à différentes études, différents seuils ont été déterminés avec différentes sensibilités et spécificités (Fowkes, 1988; Lijmer et al., 1996). Lijmer et collaborateurs ont montré que pour un seuil de 0,91, la sensibilité est de 79% et la spécificité est de 96% pour détecter des sténoses supérieures ou égales à 50% (Lijmer et al., 1996). Fowkes et collaborateurs, avec un seuil de 0,90 ont trouvé des résultats similaires avec une sensibilité de 95% et une spécificité de 100% (Fowkes, 1988). Ce seuil de 0,90 au repos est celui retenu pour le diagnostic d'AOMI (Hirsch et al., 2006). Nombre d'études ont ainsi montré la performance diagnostique de la mesure de l'IPS (Hirsch et al., 2006). La reproductibilité de cette technique a bien entendu été évaluée par plusieurs études (Baker and Dix, 1981; Carter, 1969; Strandness et al., 2002; Yao, 1970). La déviation standard entre deux mesures est de l'ordre de 0,05 à 0,08 suivant les études. Ainsi une modification des valeurs d'IPS de cheville entre deux mesures inférieures à 0,15 n'est pas considérée comme pathologique (Hirsch et al., 2006).

Chez les diabétiques, les sujets âgés et les insuffisants rénaux, les artères peuvent être incompressibles (la pression dans le brassard au niveau de la jambe n'abolit pas le flux), l'IPS ne peut alors être calculé (Hirsch et al., 2006). La méthode alternative peut être la mesure de la pression au niveau du gros orteil ou du second orteil qui permettra de définir l'index orteil-bras. Le calcul de l'index orteil-bras est obtenu en divisant la pression artérielle systolique mesurée au gros orteil par la pression artérielle systolique maximale entre les 2 bras. Une valeur d'index orteil-bras inférieure à 0,70 est considérée comme en faveur d'une AOMI (Carter, 1968; Hirsch et al., 2006). Cette mesure est sensible chez des patients ayant une rigidité artérielle car les artères digitales sont le plus souvent épargnées par le processus de calcinose, qui altère la compressibilité des artères (Hirsch et al., 2006). D'un point de vue pratique, la mesure est réalisée en mettant un petit brassard (taille adaptée à l'orteil type brassard pour nouveau-né) au niveau soit du gros orteil, soit du second, équipé d'un appareil de détection pléthysmographique qui permettra de déterminer la pression. Une alternative est l'utilisation d'une sonde laser doppler avec le brassard à pression. La mesure de la pression d'orteil et le calcul de l'index orteil-bras doivent être proposés chez les patients ayant un IPS de cheville supérieur à 1,30 (Hirsch et al., 2006).

L'IPS peut rester dans les limites de normalité notamment lorsque l'atteinte est minime car la maladie artérielle est une pathologie se manifestant à sa phase initiale à l'effort lorsque les apports en oxygène ne sont pas suffisants pour les besoins énergétiques de l'exercice. L'exemple type est l'endofibrose retrouvée chez le cycliste de haut niveau. Cette pathologie se traduit par une lésion non athéromateuse d'une artère iliaque entraînant des douleurs seulement lors d'efforts maximaux (Feugier and Chevalier, 2004). Ces sujets ont des IPS de repos normaux mais des IPS post-effort pathologiques. Ce seuil pathologique est variable en fonction des auteurs. Il est soit de 0,50 (Chevalier et al., 1991), soit de 0,66 (Abraham et al., 2001), soit de 0,54 (Schep et al., 2001). Il est d'ailleurs intéressant de noter que ces diminutions d'IPS pour l'endofibrose sont mieux mises en évidence lors des tests d'effort maximaux (à charge d'exercice croissante) que lors de tests d'efforts modérés (Ruffier-Dickson) comme nous l'avons montré dans un travail récent (Bruneau et al., 2009).

Une mesure en post-effort a été proposée chez les sujets artériopathes afin de sensibiliser la mesure (Sumner and Strandness, 1969). La mesure de l'IPS permet donc de réaliser le diagnostic d'AOMI mais l'IPS est aussi un facteur prédictif d'autres manifestations cliniques athéromateuses (accident vasculaire cérébral et infarctus) (Busch et al., 2009; Criqui et al., 2010). Cela met en lumière l'intérêt de sa réalisation chez des patients porteurs de facteurs de risque cardio-vasculaires d'autant que la plupart de ces patients sont asymptomatiques (cf. infra).

D'autres méthodes diagnostiques peuvent être proposées, mais en seconde intention, comme l'échographie-Doppler, la mesure de la pression partielle en oxygène transcutanée à l'effort, la tomodensitométrie avec injection de produit de contraste, l'imagerie par résonance magnétique avec injection de produit de contraste, et l'artériographie (Hirsch et al., 2006).

## **2.4 Les différents stades cliniques de l'artériopathie oblitérante des membres inférieurs**

L'AOMI est rencontrée chez les patients sous différentes formes cliniques qui sont au nombre de quatre d'après les recommandations de l'American College of Cardiology et de American Heart Association (ACC/AHA) : le stade asymptomatique, le

stade de claudication, le stade d'ischémie critique et le stade d'ischémie aiguë (Hirsch et al., 2006). Des classifications symptomatiques ont été décrites et sont fréquemment utilisées notamment lors des études. Ce sont la classification de Leriche et Fontaine et celle de Rutherford (Norgren et al., 2007a).

| Leriche et Fontaine |                                           | Rutherford |           |                            |
|---------------------|-------------------------------------------|------------|-----------|----------------------------|
| Stade               | Clinique                                  | Classe     | Catégorie | Clinique                   |
| I                   | Asymptomatique                            | 0          | 0         | Asymptomatique             |
| IIa                 | Claudication faible > 200 mètres          | I          | 1         | Claudication faible        |
| IIb                 | Claudication modérée à sévère <200 mètres | I          | 2         | Claudication modérée       |
|                     |                                           | I          | 3         | Claudication sévère        |
| III                 | Douleur de repos                          | II         | 4         | Douleur de repos           |
| IV                  | Ulcération, gangrène                      | III        | 5         | Perte de substance mineure |
|                     |                                           | IV         | 6         | Ulcération ou gangrène     |

**Tableau 3** : Classifications de l'artériopathie oblitérante des membres inférieurs. Adaptation d'après Dormandy et Rutherford (Dormandy and Rutherford, 2000).

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### **3 LA CAPACITÉ DE MARCHÉ : LES DIFFÉRENTS STADES**

Au cours de l'AOMI, la capacité de marche, reflétée par la distance maximale de marche d'un patient, peut être modifiée. Cette capacité de marche est importante à évaluer car elle conditionne en partie la qualité de vie des patients. Dans ce travail, nous distinguerons deux types de capacité de marche : celui où le patient est non limité appelé stade asymptomatique et celui, où le patient est limité, appelé stade de claudication intermittente.

#### **3.1 Le stade asymptomatique**

Le stade asymptomatique est défini par l'absence de symptôme ischémique douloureux au niveau des membres inférieurs. Sur 100 patients présentant une AOMI, entre 20 et 50 sont asymptomatiques (Weitz et al., 1996). La forme asymptomatique est 2 à 5 fois plus importante que la forme symptomatique. McDermott et collaborateurs ont montré que sur 933 femmes, 328 soit 35% avaient une AOMI définie par un  $IPS < 0,90$ . Chez ces 328 patientes artériopathes, la forme asymptomatique était présente chez 63%. Cependant, ces patientes "asymptomatiques", c'est-à-dire ne présentant pas de douleur à la marche, avaient d'autres manifestations comme par exemple une vitesse de marche moins rapide ou un allongement du temps pour se relever d'une position assise (McDermott et al., 2002). Il a été montré aussi par cette même équipe que les sujets présentant un stade asymptomatique avaient une dysfonction nerveuse et une moins bonne qualité de vie comparés à des sujets claudicants et à des sujets témoins appariés (McDermott et al., 2008). Ces données suggèrent que la terminologie de stade asymptomatique serait impropre et qu'il y aurait des manifestations autres que la douleur liée à la marche.

#### **3.2 La claudication intermittente**

La claudication intermittente est définie comme une fatigue, un inconfort ou une douleur qui apparaît au niveau d'un groupe musculaire pendant un effort à cause d'une ischémie induite par l'exercice et qui disparaît au repos en moins de dix minutes (Hirsch et al., 2006). En effet, au repos, la vascularisation est suffisante pour assurer le fonctionnement musculaire et la viabilité des tissus. En revanche, à l'effort, les besoins



métaboliques augmentent et en cas de sténose artérielle, les apports sont insuffisants. Il y a ainsi une inadéquation entre les besoins et les apports, ce qui conduit à l'apparition de la claudication intermittente (Hirsch et al., 2006).

La claudication intermittente touche entre 10 et 35% des artériopathes (Weitz et al., 1996). Elle se manifeste au niveau des groupes musculaires situés en aval de la lésion artérielle obstructive. Dans les premières descriptions, elle touchait essentiellement les mollets comme en témoigne le questionnaire d'évaluation de la douleur vasculaire de Rose (Rose, 1962). Puis d'autres localisations ont été établies comme la cuisse (lors de sténose de l'artère fémorale profonde par exemple), la fesse (lors de sténoses de l'artère iliaque interne notamment). Celles-ci ont été prises en compte dans les questionnaires (Edinburgh et San Diego) d'évaluation ultérieurs (Criqui et al., 1996; Leng and Fowkes, 1992). Ces questionnaires ont été développés afin d'essayer de différencier au mieux les claudications intermittentes vraies des pseudo-claudications liées à d'autres pathologies comme des pathologies neurologiques, rhumatologiques, veineuses ou autres (White, 2007).

La claudication intermittente permet de déterminer deux distances de marche intéressantes en clinique pour caractériser la capacité de marche d'un patient. D'une part, la distance de marche relative, qui est la distance de marche à laquelle la douleur apparaît. D'autre part la distance maximale de marche qui est la distance à laquelle le patient s'arrête en raison de la douleur. Ces distances de marche sont d'autant plus importantes pour les cliniciens qu'elles permettent d'évaluer la sévérité de la gêne fonctionnelle du patient, d'envisager une prise en charge chirurgicale et un suivi de la maladie (avec ou sans traitement).

L'évaluation de la distance de marche des patients apparaît donc comme un point essentiel dans la prise en charge des patients artériopathes. Différents moyens ont été développés pour appréhender au mieux cette distance de marche, véritable reflet de l'atteinte fonctionnelle de la maladie : l'évaluation par l'interrogatoire, l'évaluation en laboratoire et l'évaluation ambulatoire.

### **3.2.1 L'évaluation par l'interrogatoire**

L'évaluation par l'interrogatoire en posant simplement au patient la question suivante « Quelle est votre distance maximale de marche sans vous arrêtez ? » permet

une estimation très subjective. En pratique les patients ont d'énormes difficultés à réaliser de la sorte l'évaluation de leur distance maximale de marche (Watson et al., 1997). Pour répondre à cette difficulté, un questionnaire, le « Walking Impairment Questionnaire » (WIQ) a été développé (Regensteiner et al., 1990). Celui-ci n'évalue pas directement la distance maximale de marche mais évalue le degré de difficulté à réaliser certaines distances, à marcher à certaines vitesses et à monter des escaliers. Il présente l'avantage de standardiser les réponses et d'avoir été comparé au test de référence, le test sur tapis (Cf. Infra) (McDermott et al., 1998; Myers et al., 2008). Ce questionnaire comprend trois échelles : une échelle pour la distance de marche, une échelle pour la vitesse de marche et une échelle pour la montée des escaliers. Pour compléter ce questionnaire, il faut répondre à 14 questions : 7 questions sur la distance de marche, 4 questions sur la vitesse de marche et 3 questions sur la montée des escaliers. Pour chacune de ces questions, il y a 5 propositions de degré de difficulté (« aucune difficulté » à « infaisable ») (ANNEXE 2). Ce questionnaire étant assez complexe au niveau des questions et en raison du grand nombre de propositions de réponses, nous avons évalué la mise en place de ce questionnaire dans notre pratique chez des patients artériopathes en utilisant une version française du WIQ. Lors de cette étude, nos interrogations étaient les suivantes : si les questionnaires sont bien remplis, quelle est la corrélation des résultats issus des questionnaires avec la distance maximale mesurée sur le tapis ? Si les questionnaires sont mal remplis, quelles sont les erreurs et la correction des erreurs améliorent-elles la corrélation des résultats issus du questionnaire avec la distance maximale sur tapis ?

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Limitations of self-reported estimates of functional capacity using the Walking Impairment Questionnaire.

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Une étude prospective non interventionnelle a été réalisée. Les patients ont été inclus consécutivement sur une période de trois mois. Le questionnaire WIQ était rempli

par chaque patient avant qu'une mesure de sa vitesse de marche ne soit réalisée et qu'il ne réalise un test de marche sur tapis (3,2km/h, 10% de pente). Le patient répondait d'abord seul au questionnaire puis des erreurs étaient recherchées et corrigées par une infirmière avec le patient.

Les erreurs prises en compte pour le questionnaire étaient :

- réponse manquante définie par l'oubli de répondre à la question ou par une tâche non réalisée par le patient ;
- réponse double définie par la présence de deux propositions cochées, ou plus, pour répondre à une même question ;
- réponse paradoxale définie par une réponse indiquant une moindre difficulté à réaliser une tâche alors que le niveau de difficulté augmente (la distance augmente ou la vitesse augmente ou les étages augmentent).

Les corrections étaient faites de la façon suivante :

- pour une réponse manquante, il était demandé au patient de répondre à la question s'il s'agissait d'un oubli accidentel. Si le patient répondait qu'il n'effectuait jamais cette tâche, il lui était demandé de répondre ce qu'il se sentait capable de faire pour cette tâche. Enfin, si le patient n'était toujours pas capable de répondre, il était coché incapable de réaliser la tâche ;
- pour une réponse double, il était demandé au patient de choisir sa première réponse. Si le patient était incapable de choisir, la réponse avec le plus grand degré de difficulté était conservée. Par exemple, si le patient avait coché « léger » et « moyen » pour réaliser 20 mètres, la réponse « moyen » était conservée ;
- pour une réponse paradoxale, l'infirmière rediscutait avec le patient en lui montrant qu'il y avait une certaine logique dans les échelles (distance de marche, vitesse de marche et montée des escaliers). Le patient était alors invité à re-choisir ses réponses.

Aucun patient sur cette durée de trois mois n'a refusé de réaliser l'étude. Soixante treize patients ont été inclus dont 58 hommes. Treize patients (17,8%) étaient diabétiques. L'IPS moyen était de  $0,77 \pm 0,22$  (n=72 ; un patient manquant en raison de plaies au niveau des deux membres inférieurs rendant les mesures impossibles).

En prenant en compte l'ensemble des erreurs possibles, 37 des 73 questionnaires ont dû être corrigés soit pour réponse(s) manquante(s) (n=23, n=24 et n=24 pour les échelles de distance de marche, vitesse de marche et montée des escaliers, respectivement), soit pour réponse double (n=3, n=0 et n=1 pour l'échelle de distance de marche, vitesse de marche et montée des escaliers respectivement) soit pour réponse paradoxale (n=5, n=6 et n=1 pour l'échelle de distance de marche, vitesse de marche et montée des escaliers respectivement). Le score total WIQ sans correction (au moins deux des trois échelles complètes et valables) a pu être calculé chez 56 patients (77%). La corrélation du score WIQ avec la distance maximale mesurée sur le tapis était de 0,63 avant la correction (n=56) et de 0,65 après la correction des erreurs (n=73).

Le nombre d'erreurs est important dans le remplissage de ce questionnaire. La correction de ces questionnaires par une infirmière avec le patient est chronophage et n'améliore que très peu la corrélation avec le test sur tapis. Nous suggérons de réduire le nombre de questions du WIQ ou de développer d'autres questionnaires plus simples à utiliser en routine clinique.

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# Limitations of Self-reported Estimates of Functional Capacity Using the Walking Impairment Questionnaire

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## KEYWORDS

Claudication;  
Peripheral artery  
disease;  
Non-invasive diagnosis

**Abstract** *Objective:* A potential issue with the Walking Impairment Questionnaire (WIQ) is that it is relatively complex. We estimated the number of errors made by patients when self-completing the WIQ, and assessed the benefit of correcting missing, duplicate or paradoxical (i.e., reported lower difficulty for a higher-intensity task) answers.

*Design:* Prospective non-interventional study.

*Materials:* All consecutive new patients with claudication over a 3-month period.

*Methods:* The WIQ was self-completed before patients performed a constant-load treadmill walking test (maximised to 750 m).

*Main outcome measure:* We analysed the coefficient of determination of the linear relationship between overall WIQ score (mean of the available subscales when at least two subscales are available) and treadmill maximal walking distance (MWD), before and after correction of errors.

*Results:* We studied 73 patients. Thirty-seven questionnaires had to be corrected for one or more errors. The coefficient of determination between the overall WIQ score and MWD was  $R^2 = 0.391$  ( $n = 56$ ) and  $R^2 = 0.426$  ( $n = 73$ ) before and after correction, respectively.

*Conclusion:* Supervision of self-completed WIQs detects errors in almost half of the questionnaires, resulting in a missing overall WIQ score in 23% of cases among uncorrected questionnaires. The overall WIQ score correlates only moderately with MWD, even after correction.

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In patients with peripheral artery disease (PAD), exercise-induced limb ischaemia (claudication) limits walking capacity. The distance at which claudication forces the patient to stop walking is referred to as the maximal walking distance (MWD). Although MWD performed on a treadmill is considered the gold standard for evaluating walking capacity in patients with PAD,<sup>1</sup> many physicians do not have a treadmill. Self-reported walking capacity is therefore a widely used approach for estimating walking capacity. Self-reported functional capacity can be predicted by the Walking Impairment Questionnaire (WIQ), which correlates moderately with objective measurements of MWD or changes in walking capacity.<sup>2-6</sup> The WIQ includes subscales for walking distance and speed and for stair climbing.<sup>7</sup> It is widely used and is validated as a self-administrated tool.<sup>5,8,4</sup>

The interest in self-completing questionnaires is to avoid any influence of the physician or nurse on patient responses, and reduce the time and effort needed from the medical staff. A potential issue when patients self-complete the WIQ is its relative complexity. Indeed, to complete the WIQ, patients need to answer 14 questions: seven in the walking distance subscale, four in the walking speed subscale and three in the stair-climbing subscale. Furthermore, each question has five different 'difficulty ratings' to choose from.

We aimed to evaluate the practical aspects of putting the WIQ into practice in our medical routine. Specifically, we counted the number of errors made by the patients when self-completing the WIQ, and estimated the proportion of resulting missing final WIQ values, which has rarely been done.<sup>7</sup> An additional novel aspect was to assess whether or not supervising completion of the form with correction of errors improves the concordance of the WIQ with objective measurements of MWD.

## Material and Methods

### Study population

A prospective study was performed on all new patients referred to our laboratory for treadmill exercise testing. Treadmill walking tests are used in our department to objectively assess walking capacity in patients with claudication. Only patients speaking French or who had never previously completed the WIQ were included in the present study. The patients' characteristics (body mass and stature), treatments, smoking habits and medical histories were retrieved via interview and from available data. Ankle-to-brachial indices (ABIs) were also measured, unless previous recordings <3 months old were available and the patient's medical condition had not changed since the last recording. The study received local ethics committee approval and conforms to the Declaration of Helsinki. Written, informed consent to participate to the study was obtained from all patients. The study is accessible on the National Institutes of Health (NIH) website under reference NCT01114178.

### Self-completion of the WIQ

We used the same French version of the WIQ as in a previous study,<sup>3</sup> adapted from Myers et al. (Fig. 1).<sup>5</sup> In brief, the WIQ

measures the degree of difficulty in walking and climbing stairs. All answers are scored from 0 to 4 (4 = none, 3 = slight, 2 = some, 1 = much difficulty and 0 = unable to do). Patients were provided a blue or black pen by the admission desk to self-complete the WIQ at arrival in the department. They were given approximately 10 min to complete the questionnaire, but, if necessary, additional time was provided. Patients were asked to do their best to complete the questionnaire without medical support or supervision, respond to all questions and tick only one box per answer. Thereafter, the pen and questionnaire were collected by a technician.

### Alterations to the self-completed WIQ

Due to the well-known inverse relationship between walking speed and MWD in patients with PAD, answers showing lower levels of difficulty for higher distance (distance subscale), speed (speed subscale) or number of stairs climbed (climbing-stair subscale) were considered 'paradoxical answers'. Duplicate answers were defined as two or more boxes ticked for the same question. The self-completed questionnaire was checked by a trained nurse for missing, duplicate or paradoxical answers before the patient was admitted to the exercise-test room. When necessary, missing, duplicate or paradoxical answers were discussed with the patient and modified or completed with a red pen using the following rules and order:

- \* For each missing answer, the patient was asked to explain the reason for this. If the question was skipped accidentally, the patient was asked to complete the missing question. If the reason was, "I never perform such a task" the patient was asked to assume what would be the answer if he/she ever had to perform that task. If the patient was still unable to answer, or declared to never perform the task, the task was coded 'unable to do'.
- \* For duplicate answers to a question, the patient was asked to choose one of their initial responses. If unable to choose, the higher level of difficulty was arbitrarily kept.
- \* For paradoxical answers within a subscale, a discussion between the patient and the nurse underlined the fact that the answers within a subscale were expected to follow a logical order with unchanged or increasing difficulty with increase in task level (speed, distance or number of stairs). The patient was provided with the red pen and allowed to modify the initial answers. The questionnaires were stored separately from patient's files and blindly analysed.

### Measurement of usual walking speed

Once the questionnaires were collected and corrected, the patients were asked to walk to the test room at their usual speed. The technician or nurse walked slightly behind the patient so as not to influence their usual walking speed. The two rooms are approximately 19 m apart, and between them are two white lines on the floor separated by 10 m. The time taken to walk between these lines was recorded with a stopwatch to allow calculation of the patient's usual 10-m walking speed.

Please answer each following question with one and only one « X » in the box that best describes your situation. If you never perform an activity, estimate what it would be to perform it. If you think you would not be able to perform the task or if you cannot physically perform a specified activity without stopping to rest because of symptoms such as leg pain or discomfort, please place a “X” in the box labelled “unable to do”.

**A –Walking distance:** For each of the following walking distances, how much difficulty do you have to walk on level ground without stopping to rest.

|                                              | No<br>difficulty         | Slight<br>difficulty     | Some<br>difficulty       | Much<br>difficulty       | Unable<br>to do          |
|----------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Walk indoors (such as around your house)? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Walk 20 m(1/4 block)?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Walk 50 m(1/2 block)?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Walk 100 m(1 block)?                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Walk 200 m(2 blocks)?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Walk 300 m(3 blocks)?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Walk 500 m(5 blocks)?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**B –Walking speed:** For each of the following walking speeds, how much difficulty do you have to do one city block (~300 m) on level ground without stopping to rest.

|                                                | No<br>difficulty         | Slight<br>difficulty     | Some<br>difficulty       | Much<br>difficulty       | Unable<br>to do          |
|------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Walk 1 block slowly (slower than usual)?    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Walk 1 block at average speed (usual pace)? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Walk 1 block quickly (faster than usual)?   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Run or jog 1 block ?                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**C –Stair climbing:** For each proposition below, how much difficulty do you have to climb stairs without stopping to rest. One flight of stairs is roughly equal to 14 steps

|                               | No<br>difficulty         | Slight<br>difficulty     | Some<br>difficulty       | Much<br>difficulty       | Unable<br>to do          |
|-------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Climb 1 flight of stairs?  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Climb 2 flights of stairs? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Climb 3 flights of stairs? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

*Adapted in French from Coyne et al.; J Vasc Surg 2003;38:296-304.*

Figure 1 English translation of the French version of the WIQ used in the present study.

### Treadmill walking capacity

The tests were performed by a physician who was not aware of the WIQ answers. We used a 10% slope and 3.2 km h<sup>-1</sup>

speed. The speed was reached within 1 min to allow for the patient's adaptation to treadmill walking. Prior to starting, patients were informed that the test could be stopped on their request at any time when their symptoms force them to



stop (and not when claudication first occurs). For technical reasons, in the absence of symptoms or in the case of non-limiting symptoms, we fixed the maximum duration of treadmill exercise to 15 min (~750 m), as we previously showed that only 7.5% of patients who reach this distance would stop within the next 250 m.<sup>9</sup> Treadmill MWD was recorded for each patient.

### Data collection and analysis

A first score was performed using original answers (black or blue answers only). Indeed, the presence of some errors does not always prevent the calculation of the WIQ score. In this analysis, the highest difficulty rating of duplicate answers was kept for analysis; if >50% of the subscale items were coded as "Don't do for other reasons", the subscale was coded as missing;<sup>7</sup> when >50% of items were available within a subscale, the score for this subscale was calculated as the sum of the values obtained for each available question divided by the total possible sum for the available questions only; each sub-scale score was expressed as a percentage of the maximum possible score; and, the overall WIQ score was calculated when scores for at least two subscales were available and as the mean of the available two or three sub-scale scores. The percentage of incomplete, duplicate or paradoxical answers was noted.

A second scoring was performed after correction of the WIQ. The score was calculated according to an earlier description.<sup>4</sup> In brief, for each question, a value is obtained by multiplication of each degree of difficulty by a pre-defined number for each of the different proposed distances, speeds or stairs climbed. Within each subscale, the sum of the values obtained for each question is divided by the highest possible score, which is 14 080, 46 and 288 for distance, speed and stair climbing, respectively. The sub-scale scores are then multiplied by 100 to give the percentage (of maximum) values. The overall WIQ score is the mean value of the three sub-scale scores (i.e. (distance score + speed score + stair-climbing score)/3).

Usual walking speed and MWD are reported as median (25th–75th percentiles). The concordance of these variables with the WIQ scores was assessed using linear regression analysis. The coefficient of determination ( $R^2$ ) was reported for the distance- and overall WIQ scores with treadmill MWD and the speed- and overall WIQ scores with usual 10-m walking speed, before and after correction of the questionnaire, respectively.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0. For all tests, a two-tailed  $P < 0.05$  was used to indicate statistical

significance. Data are expressed as mean  $\pm$  SD, unless otherwise stated. A minimum of 62 observations was required to estimate the proportion of questionnaires with error with an absolute precision of 12.5% for the determination of the 95% confidence intervals and with  $\alpha = 0.05$  and 80% power. For practical reasons, due to the usual activity of the department (i.e., the number of patients referred to the laboratory each month), we decided to include all new consecutive patients referred over a 3-month period starting from January 2010.

### Results

None of the eligible patients refused to participate or had to be excluded. We recruited 73 patients, 58 of which were males. The age, stature and body mass of the whole cohort was  $59 \pm 12$  years,  $169 \pm 8$  cm and  $76 \pm 14$  kg, respectively. Thirteen (17.8%) patients were diabetic. Twelve had never smoked, and 25 and 36 were active and former smokers, respectively. All patients reported exercise-related unilateral or bilateral claudication for at least 3 months. Mean ABI was  $0.77 \pm 0.22$  ( $n = 72$ , one ABI value missing due to cutaneous lesions on both ankles). Of the whole cohort, 56 (77%) received anti-platelet drugs or anticoagulants, 42 (58%) cholesterol-lowering agents, 41 (56%) anti-hypertensive drugs and 26 (36%) beta-blockers.

Accounting for all possible errors, 37 of the 73 questionnaires (50.6%; confidence interval 39.1–62.1%) had to be corrected for missing ( $n = 23$ , 24 and 24), duplicate ( $n = 3$ , 0 and 1) or paradoxical ( $n = 5$ , 6 and 1) answers within the distance, speed and stair-climbing subscales, respectively. As shown in Table 1, the overall WIQ score (that requires that at least two subscales scores are available) could only be obtained in 56 of the 73 patients (77%).

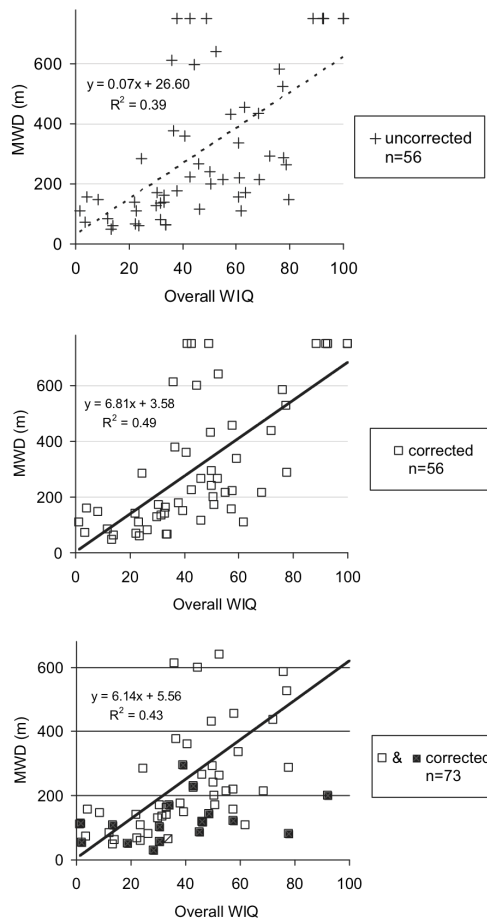
The distributions of MWD and usual 10-m walking speed did not follow a Gaussian distribution (Kolmogorov–Smirnov test:  $P < 0.05$  for both variables). Median (25–75 percentiles) MWD and 10-m speed were 171 m (109–376) and  $4.0 \text{ km h}^{-1}$  (3.5–4.1), respectively. As shown in Table 1, although coefficients of determination tended to increase after correction (except for the speed-WIQ subscale with the 10-m speed), none of these differences were statistically significant. Fig. 2 shows the relationship between the overall WIQ score and MWD before and after correction.

### Discussion

The WIQ allows for the estimation of self-reported walking capacity, and is an interesting tool for standardising the

**Table 1** Coefficients of determination ( $R^2$ ) between WIQ scores and treadmill MWD and between WIQ scores and usual 10-m walking speed. N-values indicate the number of available results.

|                                   | Questionnaires with errors only |                    | Whole group        |
|-----------------------------------|---------------------------------|--------------------|--------------------|
|                                   | Non-corrected                   | Corrected          | Corrected          |
| Distance WIQ subscale vs. MWD     | 0.252 ( $n = 56$ )              | 0.276 ( $n = 56$ ) | 0.277 ( $n = 73$ ) |
| Overall WIQ vs. MWD               | 0.391 ( $n = 56$ )              | 0.486 ( $n = 56$ ) | 0.426 ( $n = 73$ ) |
| Speed-WIQ subscale vs. 10-m speed | 0.295 ( $n = 58$ )              | 0.322 ( $n = 58$ ) | 0.362 ( $n = 73$ ) |
| Overall WIQ vs. 10-m speed        | 0.248 ( $n = 56$ )              | 0.302 ( $n = 56$ ) | 0.348 ( $n = 73$ ) |



**Figure 2** Relationship between the overall WIQ score and treadmill MWD before (upper panel) and after (middle panel) correction in the same 56 patients. The lower panel shows the patients of the middle panel (open squares) and the other 17 patients (closed squares). The regression line is for all 73 patients.

results of epidemiological or research studies. However, it is quite complex, with 14 questions and each having five possible answers (i.e., 70 boxes). When putting it into clinical practice, over half of the questionnaires needed alteration in at least one of the items. As described previously,<sup>7</sup> if more than half of the sub-scale items were coded as "Don't do for other reasons", the subscale was coded as missing. In the study of Coyne et al., from the 60 patients who were studied, 10% of values were missing for the distance subscale, 13% for the speed subscale and 23% for the stair-climbing subscale.<sup>7</sup> Unfortunately, the total number of questionnaires that needed alteration within at least one subscale was not reported, but was probably lower than 46%, as one patient could have had multiple missing subscales. Coyne et al. explained that the participants reported "Don't do for other reasons" as the cause of most of the errors found in their self-

completed WIQs.<sup>7</sup> The proportion of missing values for the stair-climbing subscale observed in our study was close to that previously reported and likely results due to our patient's lifestyle; however, the reason for missing answers was not assessed in the present study. Of importance is the fact that we checked the self-completed WIQs for duplicate and paradoxical answers and not only missing answers. This was apparently not done in previous studies and likely explains the high proportion of altered questionnaires (51%) and missing overall WIQ scores (23%) of the present study. Whether errors are due to the questionnaire being insufficient to reflect the diversity of real-life situations, or to the patients' inadequate answering is an interesting issue. Indeed, a missing answer can result from the patient not understanding or accidentally skipping the question. In both cases, these could be argued to represent patient or questionnaire errors. Duplicate answers can result from the patient having various difficulties in various clinical circumstances or experiencing different difficulties, even in a single period of walking<sup>10</sup> ('questionnaire error'), or from the patient answering that their capacity is quite constant but "somewhere between the two proposed values" (patient error = patient not strictly following the recommendation for completing the questionnaire). Paradoxical answers are more likely to result from patient error (as increasing difficulty is expected with increasing task level). Nevertheless, there are few clinical situations, such as popliteal entrapment syndrome, where paradoxical claudication may occur with a higher difficulty at walking than at running; then, a 'questionnaire error' might also occur. No patient with popliteal entrapment syndrome was included in our group.

As over half of the WIQs had to be modified after supervision, the second question of interest is to know whether, apart from increasing the number of available results, supervision improves the relationship of the scores obtained with objectively measured functional capacity. In other words, if supervision was to be done in large-scale studies, is it worth the time and effort? Probably not! Supervision of patients' answers by a nurse or a physician after self-completion is time consuming. It does improve the number of available overall WIQ scores but does not dramatically improve concordance with treadmill MWD.

Several studies have focussed on the correlation of WIQ scores to MWD.<sup>3-5</sup> We previously reported a correlation coefficient of  $r = 0.53$  (0.13–0.77) between the WIQ score and MWD assessed using a constant-load treadmill test comparable to the one used in the present study.<sup>3</sup> In another study, Spearman rank correlation coefficients ( $\rho$ ) between the WIQ distance score and the 6-min walk performance were 0.557 among 145 patients with PAD ( $P < 0.001$ ) and 0.484 among 65 patients without PAD ( $P < 0.001$ ).<sup>4</sup> Other studies have reported Pearson's correlation coefficients ranging between 0.33 and 0.52 for WIQ distance score and MWD.<sup>5</sup> The coefficients of determination calculated for these studies, which describe how well the regression line approximates the real data points, are very low, ranging between 0.10 and 0.35. In the present study, although the correlation of uncorrected overall WIQ score to MWD was higher than previously observed, it appears almost unchanged after correction and remains only moderate.

Whereas all studies report consistent results for the correlation of MWD with the WIQ scores, conflicting results are found for the correlation of WIQ with the usual speed of patients. According to Myers et al., the WIQ speed subscales did not correlate with the self-selected pace, as determined by adjustment of treadmill speed by the patient until it matched his/her typical pace ( $n = 48$ ,  $r = 0.08$ ; non-significant).<sup>5</sup> By contrast, the correlation coefficients between WIQ speed score and usual 4-m walking speed were reported to be 0.528 among patients with PAD and 0.524 among patients without PAD (both  $P < 0.001$ ).<sup>4</sup> Although increasing the distance over which speed was measured (here, 10 m instead of 4 m) was expected to increase the precision of speed calculation, the correlation observed in our group is in the range of that previously reported by McDermott et al.<sup>4</sup> Is the relatively low concordance between MWD and WIQ scores a major issue precluding the use of questionnaires (specifically, the WIQ) in clinical practice? Probably not. It should be taken into consideration that the WIQ is not meant to be an alternative for a treadmill test (which is an objective measurement), but rather as a subjective evaluation of the physical impairment as perceived by the patient. Then, what is to be done when the WIQ cannot be scored after self-completion? First, another shorter and simpler questionnaire might reduce the number of missing scores. Second, it might be better to ask how long the patient can walk rather than how far, since most patients have a watch. Last, another possible approach is to study the walking impairment through some usual daily-life situations (number of stops required to walk to the post office or to the closest bar, ability to reach the medical office from the parking lot without stopping, etc.).

There are some limitations to the present study. The population studied might not be representative of patients, who might enter a study of arterial claudication. Specifically, a high proportion of our patients are referred for proximal claudication. This might limit the generalisation of our results. The second point is that we did not study ethnic influence on the answers. In fact, the large majority of our consultants are Caucasian and local natives. For ethical reasons, we included no question dealing with ethnic origin. Last, it could be suggested that previous experience of completing a specific questionnaire might decrease the number of errors a patient makes when resubmitted to the same questionnaire. This could be of interest in areas where questionnaires are frequently used. The specific interest of the present study is that the patients included had never previously completed the WIQ, as to the best of our knowledge, no other laboratory or vascular physician in our area uses this questionnaire. This allowed us to study the intrinsic properties of the questionnaire but does not preclude that the rate of errors might be lower in other countries.

## Conclusion

Self-completion of the WIQ by the patient results in a high rate of errors. To our opinion, a simpler version of the WIQ (e.g., reducing the number of questions) or a new simpler questionnaire is needed to facilitate self-reported estimation of functional capacity in PAD patients.

## Conflict of Interest

There are no conflicts of interest related to the present study.

## Acknowledgements

The authors thank Mrs I. Laporte for technical help and Dr G. Tew (Sheffield Hallam University, UK) for grammar and English-style reviewing.

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Compte tenu des limites du questionnaire WIQ, nous avons voulu mettre au point un nouveau questionnaire avec moins de questions permettant ainsi de limiter les erreurs. La corrélation entre ce nouveau questionnaire et le test de référence sur tapis a été étudiée dans cette étude.

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Validation of a new simple questionnaire to “estimate ambulation capacity by history” (EACH) in patients with claudication.

Ouedraogo N, **Mahé G**, Marchand J, Saidi K, Lefthériotis G, Abraham P.

Une étude prospective monocentrique a été réalisée chez des patients présentant une claudication vasculaire. Ce questionnaire EACH (Estimate Ambulation Capacity by History) a été développé en partant du principe que l'évaluation du temps de marche est plus aisée que l'évaluation de la distance de marche. Cette nouvelle méthode d'estimation pourrait faciliter l'évaluation de la capacité de marche des patients et réduire d'erreurs de remplissage. De plus, nous avons pris en compte trois autres observations :

- 1) les patients souffrant de claudication peuvent avoir différentes capacités de marche (temps ou distance de marche) s'ils marchent vite ou lentement. C'est pourquoi le questionnaire EACH a été construit pour prendre en compte le temps maximal d'exercice pour différentes vitesses de marche ;
- 2) A charge constante, la distribution des distances de marche des patients présentant une AOMI suit une loi log-normale (Mahe et al., 2010b). Donc les durées possibles d'exercice proposées pour chaque vitesse de déplacement ont été définies pour qu'elles suivent une augmentation exponentielle ;
- 3) Il y a une relation exponentielle inverse entre la distance maximale de marche et la vitesse de marche chez les patients claudicants

(Degischer et al., 2002). C'est pourquoi, les valeurs attribuées à la vitesse de déplacement suivent une exponentielle croissante.

Enfin, le questionnaire EACH devait avoir un mode de calcul facile à retenir sans nécessiter l'utilisation de programme informatique.

Ce questionnaire inclut quatre questions, chacune représentant différente vitesse de déplacement (« Marcher lentement », « Marcher à vitesse moyenne », « Marcher rapidement » et « Courir »). Pour chaque question, le patient est invité à donner la durée maximale qu'il peut réaliser facilement parmi les 8 durées proposées. Pour chaque item, si le patient ne répond pas « impossible », les durées suivent une augmentation exponentielle de « 30 secondes » à « 3 heures et plus ». A chaque durée est attribuée une valeur en accord avec sa position sur la liste des durées possibles. Une réponse « impossible » vaut « 0 », « 30s » vaut « 1 », « 3 heures ou plus » vaut « 7 ». A chacune des vitesses de déplacement est attribuée un coefficient. Un score est calculé pour chaque vitesse de déplacement en multipliant le coefficient par la valeur attribuée à la réponse de durée. Le coefficient pour la vitesse de déplacement lente est « 1 », le coefficient est « 2 » pour vitesse normale, le coefficient est « 4 » pour marche rapide et le coefficient est « 7,286 » pour la course. Ces coefficients suivent une loi exponentielle croissante. Pour le coefficient valant 7,286, les 8 produits (réponse de durée multipliée par 7,286) ont été arrondis à 0, 7, 15, 22, 29, 36, 44 et 51. Le score total du questionnaire EACH est la somme des scores obtenus aux quatre vitesses de déplacement et divisée par 100 afin d'avoir un résultat maximal de 100 ( $= [1*7] + [2*7] + [4*7] + [7.286*7]$ ) (figure 7).

Entourez le temps maximal que vous pouvez pensez pouvoir tenir aux différentes allures suivantes **facilement**, **sur terrain plat** et **sans vous arrêter pour vous reposer** :

(Pour chaque question, entourez obligatoirement une et une seule des 8 réponses)

1/ **Marcher lentement**

(une vitesse plus lente que celle de vos proches, de vos amis ou des gens de votre âge)

|                                                                                                       |
|-------------------------------------------------------------------------------------------------------|
| Impossible / 30 secondes / 1 minute / 3 minutes / 10 minutes / 30 minutes / 1 heure / 3 heures & plus |
|-------------------------------------------------------------------------------------------------------|

2/ **Marcher à vitesse moyenne:**

(la même vitesse que celle de vos proches, de vos amis ou des gens de votre âge)

|                                                                                                       |
|-------------------------------------------------------------------------------------------------------|
| Impossible / 30 secondes / 1 minute / 3 minutes / 10 minutes / 30 minutes / 1 heure / 3 heures & plus |
|-------------------------------------------------------------------------------------------------------|

3/ **Marcher rapidement:**

(une vitesse plus rapide que celle de vos proches, de vos amis ou des gens de votre âge)

|                                                                                                       |
|-------------------------------------------------------------------------------------------------------|
| Impossible / 30 secondes / 1 minute / 3 minutes / 10 minutes / 30 minutes / 1 heure / 3 heures & plus |
|-------------------------------------------------------------------------------------------------------|

4/ **Courir:**

|                                                                                                       |
|-------------------------------------------------------------------------------------------------------|
| Impossible / 30 secondes / 1 minute / 3 minutes / 10 minutes / 30 minutes / 1 heure / 3 heures & plus |
|-------------------------------------------------------------------------------------------------------|

**Figure 7 : Estimated Ambulatory Capacity by History (EACH) questionnaire**

Le nombre d'erreurs de remplissage de ce questionnaire et sa corrélation avec la distance maximale mesurée sur le tapis motorisé ont ensuite été évalués et comparés aux résultats du Walking Impairment Questionnaire (WIQ).

Deux cent dix huit patients artériopathes ont accepté de participer à cette étude. Soixante pour cent des patients ont réalisé au moins une erreur sur un ou les deux questionnaires : 18 patients sur le questionnaire EACH, 71 patients sur le WIQ et 42 patients sur les deux questionnaires.

Les relations entre les scores de questionnaires corrigés et la distance maximale mesurée sur le tapis motorisé sont modérées allant de  $r=0,51$  pour le EACH questionnaire à  $r=0,60$  pour le WIQ. Il n'y avait pas de différence significative entre les coefficients de corrélation des scores des questionnaires et les distances maximales de marche obtenues sur tapis ( $P=0,357$  and  $P=0,185$ ) avant et après correction des erreurs de remplissage des questionnaires.

En définitive, le questionnaire EACH est court et facile à calculer entraînant moins de 10% de scores manquants lorsqu'il est auto-rempli. La corrélation du score du questionnaire EACH avec la distance maximale de marche mesurée sur le tapis est superposable à celle retrouvée avec d'autres questionnaires. D'autres études sont

nécessaires pour évaluer l'intérêt d'un tel questionnaire dans d'autres populations que chez les artériopathes.

En outre, nous nous sommes aperçus que la plupart des questionnaires développés ne prennent pas en considération la vitesse de marche des patients, alors même que la capacité de marche peut être différente selon que le patient marche rapidement ou lentement. La non prise en compte de ce facteur, la vitesse de marche, pourrait être une explication à la discordance entre les résultats de distance maximale de marche obtenus par questionnaire et ceux obtenus sur le tapis. Nous faisons l'hypothèse que la correction de la distance maximale de marche obtenue avec un questionnaire par un coefficient provenant de la vitesse habituelle de marche du patient pourrait améliorer la corrélation entre la distance estimée par questionnaire et celle mesurée lors d'un test sur tapis motorisé.

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Self-reported estimation of usual walking speed improves the performance of questionnaires estimating walking capacity in patients with vascular-type claudication.

**Mahé G**, Ouedraogo N, Marchand J, Vielle B, Picquet J, Lefthériotis G, Abraham P.

Nous avons réalisé une étude prospective incluant tous les nouveaux patients adressés dans notre service pour un test de marche sur tapis et qui avaient une claudication de type vasculaire. La claudication de type vasculaire était définie par l'apparition d'une douleur à la marche, forçant le patient à s'arrêter et disparaissant au repos en moins de dix minutes (Hirsch et al., 2006).

Chaque patient remplissait le « Walking Impairment Questionnaire » (WIQ) et le « Estimated Ambulatory Capacity by History » (EACH) questionnaire avant la réalisation du test sur tapis roulant (10% de pente et 3,2km/h). Le patient cochant aussi sa vitesse de marche habituelle entre 5 propositions (figure 8).



**Par rapport à la vitesse de marche moyenne (celle de vos proches, de vos amis et des gens de votre âge), pensez-vous marcher habituellement...** (cocher une seule case)

- ☐ **Nettement moins vite**
- ☐ **Un peu moins vite**
- ☐ **A la même vitesse**
- ☐ **Un peu plus vite**
- ☐ **Nettement plus vite**

**Figure 8 : Vitesse habituelle de marche du patient**

A chaque vitesse était attribuée arbitrairement un coefficient allant de 1 pour « nettement moins vite » à 5 pour « plus vite ». Le calcul des différents scores initiaux pour chaque questionnaire était réalisé comme précédemment expliqué. Des scores corrigés étaient calculés en multipliant le score initial de chaque score par le coefficient attribué à la vitesse habituelle du patient et divisé par 5 afin de conserver un score corrigé allant de 0 à 100. Par exemple, un score de WIQ initial à 63 chez un patient qui marchait « moins vite » (coefficient = 2) donnait un score de WIQ corrigé à 25,2 (=  $63 \times 2 / 5$ ).

Trois cent dix patients ont été inclus. La corrélation entre les trois échelles du WIQ (WIQ distance, WIQ vitesse et WIQ escalier) et la distance maximale de marche sur tapis étaient significativement améliorées ( $r=0,47$  à  $r=0,61$  ;  $P<0,05$ ) par l'utilisation du coefficient de vitesse alors que le score WIQ total (moyenne des 3 échelles) était amélioré mais non significativement ( $r=0,61$  à  $r=0,64$ ). Le score EACH était amélioré significativement passant de  $r=0,56$  à  $r=0,64$  ( $P<0,001$ ).

Les questionnaires d'évaluation de la distance maximale de marche corrigés par l'estimation de la vitesse habituelle de marche des patients améliorent la corrélation à la distance maximale de marche mesurée sur tapis. Cependant, ces évaluations restent imparfaites et des tests plus objectifs peuvent être proposés pour une meilleure quantification de la capacité de marche des patients.





## ARTICLE IN PRESS

# Self-reported estimation of usual walking speed improves the performance of questionnaires estimating walking capacity in patients with vascular-type claudication

Guillaume Mahe, Nafi Ouedraogo, Johann Marchand, Bruno Vielle, Jean Picquet, Georges Leftheriotis, and Pierre Abraham, MD, PhD, Cedex, France

AQ: 1

**Objective:** Most questionnaires do not estimate the usual walking speed of the patient, although it is well known that patients may experience apparently different walking capacities if walking slow or fast. We hypothesized that correcting the self-reported estimated walking capacity by a coefficient issued from the self-reported estimation of usual walking speed would significantly improve the correlation between questionnaire-estimated and treadmill-measured walking capacity.

**Methods:** Three hundred ten consecutive patients complaining of vascular-type claudication were asked to estimate their usual walking speed in comparison to people of their age (or friends or relatives) with ratings ranging from much slower (1 pt) to much faster (5 pts), in addition to the filling of the walking impairment questionnaire (WIQ) and of the estimated ambulatory capacity by history questionnaire (EACH-Q). Corrected WIQ (WIQc) and corrected EACH-Q (EACH-Qc) scores were obtained by multiplying the scores of each questionnaire by the "usual-speed" coefficient and dividing by 5. Results for questionnaire scores were compared to maximal walking time (MWT) on a treadmill.

**Results:** All but 4 patients self-completed the usual-speed question. Median scores (25-75 centiles) were 41% (26-59) for the WIQ and 24% (11-41) for the EACH-Q. Coefficients of correlation of the three WIQ subscales and of the EACH-Q with treadmill results were significantly improved after correction by the "usual-speed" question. Overall, WIQ (mean of the three WIQ subscales) tended to improve but did not reach significance.

**Conclusion:** Correcting the self-reported estimation of walking capacity by a self-reported estimation of usual walking pace significantly improves the correlation of all WIQ subscale scores and of the EACH-Q score with treadmill measurements of capacity. This confirms the interest of speed estimation in patients with peripheral arterial occlusive disease and claudication. (J Vasc Surg 2011;■■■■■.)

Limitation of walking capacity is frequent in elderly patients and is observed in various diseases such lumbar spine stenosis, heart failure, hip or knee arthritis, or peripheral arterial occlusive disease (PAOD). In typical vascular-type claudication,<sup>1</sup> pain is absent at rest, occurs after a certain distance at exercise, and forces the person to slow down or stop. The time or distance that can be performed without slowing down or stopping, grades the severity of the disease. Treadmill testing is a gold standard for estimating walking ability<sup>2</sup> but is not accessible to all physicians. Estimation of walking capacity by history is easy and readily accessible to the clinician. In order to standardize patient's self-reports, questionnaires are largely used.<sup>3-13</sup> One point of interest is that most questionnaires do not estimate the usual walking speed of the patient, although it is well known that patients may experience apparently different walking capacities if walking slow or fast.<sup>14,15</sup> Then, discordant

results between self-reported and measured walking capacity might partly rely on differences in individual usual walking speed. We hypothesized that correcting the self-reported estimated walking capacity by a coefficient issued from the self-reported estimation of usual walking speed would significantly improve the correlation between questionnaire-estimated and treadmill-measured walking capacity.

## METHODS

**Study population.** A prospective study was performed on all new patients referred for treadmill testing to our laboratory and that fulfilled vascular-type claudication criteria (as such suspected of vascular origin). Vascular-type claudication is defined as the occurrence of limb pain or discomfort while walking that forces the patient to slow down or stop and recovers within 10 minutes after walking is stopped.<sup>2</sup> We analyzed the correlation of walking capacity estimated by the "Walking Impairment Questionnaire"<sup>9-11</sup> (WIQ) and by the recently proposed "Estimated Ambulatory Capacity by History-Questionnaire"<sup>16</sup> (EACH-Q) with treadmill measurement. Analyses were performed before and after correction of questionnaire scores by a coefficient issued from the self-reported estimation of their usual walking speed by the patients. Patients that were referred twice during the study period were only included

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Competition of interest: none.

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at their first visit. Patient's characteristics, medical history, and medications were retrieved from patients' files and completed during the visit if necessary. The study was submitted to the ethics committee and conforms to the Helsinki Declaration, the study design and study recording is accessible on the National Institute of Health website under reference NCT01114178. A signed informed consent to participate in the study was obtained from all patients.

**Diagnosis of peripheral arterial occlusive disease.** The evidence of PAOD was based on the presence of at least one of the following criteria at the date of inclusion:

- Ankle brachial index (ABI) at rest less than 0.90 on one or both legs or an ultrasound or radiological investigation showing stenosis (>50% diameter) on arteries to the lower extremities;
- A history of revascularization (surgery/angioplasty) for lower extremity arterial disease;
- An abnormal result for transcutaneous oxygen pressure at exercise decrease from rest of oxygen pressure-index (below negative 15 mm Hg) at least on one side. This last criterion is of specific interest since many patients referred to our laboratory report proximal claudication. Indeed, in this specific situation, ultrasound imaging and ABI measurements may frequently be noncontributive, whereas transcutaneous oxygen pressure measurements has shown a high diagnostic performance in this context.<sup>17</sup>

**Filling of questionnaires.** The EACH-Q and WIQ were self-completed by each patient at arrival and checked for completion by a technician or a nurse before the treadmill test. When necessary, missing (no answer to a question), duplicate (two or more answers to the same question), or paradoxical answers (eg, higher duration at higher displacement speed in the new questionnaire) were discussed with the patient and corrected as previously reported.<sup>16</sup> The EACH-Q<sup>16</sup> was used as a locally developed questionnaire assumed to account for usual walking speed, whereas the WIQ was used as one of the most widely used available questionnaire from the literature. In brief, the EACH-Q<sup>16</sup> is a four items questionnaire that estimates the maximal time (choice of one among seven possible answers) that can be attained easily without stopping while performing a displacement at four different paces ranging from slow walking to running. The WIQ<sup>9,11,16,18</sup> is a 14-item questionnaire divided into three subscales. For each item, the patient is asked to estimate the degree of difficulty to perform a defined task (choice of one among five possible answers). The first seven items refer to different distances at a normal speed (WIQ-Distance subscale), the following four items refer to different displacement speed for a defined distance (WIQ-speed subscale), and the last three items refer to different number of stairs (WIQ-stair subscale). Complete English translations of the two questionnaires used for this study are available in our previous publications.<sup>16,18</sup>

**Self-reported usual walking speed.** In addition to the WIQ and EACH-Q, patients were submitted the following question at admission: "Compared to the usual walking speed of your relatives, friends, or people of your age, do you think that you usually walk . . ." (Tick only one box).

Much slower ☐  
Moderately slower ☐  
At the same speed ☐  
Moderately faster ☐  
Much faster ☐

**Scoring of the questionnaires.** Scoring of the WIQ and of the EACH-Q were performed as previously reported,<sup>9,11,16,18</sup> and both scorings resulted in scores ranging from 0 to 100. For the usual-speed question, each answer was attributed a coefficient from 1 point for "much slower," 2 points for "slightly slower," and up to 5 points for "much faster." Corrected scores were calculated for both the WIQ (WIQc) and the EACH-Q (EACH-Qc) by multiplying the original scores by the coefficient observed on the usual-speed answer and dividing the result by 5. Thus, the final WIQc and EACH-Qc scores are still expressed on scales ranging from 0 to 100. For example, a patient with a WIQ score of 63 and reports to walk moderately slower than other people will have a WIQc result of 25.2 ( $= 63 \times 2/5$ ).

**Measurement of walking speed.** Walking speed was measured, blinded to the results of questionnaires, by the time (in seconds with one decimal precision) needed to walk 10 meters in the corridor between the waiting room and the room where the treadmill tests were performed. The two rooms are separated by approximately 20 m. Patients were not aware that the technician accompanying them recorded their speed between two thin lines drawn on the floor and attention was paid by the technician not to precede the patient to avoid influencing his/her usual walking speed.

**Walking capacity on treadmill.** The treadmill test was done blinded to the results of the questionnaires after a minimum of 15 minutes at rest in the exercise room. Before the test, patients were informed that the test could be stopped at any time when their symptoms forced them to stop (and not when claudication first occurs). Initial slope was 10%. Speed was increased from 0 to 3.2 km/hour within 1 minute to allow for the patient's adaptation to treadmill walking and then stabilized until 15 minutes.<sup>19</sup> It was previously shown that approximately 15% of the patients with claudication undergoing a 15-minute constant load (3.2 km/hour 10% slope) test did not have to stop. Then, in order to have all patients being limited on the treadmill, at minute 15 of the constant-load test, slope and speed were progressively increased by steps of 1 minute. The increment was done such a way that every 3 minutes the slope and speed corresponded to a slope and speed of a "Bruce" protocol (Table). The purpose here was to improve tolerance of step changes of the Bruce protocol in the elderly population studied. For all tests, we recorded the maximal walking time (MWT) performed on a treadmill.

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**Table.** Comparison of the protocol used in the present study with the Bruce protocol

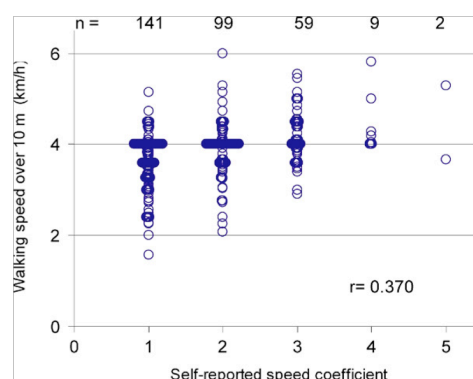
| Bruce protocol |         |    | Study protocol |         |    |
|----------------|---------|----|----------------|---------|----|
| Time (minutes) | km/hour | %  | Time (minutes) | km/hour | %  |
| 3              | 2.7     | 10 | 15             | 3.2     | 10 |
|                |         |    | 16             | 3.7     | 11 |
| 6              | 4.0     | 12 | 17             | 4.0     | 12 |
|                |         |    | 18             | 4.8     | 12 |
|                |         |    | 19             | 5.1     | 13 |
| 9              | 5.5     | 14 | 20             | 5.5     | 14 |
|                |         |    | 21             | 6.1     | 14 |
|                |         |    | 22             | 6.3     | 15 |
| 12             | 6.8     | 16 | 23             | 6.8     | 16 |
|                |         |    | 24             | 7.3     | 16 |
|                |         |    | 25             | 7.6     | 17 |
| 15             | 8.0     | 18 | 26             | 8.0     | 18 |
|                |         |    | 27             | 8.5     | 18 |
|                |         |    | 28             | 8.7     | 19 |
| 18             | 8.9     | 20 | 29             | 8.9     | 20 |
|                |         |    | 30             | 9.4     | 20 |
|                |         |    | 31             | 9.5     | 21 |
| 21             | 9.6     | 22 | 32             | 9.6     | 22 |
|                |         |    | 33             | 10.2    | 22 |
|                |         |    | 34             | 10.3    | 23 |
| 24             | 10.5    | 24 | 35             | 10.5    | 24 |

**Calculation of the number of patients and statistical analysis.** Results are presented as mean (SD) or median (25-75 centiles) according to distribution. We estimated that the correlation coefficient  $r_{\text{WIQ-MWT}}$  between the noncorrected WIQ and MWT would be 0.52,<sup>7-13</sup> that correcting the score with the usual-speed question would increase the correlation coefficient  $r_{\text{WIQc-MWT}}$  between the corrected WIQ and MWT to 0.65, and that the correlation coefficient  $r_{\text{WIQc-WIQc}}$  between the noncorrected WIQ and the corrected WIQ would be 0.67. Using these estimations and the method developed by Meng et al,<sup>20</sup> we calculated that 310 patients were needed to obtain a 95% power with a type I error rate of 0.05 for the comparison of the two coefficient correlations  $r_{\text{WIQ-MWT}}$  and  $r_{\text{WIQc-MWT}}$ . Statistical analyses were performed with SPSS version 15.0. A two-tailed  $P < .05$  was used to indicate statistical significance for all tests.

## RESULTS

Three hundred seventeen consecutive different patients were selected to participate. Seven patients were not included, among which 5 patients refused to participate and 2 patients were unable to sign the informed consent due to low intellectual or educational level.

**Population studied.** The 310 studied patients were 248 men, 62 women, 170<sup>8</sup> cm height, body weight 76.8 kg (14.8), and 62.7 years old (11.3). Risk factors included diabetes ( $n = 71$ ), active or former smoking ( $n = 250$ ), hypertension ( $n = 57$ ), dyslipidemia ( $n = 115$ ). Of the 310 patients, 253 (81.6%) were proved to have PAOD based on either ABI  $< 0.9$  or a positive imaging ( $n = 199$ ), a history of surgery or angioplasty ( $n = 101$ ), or positive transcutaneous oxygen tension recording ( $n = 216$ ). Among non-

**Fig 1.** Mean and SE to mean of measured walking speed according to the self-reported estimation of usual speed.

PAOD comorbid conditions that may alter walking capacity, 45 patients had a history of coronary or valvular heart disease, 10 patients have had a stroke, 48 patients had been investigated or treated for osteoarthritis or lumbar spine stenosis, and 8 patients were known to have chronic pulmonary disease. On the average, patients were symptomatic for more than 2 years when referred to the laboratory; median 1 year (3 months-3 years). Of the 310 patients, 21 received no medication at all or were unable to indicate their medication, and no indication for medication was available in the patient's file. Of treated patients, 241 (77.7%) received antiplatelet drugs or anticoagulants, 205 (66.1%) received cholesterol lowering agents, 193 (62.3%) received antihypertensive drugs, 63 (20.3%) received antidiabetic drugs, 10 (3.2%) received pentoxifylline, and 85 (27.4%) received beta-blockers.

**Filling of the questionnaires.** After self-completion, 150 (48.4%) of the WIQs and 69 (22.3%) of the EACH-Qs were corrected for one or more errors ( $P < .05$ ). The additional speed question was correctly completed by all but 4 patients (1.3%). In all 4 cases, the error was a missing answer and associated to one or more errors in one or both of the WIQ and EACH-Q. There was no duplicate answer to the usual-speed question.

**Questionnaire scores.** Median scores for the questionnaires were 40 (24-71) for the WIQ-distance subscale, 33 (18-50) for the WIQ-speed subscale, 42 (25-67) for the WIQ-stair subscale, 41 (26-59) for the average WIQ score, and 24 (11-41) for the EACH-Q score. Most patients ( $n = 240$ ; 77.4%) declared to walk slower than their relatives, friends, or people of their age. Distribution of answers to the "usual-speed" item is presented in Fig 1.

**Measured walking speed.** Walking speed was 3.8 (0.6) km/hour for the whole population. As shown, the mean measured speed increased as a function of the increase in self-reported estimated speed. It was 3.6 (0.6), 3.9 (0.6), 4.1 (0.5), 4.4 (0.6), and 4.5 (1.1) km/hour for self-reported speed being much slower, moderately slower, at

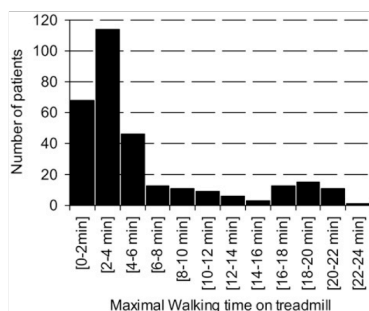


Fig 2. Distribution of maximal walking time on treadmill by intervals of 2 minutes among the 310 studied patients.

the same speed, moderately faster, and much faster, respectively. The coefficient of correlation between the self-estimated category and measured walking speed was relatively low ( $r = .370$ ), although statistically significant, as shown in Fig 1. Measured walking speed was 3.93 (0.57) km/hour in patients with a history of surgery or angioplasty, and was 3.79 (0.63) km/hour in patients reporting no prior vascular procedure ( $P = .062$ ). Measured walking speed was 3.81 (0.64) km/hour in patients with one or more suspected or confirmed vascular or nonvascular comorbid condition that may impair walking capacity, and was 3.87 (0.58) km/hour in patients reporting no comorbidity ( $P = .391$ ).

**Maximal walking time on treadmill.** Most patients ( $n = 269$ ; 86.8%) were stopped during the constant load phase of the walking tests. The mean duration of the incremental phase (past minute 15 of constant-load exercise) for the other 41 patients was 4 minutes, with the highest MWT being 22 minutes and 15 seconds. Distribution of MWT in the studied group is presented in Fig 2.

**Correlation of maximal walking time with questionnaires before and after “usual-speed” correction.** Coefficients of correlation of the WIQ subscales, WIQ, and EACH-Q, with MWT performed on a treadmill, were all improved by the use of the “usual-speed” question, although the difference did not reach significance for the overall WIQ score on a two-tailed statistic test. The “ $r$ ” values ranged from 0.469 to 0.605 before correction and 0.585 to 0.638 after correction by usual walking speed as shown in Fig 3. After correction by the “usual-speed” question, coefficients of correlation were almost similar for the  $r_{WIQ-MWT}$  ( $r = .638$ ) and for the  $r_{EACH-Q-MWT}$  ( $r = .637$ ).

## DISCUSSION

Estimation of usual walking speed is of interest when one aims at estimating walking capacity of patients, specifically in patients with suspected PAOD.<sup>9-12</sup> The walking speed may vary from 1 patient to another,<sup>21,22</sup> and asymptomatic patients with peripheral artery disease have slower usual walking speed than patients with PAOD with claudi-

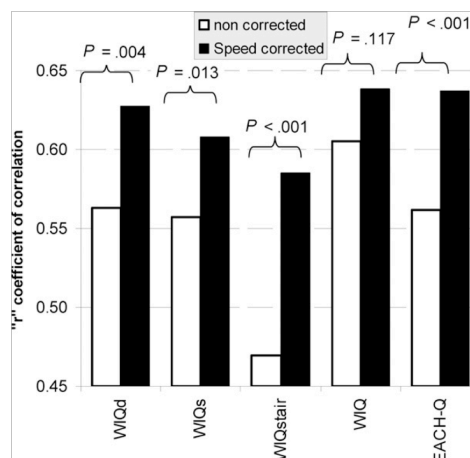


Fig 3. Correlations of the Walking Impairment Questionnaire-Distance (WIQd), WIQspeed (WIQs) and WIQstairs subscales, overall WIQ, and Estimated Ambulatory Capacity by History-Questionnaire (EACH-Q) to maximal walking time on a treadmill before (noncorrected) and after (speed corrected) correction by the “usual-speed” answer.

cation.<sup>22</sup> Nevertheless, it seems that for 1 patient, the variability of walking speed is small both in test-retest recordings<sup>23,24</sup> and within a prolonged 1-hour stroll.<sup>25</sup> Amazingly, many studies have focused on the measurement of walking speed over various test distances,<sup>21,26-30</sup> but to the best of our knowledge, only one large-scale study has ever estimated the usual walking pace with a questionnaire.<sup>26</sup> Adding one question to the WIQ and EACH-Q changes the initial 70 boxes to 75 boxes and 32 to 37 boxes, respectively, but does not seem to result in more missing values. Indeed, only 4 of 310 patients could not complete the “usual-speed” question and all had missing answers to the other questionnaires.

The WIQ estimates the degree of difficulty of the patient to perform different tasks (different walking distances, different speeds for a defined walking distance, or different number of stair flights). Then, the WIQ is assumed to be sensitive to usual speed. Indeed, it does correlate to the “4-meters usual pace” speed through its speed subscale.<sup>10</sup> It is worth noting that, by construction the “weight” of speed subscale over the final WIQ score is assumed to be one-third, because the final WIQ score is the mean of the three subscores. In fact, the “weight” of speed in the WIQ score is variable and ranges from zero to 50%. Indeed, when only two subscales are available, the “weight” of speed over the final score may be zero (if the missing score is that of the speed subscale) or 50% (if the missing scale is not the speed scale).<sup>6,10</sup> Finally, the WIQ speed subscales focus on the difficulty to perform a defined walking distance, but in fact not on the usual walking pace of the patient itself. Then we expected that accounting



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for usual walking pace as done in the present study would have improved the correlation with treadmill results. Using a two-tailed statistical approach, we failed to confirm this, although all subscale scores were indeed significantly improved. This might partly be because the coefficient observed for uncorrected overall-WIQ results, were unexpectedly already in the high range of the results previously reported in the literature.<sup>10,12</sup> As a result of this high coefficient and in perspective of the “P” value attained on the two-tailed statistical test, it is likely that a study including more patients would statistically confirm our initial hypothesis. Of interest and quite unexpectedly, the correction of the EACH-Q did result in a significant improvement of the correlation of the questionnaire to treadmill-measured capacity. The EACH-Q was designed to estimate the maximal ambulatory time for different ambulatory speeds. Then, the EACH-Q was expected to be sensitive to usual walking pace and was less likely to benefit a correction through the additional “usual-speed” question. The fact that correction of the EACH-Q through the usual-speed question improved the correlation with the treadmill result might suggest that the coefficients that were arbitrarily chosen for the scoring of the EACH-Q were inadequate to satisfactorily account for the effect of speed over walking capacity.

An original point of the present study was the use of a treadmill test combining a constant load and an incremental procedure. Constant load tests seem to better fit to a usual walk but do not allow all patients to be symptom-limited, whereas incremental procedures may result in patients being stopped for cardiorespiratory reasons and not by claudication. Further incremental tests do not reproduce usual walking. In the present study, combining the two approaches allowed 85% of patients to reach their limit over the constant load period and the remaining 15% to reach their limit during the incremental load period. We found a similar proportion of patients that had test duration in excess of 15 minutes in previous reports.<sup>31</sup> Future works must be done to confirm the results presented here with other exercise test protocols.

Among limitations of the present study are specificities of our population, with most of the studied patients having PAOD, with a high proportion of men and of patients with proximal claudication. These proportions are consistent with those observed in our previous articles but may limit the use of these results in the general population. It should be noted that in this prospective study, the number of patients that refused to participate was very low (~2%). Then, the studied population is assumed to be representative of the patients that attend our laboratory for the estimation of vascular-type claudication. Secondly, we did not study the correlation of the speed-item answer with other measures of walking speed as could be attained with a 4-minute walking velocity test<sup>29,32</sup> or with the GPS technique.<sup>13,25</sup> Such analyses have to be performed and might provide results slightly different from those observed over 10 minutes. Thirdly, we did not account for the patient's level of education or for socioeconomic issues. We think that this would have been of little interest because we had very few errors or missing answers in the usual-speed ques-

tion. Last, validation in other causes of walking limitation (hip or knee arthritis, lumbar spine stenosis) is to be done.

In practice, most results from the literature show a relatively low correlation between the self-reported estimation of walking capacity by questionnaires and the objective measurements, whatever the objective tests are.<sup>9-12</sup> Nevertheless, questionnaires are not aimed at replacing objective recordings except in epidemiologic studies or if estimation of walking is to be performed through a telephone interview.<sup>6,33</sup> Objective tests (treadmill, pedometers, satellite positioning, 6-minute walking test) also have their own limits, and the results of these “objective” tests may depend on the procedure used. Even when objective measurements are performed, questionnaires are useful and should be used as standard tools to estimate patient's perception of walking disability. Usual walking speed is certainly one major candidate to explain discrepancies between objective and subjective results. What is shown here is that self-reported estimation of usual walking pace is feasible, is easily done by the patients, and results in very few missing answers.

In conclusion, correcting the self-reported estimation of walking capacity by a self-reported estimation of usual walking pace: (1) significantly improves the correlation of all the WIQ subscales and the EACH-Q scores with treadmill measurements, and (2) tends to improve the correlation for the overall-WIQ score with the objective measurement of capacity on treadmill. Corrected-scores for both WIQ and EACH-Q reach high coefficients of correlation with walking time on a treadmill that were rarely observed in any previous experiments, among patients with claudication, thus confirming the interest of speed estimation in patients with PAOD and claudication.

## AUTHOR CONTRIBUTIONS

Conception and design: GM, PA  
Analysis and interpretation: GM, NO, JM, BV, JP, GL, PA  
Data collection: GM, NO, JM, PA  
Writing the article: GM, PA  
Critical revision of the article: NO, JM, BV, JP, GL  
Final approval of the article: GM, NO, JM, BV, JP, GL, PA  
Statistical analysis: GM, BV, PA  
Obtained funding: PA  
Overall responsibility: PA

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### 3.2.2 L'évaluation de laboratoire

Nous définissons les tests en laboratoire comme des tests qui nécessitent la présence d'un ou plusieurs opérateurs pour leur réalisation. Ils peuvent être aussi bien réalisés en intérieur qu'en extérieur. L'évaluation de la marche au laboratoire permet (Hirsch et al., 2006):

- (1) d'établir le diagnostic d'AOMI lorsque l'IPS de repos est normal en mesurant notamment l'IPS post-effort immédiatement après l'arrêt de l'effort suite à la douleur ressentie par le patient ;
- (2) d'objectiver l'importance de la gêne fonctionnelle avec notamment la détermination de la distance de marche maximale et relative;
- (3) de mesurer objectivement l'amélioration ou la détérioration clinique après l'intervention thérapeutique ;
- (4) de différencier la claudication d'origine vasculaire des pseudo-claudications notamment lorsque l'évaluation de la distance de marche sur tapis est couplée à une mesure d'oxygénation tissulaire comme la mesure de la pression partielle en oxygène transcutanée (TcPO<sub>2</sub>) ou la mesure de la saturation tissulaire en oxygène par la spectroscopie en proche infra-rouge (NIRS) ;
- (5) de donner des données objectives pour montrer l'innocuité de l'exercice chez les patients lors des programmes de réentraînement et individualiser la prescription d'exercice chez les patients.

Les trois tests utilisés au laboratoire pour évaluer la marche et en particulier la distance maximale de marche sont le test sur tapis motorisé, le test de 6 minutes et le test navette.

#### 3.2.2.1 Le test sur tapis motorisé

Le test sur tapis est le test de référence pour déterminer la distance maximale de marche et la distance maximale relative du patient (Hirsch et al., 2006). Le protocole doit être standardisé et fournir une charge de travail moins intense que celle utilisée



lors des tests chez le patient coronarien (Hirsch et al., 2006). Le test sur tapis doit permettre de déterminer le début de l'apparition de la symptomatologie des membres inférieurs, le côté douloureux, la localisation de la douleur (groupe musculaire impliqué), la présence de symptomatologie (dyspnée, douleur thoracique,...) coronarienne associée et la durée totale de marche. La réalisation d'un électrocardiogramme (ECG) pendant l'épreuve n'est pas requise mais celle-ci est souhaitée afin de mettre en évidence une éventuelle coronaropathie associée.

Pendant l'épreuve sur tapis, le patient est invité à signaler tout symptôme limitant l'exercice. Il précise le moment où les symptômes apparaissent, leurs types (douleur de mollet, douleur articulaire, fatigue,...) et si l'exercice induit une douleur thoracique ou un essoufflement (dyspnée).

Le patient doit marcher jusqu'à présenter la douleur habituelle qui le conduit à s'arrêter dans sa vie quotidienne afin de ne pas minimiser la véritable distance de marche du patient. Le test est arrêté lorsque le patient atteint sa douleur habituelle à la marche ou si des signes d'ischémie myocardique apparaissent (signes cliniques et ECG).

A la fin du test, si les valeurs d'IPS de repos étaient normales, les pressions artérielles de chevilles et humérales sont mesurées toutes les minutes jusqu'à ce qu'elles reviennent à leurs valeurs pré-test. Les valeurs d'IPS post-exercice sont ainsi obtenues (Sumner and Strandness, 1969). Une valeur inférieure à 0,80 en post-exercice peut être reconnue comme pathologique (Sumner and Strandness, 1969).

Différents types de protocole existent : des tests triangulaires (graded protocol) et des tests rectangulaires (continuous protocol) (Labs et al., 1999; Nicolai et al., 2009b). Lors d'un test triangulaire, la charge de travail (la pente et/ou la vitesse du tapis) augmente progressivement et continuellement jusqu'à ce que le sujet devienne limité (Gardner et al., 1991; Hiatt et al., 1988). Les deux protocoles plus utilisés sont ceux de Gardner et al. et de Hiatt et al. (Gardner et al., 1991; Hiatt et al., 1988). Les deux utilisent une vitesse constante de 3,2 km/heure. Le protocole de Gardner débute avec une pente nulle puis celle-ci augmente toutes les deux minutes de 2% alors que le protocole de Hiatt débute avec une pente nulle et augmente de 3,5% toutes les trois minutes. Lors d'un test rectangulaire, la vitesse du tapis et la pente sont constantes entraînant une charge de travail identique pendant toute la procédure (Labs et al., 1999). Les pentes s'échelonnent classiquement de 0% à 12% et les vitesses de 2 à 4 km/heure. Avec ce type de protocole, la charge initiale est souvent mal tolérée chez les patients ayant une

AOMI sévère et un âge avancé. Afin de palier à cette difficulté, Strandness et Bell ont développé un protocole rectangulaire à 12% de pente et 3,2 km/heure mais avec une phase initiale progressive permettant de diminuer la charge initiale de travail (Strandness and Bell, 1964). Cette phase initiale débute avec une pente nulle et une vitesse de 1 km/heure pour arriver en deux minutes à 12% et 3,2 km/heure.

La reproductibilité des tests triangulaires et rectangulaires a été étudiée dernièrement par méta-analyse (Nicolai et al., 2009b). Il s'avère que la meilleure corrélation intra-classe (0,95 - 95% IC : 0,94-0,96) est obtenue pour le test triangulaire lorsque celui-ci détermine la distance maximale de marche (distance à laquelle la douleur force le patient à s'arrêter). La meilleure corrélation intra-classe (0,91 - 95% IC : 0,88-0,92) pour le test rectangulaire était obtenue pour une pente de 12% avec une vitesse de 3,2 km/heure pour la détermination de la distance maximale de marche. Il est intéressant de noter que la reproductibilité du test rectangulaire augmente avec la pente passant d'une corrélation intra-classe de 0,76 (95% IC : 0,54-0,88) quand la pente est nulle à 0,91 (95% IC : 0,88-0,92) quand la pente est de 12% pour la détermination de la distance maximale de marche. Pour l'évaluation de la distance relative de marche (distance à laquelle la douleur apparaît), les deux tests (triangulaire et rectangulaire) ont une reproductibilité similaire avec une corrélation intra-classe de 0,85 (95% IC : 0,82-0,88) et 0,83 (95% IC : 0,80-0,85).

Les tests triangulaires permettent d'obtenir une limitation de la marche à un degré plus ou moins important contrairement aux tests rectangulaires qui étant à charge constante peuvent ne pas limiter le patient. Les deux types de tests (triangulaire et rectangulaire) sont validés pour évaluer l'AOMI (Labs et al., 1999). Cependant, si le test à charge constante est utilisé, la question essentielle est de définir combien de temps celui-ci doit durer au minimum et combien de temps il doit durer au maximum? S'il dure 5 minutes, combien de patients n'auront pas été diagnostiqués? S'il dure 30 minutes, est-il nécessaire d'aller plus loin alors que des patients ayant atteints ce temps de marche ne s'arrêteront peut-être pas avant 45 minutes? Si la distance déclarée par le patient est prise comme référence alors, quelle est la distance sur tapis qui prédit le mieux la distance déclarée par le patient? La détermination objective de ce seuil de distance pourrait être proposée pour calculer la durée minimale prédéfinie qui devrait être utilisée pour ces tests sur tapis à charge constante. En effet, si la durée prédéfinie du test sur tapis est trop courte, il y a un risque de mauvaise classification des patients.

La distance maximale de marche sur le tapis roulant est définie par les recommandations comme le « gold standard » dans l'évaluation de la capacité de marche chez les patients artériopathes claudicants (Hirsch et al., 2006). Quelque soit la pente et la vitesse lors du test, il est probable que si la durée du test tapis est trop courte, les patients terminant le test sans s'arrêter soient classés comme « illimités » alors qu'ils se seraient arrêtés en raison de leur claudication si le test avait été poursuivi quelques minutes supplémentaires. Inversement, tous les patients doivent théoriquement atteindre une limite (au moins à cause de la fatigue) si la durée de l'exercice est étendue à l'infini. Cependant, quand la probabilité que le patient s'arrête, malgré l'augmentation de la durée du test, devient faible, il est inutile et coûteux d'augmenter la durée du test sur tapis. En effet, en marchant sur le tapis à charge constante, certains patients (par exemple, ceux qui marchent vite) peuvent rester asymptomatiques ou peuvent avoir une claudication non limitante et peuvent être en mesure de marcher en dépit de l'apparition d'une claudication. Nous émettons l'hypothèse que la distribution des distances marchées par les patients claudicants pourrait permettre de définir la limite supérieure de la durée du test sur tapis à charge constante. Ainsi, notre but était de déterminer de façon objective les durées minimale et maximale du test rectangulaire sur tapis (vitesse de 3,2 km/h et une pente de 10%), permettant de définir la distance maximale de marche des patients ayant une claudication d'origine artérielle suspectée.

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Objective determination of the predefined duration of a constant-load diagnostic test in arterial claudication.

**Mahé G**, Abraham P, Zeenny M, Bruneau A, Vielle B, Lefthériotis G.

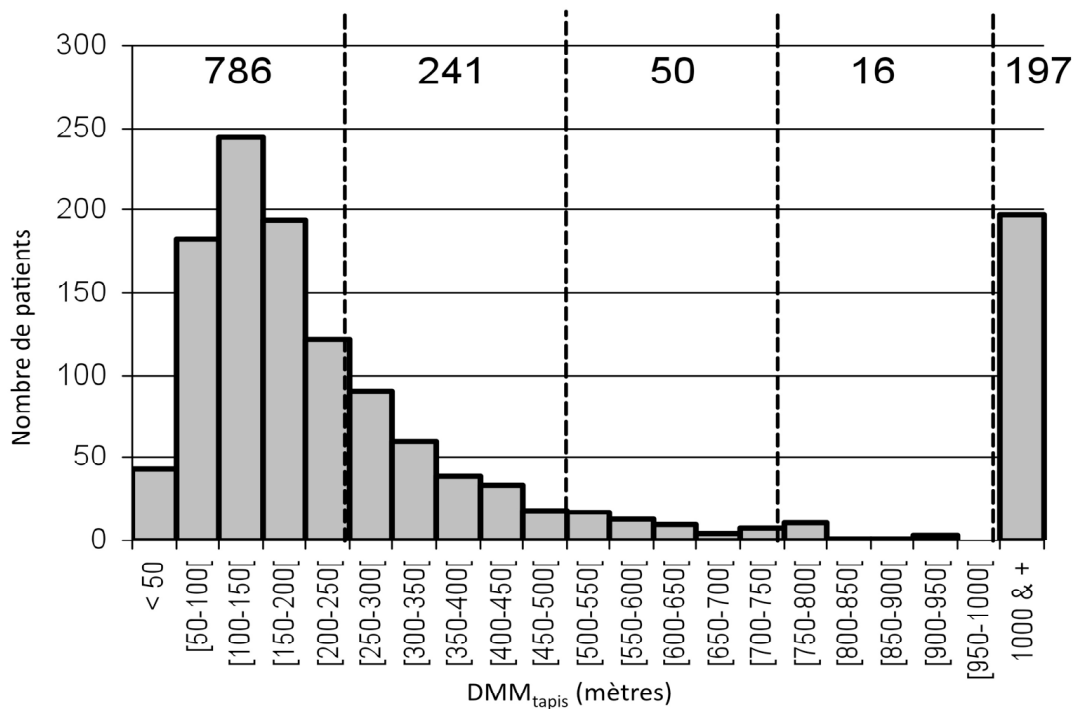
Une analyse rétrospective des données de tous les nouveaux patients adressés dans notre laboratoire pour un test de marche entre 2001 et 2009 a été réalisée. La population étudiée représentait 1290 patients dont 1109 hommes (86%) et 181 femmes (14%).

Avant le test sur tapis roulant, les patients étaient invités à estimer leur capacité de marche en donnant leur distance maximale de marche en répondant à la question

« Quelle est la distance de marche maximale que vous pensez atteindre, en marchant à votre rythme habituel sur terrain plat, avant qu'une douleur ou une gêne de membre inférieur apparaisse et vous force à vous arrêter ? ». Cette distance de marche obtenue par l'interrogatoire définissait la distance de marche maximale rapportée par le patient ( $DMM_{\text{patient}}$ ).

Le test standard sur tapis roulant était effectué avec une pente à 10% et une vitesse de 3,2 km/h. Cette vitesse de 3,2 km/h était atteinte en 1 minute pour permettre l'adaptation du patient à la marche sur tapis. Avant le test sur tapis, les patients étaient chargés de rapporter tous les symptômes limitants ou non limitants (claudication ou autres) apparaissant durant le test. Ils étaient aussi informés qu'ils pouvaient arrêter le test à leur demande à n'importe quel moment quand les symptômes apparaissaient et les forçaient à s'arrêter. En l'absence de symptômes ou en cas de symptômes non limitants, la durée maximale fixée du test sur tapis était de 20 minutes correspondant à une distance parcourue d'environ 1000 mètres. Pour tous les tests, nous avons enregistré la distance de marche maximale réalisée sur le tapis ( $DMM_{\text{tapis}}$ ).

Avant le test de marche sur tapis roulant, 563 patients (43,6%) déclaraient être limités pour une distance inférieure à 250 mètres, 223 (17,3%) étaient limités pour une distance comprise entre 250 et 500 mètres, 224 (17,4%) pour une distance entre 500 et 750 mètres et 24 patients pour une distance comprise entre 750 et 1000 mètres. Deux cent cinquante six (19,8%) patients ne déclaraient aucune limitation ou une limitation au delà de 1000 mètres. Comme présenté sur la figure 9, 197 (15,3%) patients sur les 1290 ont terminé le test de 20 minutes sur tapis.



**Figure 9 : Distribution des distances de marche maximales classées par intervalle de 50 mètres. Les valeurs en gras indiquent le nombre de patients par intervalle de 250 mètres.**

Mille quatre-vingt treize patients se sont arrêtés avant 20 minutes de marche. En outre, 241 (47,8%) patients sur 504, qui ne se sont pas arrêtés dans les 250 premiers mètres, se sont arrêtés dans les 250 mètres suivants. Ces 241 patients étaient donc incapables de marcher plus de 500 mètres. Cinquante patients (19%) sur 263 et 16 (7,5%) patients sur 213 de ceux qui ne se sont pas arrêtés avant 500 mètres et avant 750 mètres se sont arrêtés dans les 250 suivants.

Les principaux résultats originaux de cette étude peuvent être résumés comme suit. Quand les patients artériopathes adressés pour une claudication font un test sur tapis roulant (3,2 km/heure, 10% de pente) : (1) la distribution de la distance maximale de marche sur le tapis suit une distribution log normale chez les patients qui s'arrêtent avant la fin théorique du test (<1000 mètres). La probabilité qu'un patient qui a marché 750 mètres s'arrête dans les 250 mètres suivants est inférieure à 10%. (2) Si l'objectif est de confirmer la distance déclarée à l'interrogatoire par le test sur tapis, le seuil optimal retrouvé par les courbes ROC (Receiver Operating Characteristics) est de 299 mètres.

Limiter la durée maximale du test à 5 minutes ( $\approx 250$  mètres) est probablement insuffisant parce que presque la moitié des patients qui ont marché 250 mètres se sont arrêtés dans les 250 mètres suivants. En d'autres termes, si la limitation de la marche est basée sur l'aptitude à terminer le test sur tapis, ces patients seraient classés différemment si le test avait duré 5 minutes supplémentaires. Au contraire, compte tenu de la distribution des distances de marche sur tapis, il apparaît que les tests de durée supérieure à 15 minutes ( $\approx 750$  mètres) sont probablement de faible intérêt. En effet, seuls 16 des 213 patients (7,5%) qui ont marché 750 mètres se sont arrêtés dans les 250 mètres suivants. Par conséquent, 15 minutes peuvent être proposées comme la limite maximale supérieure raisonnable du test sur tapis roulant à charge constante.

Si le test sur tapis roulant est utilisé pour confirmer la distance de marche déclarée à l'interrogatoire (distance de marche par l'interrogatoire utilisée comme gold standard), d'après l'analyse des courbes ROC, nous suggérons que la durée minimale du test tapis est celle pour atteindre 299 mètres (Le seuil optimal pour prédire la  $DMM_{\text{patient}}$  à partir de la  $DMM_{\text{tapis}}$ ). En utilisant notre protocole, cette durée est de 6 minutes et 10 secondes. Ainsi, une durée de 7 minutes peut être proposée comme la durée minimale raisonnable du test sur tapis roulant.

En définitive, une durée minimale de 7 minutes et une durée maximale de 15 minutes pour un test à charge constante peuvent être proposées pour évaluer la capacité de marche des patients artériopathes. Cependant, d'autres tests moins chronophages et nécessitant moins de matériels peuvent être proposés comme le test de 6 minutes.

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# Objective determination of the predefined duration of a constant-load diagnostic tests in arterial claudication

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**Objective:** The predefined duration to arbitrarily stop the tests during constant-load treadmill exercise is a subject of debate and widely variable in the literature. We hypothesized that the upper and lower limits for predefined durations of constant-load 3.2 km/hour 10% grade tests could be derived from the distribution of walking distances observed on a treadmill in a population of subjects referred for claudication or from the optimal cutoff point distance on a treadmill to confirm a limitation self-reported by history.

**Methods:** We conducted a retrospective analysis using a referral center, institutional practice, and ambulatory patients. We studied 1290 patients (86% male),  $62.1 \pm 11.2$  years of age,  $169 \pm 8$  cm height,  $75.7 \pm 14.2$  kg weight. Patients performed a standard constant-load treadmill test: 3.2 km hour<sup>-1</sup>, 10% slope, maximized to 1000 meters (~20 minutes). We analyzed the maximal walking distance self-reported (MWD<sub>SR</sub>) by history and the maximal walking distance measured on the treadmill (MWD<sub>TT</sub>). Patients reporting MWD<sub>SR</sub>  $\geq 1000$  meters were considered unlimited by history.

**Results:** Only 197 patients (15.3%) completed the 20-minute treadmill test. Among the 504 patients who did not stop before 250 meters, 47.8% stopped within the next 250 meters (were unable to walk 500 meters). This proportion falls to 7.5% among the 213 patients who did not stop before 750 meters. When the final goal was to estimate whether the treadmill test can discriminate patients with or without limitation by history, area under the receiver operating characteristic (ROC) curve was  $0.809 \pm 0.016$  (95% confidence interval [CI], 0.778-0.841;  $P < .0001$ ), the best diagnostic performance was attained for an MWD<sub>TT</sub> of 299 meters (~6.15 minutes).

**Conclusion:** In patients undergoing constant-load treadmill exercise with a protocol of 3.2 km hour<sup>-1</sup> and 10% slope: a predefined duration of 7 minutes could be proposed as a lower limit for the predefined duration of the tests specifically if one aims at confirming the limitation by history with treadmill testing. Owing to the low risk that patients that could walk 750 meters (~15 minutes) will have to stop in the next 250 meters, 15 minutes seems a reasonable upper limit for the predefined test duration in clinical routine. (J Vasc Surg 2010;51:863-8.)

Treadmill diagnostic tests are used in patients with peripheral artery disease (PAD) to try to reproduce symptoms reported by history and argue for their arterial origin, or to objectively estimate maximal walking distance (the distance at which claudication forces the patient to stop exercise). Constant-load exercise is largely used since this procedure is expected to better reproduce usual walking rather than incremental exercise. In constant-load treadmill tests, there is a direct linear relationship between the distance performed and duration of the test. The predefined duration to stop the tests during constant-load treadmill exercise is generally defined arbitrarily but remains widely variable in the literature and is a subject of debate.<sup>1-7</sup>

Estimation of walking capacity by the patient's interview is readily accessible, whereas treadmill testing is not accessible to most physicians. Further, a person's functionality and need for daily walking distances may be less than that tested on a treadmill, questioning the need of a treadmill test to assess walking ability. Last, as many treadmill tests are performed with a slope, a climb on a treadmill at a steady pace is not a natural walking scenario, and this particular test cannot be expected to correspond exactly to the walking that patients do in their everyday life. Therefore, many physicians take patients' reports of their everyday experience at the reference value. If the self-reported walking capacity is taken as a reference, then what is the distance on a treadmill that better predicts self-reported distance? The objective determination of this cutoff treadmill distance could be proposed to calculate the lower limit for the predefined duration to be used for these treadmill tests. Indeed, if the predefined duration is too short, there is a risk of misclassification of the patients.

Maximal distance walked on a treadmill is suggested in guidelines as the gold-standard in the evaluation of walking capacity in patients with PAD.<sup>8</sup> Whatever the speed and slope used, it is likely that if the treadmill test duration chosen is too short, patients completing the test may be declared "unlimited" from the result of the treadmill test, whereas they would have had to stop for claudication if the

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test had been continued a few more minutes. Inversely, all patients will theoretically reach a limit (at least due to fatigue) if exercise duration is extended infinitely, but when the probability that the patient will stop if the test duration is extended becomes too low, it is useless and costly to increase the test duration. Indeed, when walking on a treadmill at a constant load, patients (eg, patients who usually walk fast) may remain asymptomatic or may show nonlimiting claudication and be able to carry on walking despite the occurrence of claudication. We hypothesized that the distribution of distances walked by patients referred for claudication could provide useful information toward the reasonable upper limit for the predefined duration that should be used for constant-load treadmill tests.

In perspective of which gold-standard is used, we aimed to objectively determine the lower and upper limit that could be proposed for predefined test duration (the duration at which the test is ended) when one aims at determining walking capacity during constant-load 3.2 km/hour 10% slope treadmill diagnostic testing in patients with claudication of suspected arterial origin.

## MATERIALS AND METHODS

**Study population.** A retrospective analysis of data from all new patients referred to our laboratory for treadmill exercise walking tests between 2001 and 2009 was performed. These tests are used in our department for patients with claudication to have an objective measurement of walking capacity, specifically for patients who are referred for eventual surgery or re-education. Many patients are also referred for claudication of suspected arterial origin, atypical (proximal) claudication, or claudication of questionable vascular origin (eg, association of PAD with lumbar spine syndrome). Asymptomatic patients (eg, patients undergoing systematic screening) were excluded from the study. Patients who had multiple tests during the study period (eg, to control the treatment's efficacy) were included only for their first visit. The study was submitted to the ethics committee and conforms to Helsinki Declaration but, as an observational noninterventional study, is not registered in a web-accessible database, and does not require patient's consent.

**Walking capacity by history.** Before the treadmill test, patients were asked to estimate their walking capacity through the self-reported maximal walking distance ( $MWD_{SR}$ ) by answering the question "What is the maximal distance that you think you may attain all-at-once at usual pace and on a flat area before limb pain or discomfort forces you to stop walking?"

**Walking capacity on treadmill.** Patients who were able to walk 10 meters in 12 seconds in the corridor before the treadmill test were proposed a standard treadmill test under cardiac monitoring as previously described.<sup>9</sup> Patients unable to walk the 10 meters in 12 seconds were considered unable to perform the standard treadmill tests, were proposed a specific low-speed protocol, and were excluded from the present study. The standard test uses a 10% slope, at a speed of 3.2 km/hour. The 3.2 km/hour speed was

reached within 1 minute to allow for the patient's adaptation to treadmill walking. Before the tests, patients were instructed to report all symptoms (limiting and nonlimiting) occurring during the test (claudication and other than claudication). They were also informed that the test could be stopped on their request at any time when their symptoms forced them to stop (and not when claudication first occurs). In the absence of symptoms or in case of nonlimiting symptoms, we fixed the maximum duration of treadmill exercise to 20 minutes (~1000 meters). For all tests, we recorded the maximal walking distance performed on treadmill by the patient ( $MWD_{TT}$ ).

**Analysis of the results and statistical analysis.** To avoid confusion, throughout the manuscript the predefined test limit is expressed as time (minutes) and self-reported or treadmill-measured maximal capacity ( $MWD_{SR}$  and  $MWD_{TT}$ ) are reported as distances (meters). The receiver operating characteristics (ROC) curve analysis was performed on raw data of  $MWD_{TT}$ . Distribution of  $MWD_{TT}$  among all patients and among the patients who did not complete the test, respectively, was tested for normality with the Z for Kolmogorov-Smirnov test on raw data and log-transformed data to test for a normal and log-normal distribution, respectively. For the histogram representation of its distribution,  $MWD_{TT}$  were grouped by intervals of 50 meters, starting with "less than 50 meters" to "1000 meters or more" (1000 or +). Walking limitation by history was defined as an  $MWD_{SR} < 1000$  meters because we previously showed that  $MWD$  at a usual pace is on average 2 to 3 times higher than that walking on a treadmill in PAD patients.<sup>10</sup> Comparison between groups was performed with a  $\chi^2$  test for categorical variables and Mann-Whitney test or unpaired *t* test for continuous variables pending normal distribution. Last, we used the ROC curve to analyze the diagnostic accuracy of treadmill testing, and define the optimal cutoff point for  $MWD_{TT}$  to confirm walking limitation by history. On ROC curves, the distance (arbitrary units) to the 100/100% sensitivity/specificity angle can be calculated for each point of the curve (each possible cutoff point). The lowest value of this distance represents the optimal cutoff point for clinical use assuming an equal cost of false positive and false negative results. Statistical analyses were performed with SPSS v 15.0. For all tests, a two-tailed  $P < .05$  was used to indicate statistical significance.

## RESULTS

**Population studied.** Patients included were 1109 males and 181 females. Characteristics of included patients by gender are presented in Table I. All patients reported exercise-related proximal ( $n = 324$ ; 21.1%), distal ( $n = 598$ ; 46.4%) or proximodistal ( $n = 368$ ; 28.5%) unilateral or bilateral claudication. Of the 1290 patients, 304 (23.6%) previously had surgery and/or angioplasty at the aortoiliac and/or femorodistal level. It is of interest to note that 91 patients (7.1%) had undergone negative investigations toward, or were symptomatic after surgery of, lumbar spine syndrome.

**Table I.** Characteristics of the patients studied. Results are reported as mean  $\pm$  SD or as numbers (percentages)

|                                               | Females         | Males           | P values |
|-----------------------------------------------|-----------------|-----------------|----------|
| Characteristics                               |                 |                 |          |
| Age (years)                                   | 63.3 $\pm$ 14.0 | 61.9 $\pm$ 10.7 | .12      |
| Height (cm)                                   | 158.0 $\pm$ 6.0 | 170.6 $\pm$ 6.6 | <.01     |
| Weight (kg)                                   | 63.2 $\pm$ 12.7 | 77.8 $\pm$ 13.4 | <.01     |
| Body mass index (kg/m <sup>2</sup> )          | 25.3 $\pm$ 4.8  | 26.7 $\pm$ 4.2  | <.01     |
| Vascular results                              |                 |                 |          |
| ABI (units) <sup>a</sup>                      | 0.77 $\pm$ 0.24 | 0.77 $\pm$ 0.25 | .82      |
| Abnormal vascular investigations <sup>b</sup> | 134 (55.2)      | 848 (76.5)      | .51      |
| Reported history of vascular surgery          |                 |                 |          |
| Aortoiliac/femorodistal                       | 8/6 (7.7)       | 243/64 (27.7)   | <.01     |
| Cardiac/other peripheral vascular beds        | 8/7 (8.3)       | 109/52 (14.5)   | <.03     |
| Reported comorbid conditions                  |                 |                 |          |
| History of cancer                             | 2 (1.1)         | 29 (2.6)        | .30      |
| Arthritis/arthroplasty                        | 12 (6.6)        | 56 (5.0)        | .28      |
| Pulmonary disease/diabetes                    | 3 (1.7)         | 33 (3.0)        | .46      |
| Lumbar spine syndrome excluded/operated       | 6/0 (3.3)       | 75/10 (7.7)     | <.05     |
| Diabetes                                      | 28 (15.5)       | 198 (17.9)      | .46      |
| Active smokers <sup>c</sup>                   | 40 (22.1)       | 267 (24.1)      | .64      |

ABI, Ankle brachial index.

<sup>a</sup>Data for ABI was available in 130 females and 872 patients.<sup>b</sup>Abnormal vascular investigation means either ABI <0.9; ABI >1.3, presence of a >50% stenosis at ultrasound scan or radiologic imaging, or exercise tcpO<sub>2</sub> DROP value <-15 mm Hg.<sup>c</sup>Data for smoking was available in 132 females and 808 males.

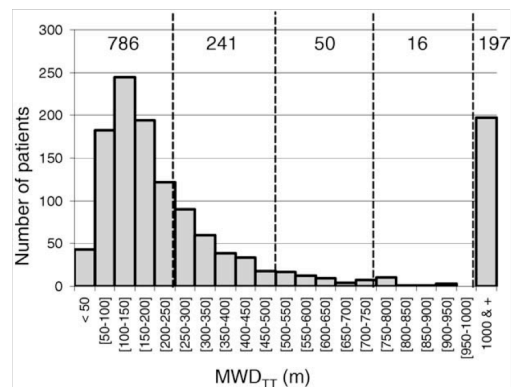
Of the 1290 patients, 35 received no treatment at all or were unable to precise their treatment that was not available in the patient's files. Of all patients, 926 (71.8%) received antiplatelet drugs or anticoagulants, 581 (45.0%) received cholesterol-lowering agents, 586 (45.4%) received antihypertensive drugs,\* and 245 (19.0%) received beta blockers.

Last, on the average, patients were symptomatic for more than 2 years (range, 0.25-23 years) when referred to the laboratory, mean  $\pm$  SD being 2.1  $\pm$  2.9 years in females, and 2.4  $\pm$  3.1 years in males.

**Maximal walking distance by history.** Before exercise, limitation by history to less than 250 meters was reported by 563 patients (43.6%), limitation by history from 250 to less than 500 meters was reported by 223 patients (17.3%), from 500 to less than 750 meters by 224 patients (17.4%), and from 750 to less than 1000 meters by 24 patients (1.9%). No limitation or limitation in excess of 1000 meters was reported by history by 256 patients (19.8%).

**Maximal walking distance on treadmill.** The distribution of distance walked during the 1290 tests is presented in the Fig. The distribution of all data values neither fits to a normal or log-normal distribution ( $Z = 8.028$ ,  $P < .0001$  and  $Z = 3.742$ ,  $P < .0001$ , respectively). Among these completed tests, 61 tests were performed with the patient remaining asymptomatic throughout the tests, 6 patients reported nonlimiting dyspnea or fatigue, whereas nonlimiting claudication was reported during the other 130 tests. In 1093 patients (84.7%), the treadmill was stopped before 1000 meters. Reason for exercise stop was: claudication only ( $n = 828$ ), claudication associated with

\*Antihypertensive include: sartans, converting enzyme inhibitors, calcium channel blockers, alpha blockers, and diuretics.



**Fig.** Maximal walking distance observed on treadmill (MWD<sub>TT</sub>) stratified by intervals of 50 meters. The numbers in bold indicate the total number of patients by intervals of 250 meters.

non-lower limb symptoms ( $n = 207$ ), and non-limb symptom without claudication ( $n = 58$ ). When the distribution of MWD<sub>TT</sub> was analyzed only among the 1093 patients who could not complete the test, results were  $Z = 4.667$  ( $P < .0001$ ) on raw data and  $Z = 0.721$  ( $P = .676$ ) on log-transformed MWD<sub>TT</sub>. Then the distribution of MWD<sub>TT</sub> among patients who could not complete the treadmill test follows a log-normal distribution.

As shown, 197 of the 1290 patients (15.3%) completed the 20-minute treadmill test. In brief, for the whole population, 241 of 504 patients (47.8%) who did not stop within the first 250 meters, stopped within the next 250 meters

**Table II.** Diagnostic performance observed for different cutoff point values of MWD<sub>TT</sub>, when the goal is to use treadmill results to predict self-reported limitation vs no limitation

| Gold standard used for MWD <sub>SR</sub> (meters) | MWD <sub>SR</sub> < 1000 |     |     |      |
|---------------------------------------------------|--------------------------|-----|-----|------|
| Cutoff limit used for MWD <sub>TT</sub> (meters)  | 250                      | 500 | 750 | 1000 |
| True negative (n)                                 | 195                      | 147 | 134 | 129  |
| False positive (n)                                | 61                       | 109 | 122 | 127  |
| False negative (n)                                | 309                      | 116 | 79  | 68   |
| True positive (n)                                 | 725                      | 918 | 955 | 966  |
| Sensitivity (%)                                   | 70                       | 89  | 92  | 93   |
| Specificity (%)                                   | 76                       | 57  | 52  | 50   |
| Positive predictive value (%)                     | 92                       | 89  | 89  | 88   |
| Negative predictive value (%)                     | 39                       | 56  | 63  | 65   |

MWD<sub>SR</sub>, Maximal walking distance self-reported; MWD<sub>TT</sub>, maximal walking distance on a treadmill.

Results are presented for self-reported limitation defined as a maximal walking distance of less than 1000 meters.

(were unable to walk 500 meters). Consistently 50 of 263 patients (19.0%) and 16 of 213 patients (7.5%) of those that did not stop before 500 meters and before 750 meters, respectively, stopped within the next 250 meters of the test.

**Maximal walking distance on a treadmill to predict maximal walking distance by history.** Table II shows the diagnostic performance of treadmill in predicting limitation defined by history. As expected, 966 of the 1034 patients (93.4%) reporting limitation by history did not complete the 20-minute (~1000 meter) treadmill test. Nevertheless, 127 of the 256 patients (49.6%) reporting unlimited walking capacity by history had to stop the treadmill test and were unable to walk 1000 meters on a treadmill (between group  $\chi^2 = 301$ ;  $P < .0001$ ).

Area under the ROC curve was  $0.809 \pm 0.016$  (95% confidence interval [CI], 0.778-0.841;  $P < .0001$ ) for treadmill distance to predict exercise limitation defined by history. The best diagnostic performance of MWD<sub>TT</sub> to discriminate patients with or without walking limitation was attained for a MWD<sub>TT</sub> of 299 meters (~6.15 minutes).

## DISCUSSION

The major original findings of this study can be summarized as follows. When using a standard treadmill constant-load test at 3.2 km/hour and 10% slope in patients tested for claudication suspected of vascular origin: (1) the distribution of distance walked on treadmill is a log-normal distribution among subjects who could not complete the full 1000 meters. The probability that the patient who walked 750 meters will stop in the next 250 meters is lower than 10%; (2) if one aims at confirming a self-reported walking capacity of less than 1000 meters with a treadmill test (MWD<sub>SR</sub> as a gold-standard) the optimal cutoff MWD<sub>TT</sub> issued from the ROC curve analysis is 299 meters.

**Constant-load treadmill exercise.** There is a debate about which technique is preferable to test patients with claudication on a treadmill: incremental or constant-load

exercise.<sup>11</sup> Advantages of constant-load treadmill testing are that tests are well accepted by patients, that this procedure provides a consistent comparison with the existing literature for more than 2 decades, and requires minimal equipment. Criticisms of constant-load, as opposed to graded treadmill testing, include the problem of using a single stress level for a population with potential heterogeneous usual walking speed and an apparent higher variability than incremental testing. Respective advantages and limits of constant-load vs incremental tests have been largely reviewed by Hiatt et al.<sup>11</sup> A wide variety of treadmill protocols have been used in patients with PAD for treadmill tests, with speeds ranging from 2.5 to 4.0 km hour<sup>-1</sup> and grades ranging from 0 to 12.5%.<sup>5,6,12-14</sup> Whatever the protocols, using a speed of 3.2 km/hour<sup>-1</sup> with a 10% to 12% grade are the most largely used ones.<sup>15,16</sup>

**Treadmill maximal walking distance as a gold standard.** Defining a duration at which the test is stopped is a problem specific to all constant-load treadmill tests. It is well known that patients with claudication may remain asymptomatic and be unlimited if the walking speed is decreased.<sup>17</sup> Further, all patients with claudication do not experience walking limitation. In patients without pain at rest, nonlimiting claudication may represent 11% of PAD patients and 14.6% of patients with exercise-induced lower limb symptoms.<sup>18</sup>

Various limits for treadmill test durations are reported in the literature. Very short walking tests (3 minutes) are likely to be sufficient to induce ischemia and allow hemodynamic or metabolic investigations in PAD patients<sup>19-21</sup> but unlikely sufficient to reach maximal walking distance in most patients. Following the initial suggestion by Rutherford,<sup>1</sup> many authors evaluate therapies for PAD on the subject's ability to complete a constant-load exercise test of 5 minutes (~250 meters).<sup>2</sup> Other authors use 5- or 10-minute tests.<sup>3,4</sup> Lundren et al<sup>5</sup> apparently maximized their tests to 9 minutes (~600 meters), although this was not specified in the method of the manuscript. We previously used a maximum duration of 20 minutes (3.2 km/hour, 10% slope, ~1000 meters) as did Womack et al<sup>6</sup> with a 0% slope, whereas other authors maximized their test to 30 minutes (~1600 meters).<sup>7</sup> It is likely that longer durations for the tests would lead to fatigue. Indeed, more than half of the patients with PAD walk less than 2 miles per week.<sup>22</sup> It is of interest to note here that fatigue was recorded as the cause of exercise ending in less than 10% of our patients who stopped between 250 and 1000 meters. Maximizing the test duration to 5 minutes (~250 meters) is probably not long enough because almost half of the patients who walked up to 250 meters had to stop within the next 250 meters. In other words, if limitation was based on the ability to complete a treadmill test, these patients would be classified differently if only the test had been prolonged 5 more minutes. On the contrary, with respect to the distribution of MWD<sub>TT</sub>, it seems that tests lasting more than 15 minutes (~750 meters) are probably of little interest. Indeed, only 16 of 213 patients (7.5%) who walked 750 meters stopped in the next 250 meters. Thus, 15 minutes could be



proposed as a reasonable upper limit for the predefined duration of these tests.

**Self-reported maximum walking distance as a gold standard.** One might argue that using self-reported maximal walking distance as the gold standard for assessing functional limitations is easier than to perform a treadmill test. A low concordance of  $MWD_{SR}$  and  $MWD_{TT}$  in patients with claudication as observed in our population is a constant finding in the literature. The apparently most intuitive reason for this discordance is that subjects may report limitation on a treadmill whereas they do not experience exercise-related pain or limitation in daily living due to limited ambulation.<sup>23</sup> It is possible that walking on a treadmill at 3.2 km/hour<sup>-1</sup> and with a 10% slope may decrease the walking capacity as compared to usual walking, because different exercise modalities of comparable work load may result in differences in exercise-induced symptoms.<sup>24</sup> Inversely, patients may underestimate their walking capacity and be unlimited on a treadmill while reporting limitation by history. Despite walking capacity estimated to be less than 250 by history, 27 patients were able to complete the 20-minute (~1000 meter) treadmill test. Among many other possible reasons, evidence exists that patients suffering peripheral vascular disease poorly estimate their walking distance by history.<sup>25</sup> Whatever, if constant-load treadmill testing is used for the confirmation of walking limitation ( $MWD_{SR}$  being used as a gold-standard), from the ROC curve analysis, we suggest that the lower limit for test predefined duration is the one allowing to reach 299 meters (the optimal cutoff point for the prediction of  $MWD_{SR}$  from  $MWD_{TT}$ ). Using our protocol, this duration is precisely 6 minutes and 10 seconds. Then 7 minutes could be proposed as a reasonable lower limit for the predefined duration of these tests.

**Study limitations.** A population bias may have occurred in the present study because, as a referral center, the patients who are referred to our laboratory may not be representative of patients who may enter a study of arterial claudication. Specifically our interest in buttock claudication<sup>9,26-28</sup> results in a large number of studied patients referred for atypical (proximal "buttock" and not distal "calf") symptoms. It cannot be excluded that treadmill walking capacity may differ between a patient with proximal vs distal symptoms. The fact that 7.1% of our patients had been treated or investigated for lumbar spine syndrome is unlikely to bias the results because it is in the same range as previous reports of an 11% prevalence of spinal stenosis in patients with PAD.<sup>29</sup>

Furthermore, 86% of our patients were male. Although most studies of patients with PAD include dominantly males, this proportion is particularly high, and the explanation for this is not readily apparent. Last, it is clear that our results are of little interest (at least for the maximum duration) for physicians who use an incremental treadmill test and may not be transferable to other constant-load procedures.

## CONCLUSION

The predefined duration of exercise at which the test should be stopped depends on the goal of the treadmill test. On the one hand, if  $MWD_{SR}$  is the gold standard and one aims at confirming a self-reported limitation by history, our results suggest that when limitation by history is defined as an  $MWD_{SR}$  lower than 1000 meters in patients undergoing constant-load treadmill exercise with a protocol of 3.2 km/hour<sup>-1</sup> and 10% slope, a test duration of at least 7 minutes allows for the optimal cutoff point for  $MWD_{TT}$  (299 meters) to be reached. Then 7 minutes could be proposed as a reasonable lower limit for the predefined duration of the test. On the other hand, if  $MWD_{TT}$  is used as a gold standard to define exercise limitation, one should keep in mind that the probability that the patients who could reach a certain distance will stop in the next 5 minutes if the test is not ended, decreases almost exponentially with time and was less than 10% after 750 meters (~15 minutes). All patients will theoretically reach a limit (at least due to fatigue) if time was extended indefinitely, but 15 minutes could be proposed as a reasonable upper limit for the predefined test duration.

## AUTHOR CONTRIBUTIONS

Conception and design: AB, PA  
Analysis and interpretation: GM, MZ, AB, GL, BV, PA  
Data collection: GM, AB, PA  
Writing the article: PA  
Critical revision of the article: GM, MZ, AB, GL, BV, PA  
Final approval of the article: GM, MZ, AB, GL, BV, PA  
Statistical analysis: PA, BV  
Obtained funding: PA  
Overall responsibility: PA

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### 3.2.2.2 Le test de 6 minutes

Lorsque le tapis motorisé fait défaut, ou que le patient n'est pas en mesure de marcher sur un tapis motorisé, le test de 6 minutes peut être proposé (Hirsch et al., 2006). Il consiste à évaluer soit la distance cumulée de marche des patients sur un « terrain plat » soit le nombre de pas sur une durée de 6 minutes (Montgomery and Gardner, 1998). Le test de 6 minutes évaluant le nombre de pas est très peu utilisé. Les coefficients de variation des « tests-retests » sont respectivement de 10,4% et 11,7% dans l'étude de Montgomery et Gardner (Montgomery and Gardner, 1998). Ce test présente l'avantage de pouvoir être réalisé sans matériel particulier hormis un chronomètre. Il existe en outre une corrélation significative avec la distance maximale de marche évaluée sur tapis motorisé ( $r = 0,525$ ,  $p < 0,01$ ). Il peut être aussi proposé en pré- et post- traitement afin d'évaluer objectivement l'amélioration clinique des patients (McDermott et al., 2009). La pertinence de ce test pour montrer l'amélioration clinique reste toutefois discutable compte tenu de son caractère temps limité.

### 3.2.2.3 Le test navette (Shuttle test)

Ce test est réalisé en extérieur et fait partie des tests de terrain mais il nécessite la présence d'un opérateur (Singh et al., 1992; Zwierska et al., 2004). Ce test consiste à faire marcher le patient entre deux plots séparés de 10 mètres et placés sur un terrain plat. Un bip sonore indique au patient qu'il doit commencer à marcher. Le patient doit arriver au second plot avant le bip suivant. Deux types de tests sont possibles : l'un à vitesse constante (4km/h) (test navette-constant), l'autre à vitesse croissante (bips sonores de plus en plus rapprochés) (test navette-incrémentiel) (Singh et al., 1992). Pour le test incrémentiel, la vitesse de marche débute à 3km/h puis augmente de 0,5km/h. Si le patient arrive avant le bip sonore suivant, il doit attendre 1 minute de repos. Si le patient arrive après le bip sonore, il est encouragé à augmenter sa vitesse de marche pour arriver avant le bip suivant. Le patient doit signaler lorsqu'il ressent le début de la douleur et s'arrête lorsque celle-ci l'empêche de continuer. La reproductibilité du test-retest est bonne pour la détermination de la distance maximale de marche. Elle est comprise entre 15,5% et 16,4% pour le test navette-incrémentiel et entre 19,9% et 22,4% pour le test navette-constant (Zwierska et al., 2004). Par

comparaison dans cette même étude, la reproductibilité de la détermination de la distance maximale de marche par le test sur tapis motorisé à vitesse constante de 3,2km/h avec une pente de 12% est comprise entre 18,1% et 19,4%. La variabilité de la détermination de la distance de marche à laquelle débute la douleur (distance de marche relative) est plus importante pour l'ensemble de ces 3 tests (test navette incrémentiel, test navette constant et test tapis) et comprise entre 19,8% et 31,3% avec une moindre variabilité obtenue avec le test tapis (Zwierska et al., 2004). Il est intéressant de noter que d'après les auteurs, ce test est mieux accepté par les patients (43% préfèrent le test navette contre 23% préfèrent le test tapis).

### **3.2.3 L'évaluation ambulatoire**

Contrairement aux tests en laboratoire, les tests ambulatoires sont des tests réalisés sans contrainte de vitesse ou de pente imposées. Ils seraient ainsi plus proches des conditions de marche réelles des patients.

#### **3.2.3.1 Le PADHOC (Peripheral Arterial Disease Holter Control)**

Le dispositif PADHOC permet de mesurer en ambulatoire la distance à laquelle le patient ressent le début de la douleur, la distance maximale de marche et la vitesse de marche par une technologie utilisant la télémétrie ultrasonore couplée au test dit de « la double épreuve physiologique de marche » (Boissier et al., 1997; Coughlin et al., 2001). « La double épreuve physiologique de marche » est un test qui permet d'analyser deux périodes de marche consécutives limitées par la douleur (Merci de se référer à l'ANNEXE 3 pour plus d'information sur la technique). Compte tenu de la méthodologie utilisée, deux distances à laquelle la douleur apparaît peuvent être déterminées ainsi que 2 distances maximales de marche. Ce mode d'évaluation de la marche des patients artériopathes a été développé afin d'étudier la marche chez des patients ne pouvant pas être testés sur tapis et dans le but de réaliser une évaluation sans aucune contrainte imposée aux patients comme la vitesse du tapis ou la pente de celui-ci. Coughlin *et al.* ont montré une bonne corrélation entre la distance d'apparition de la douleur évaluée par tapis (2,5km/h et 10%) et celle évaluée par le PADHOC (1<sup>ère</sup> mesure) ( $r=0,61$  ;  $p<0,01$ ) ainsi qu'entre la distance maximale de marche évaluée par le tapis et celle évaluée par le PADHOC (1<sup>ère</sup> et 2<sup>ème</sup> mesures avec  $r=0,60$ ,  $p<0,01$  et  $r=0,50$ ,  $p<0,01$

respectivement) (Coughlin et al., 2001). Bien que cette technique soit très intéressante intellectuellement, celle-ci a été peu utilisée probablement en raison des contraintes liées à la mise en place du système notamment au niveau des chevilles (Boccalon et al., 2001; Boissier et al., 1997; Coughlin et al., 2006; Coughlin et al., 2001). Enfin, cette technique couplée à « la double épreuve physiologique de marche » peut s'avérer contraignante pour certains patients car elle impose de marcher deux fois consécutivement (Boissier et al., 1997).

### **3.2.3.2 La mesure par Géo-Positionnement Satellitaire**

Dernièrement, une nouvelle méthode d'évaluation ambulatoire de la capacité de marche par le système de Géo-Positionnement Satellitaire (GPS) a été validée chez les patients artériopathes dans notre laboratoire (Le Faucheur et al., 2008). En effet, ce système permet de détecter les durées de marche et d'arrêt et d'estimer avec précision la distance et la vitesse de marche en utilisant une méthode simple de traitement du signal (Le Faucheur et al., 2007). Ainsi, par un post-traitement du signal GPS, les distances maximales de marche de patients artériopathes peuvent être déterminées. Cette mesure nécessite seulement le port d'un GPS (10cm par 2cm par 10cm) comme un holter. La corrélation entre la distance maximale de marche mesurée sur le tapis (3,2km et pente 10%) et la distance maximale de marche mesurée par la technique GPS était élevée (0,81 ;  $p < 0,001$ ) avec des distances maximales de marche en moyenne 3 fois supérieures à celles mesurées sur le tapis. Lors de cette étude, les autres méthodes d'évaluation de la capacité de marche (distance estimée par l'interrogatoire, le WIQ et le test de 6 minutes) ont été étudiées par rapport au test sur tapis motorisé. Le meilleur coefficient de corrélation a été obtenu avec le GPS (tableau 4).



| Mode d'estimation de la distance maximale de marche | Médiane (25 <sup>ème</sup> et 75 <sup>ème</sup> percentiles) | Coefficients de corrélation (IC à 95%) avec la distance maximale de marche mesurée sur tapis (3,2km/h et 10% de pente) |
|-----------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Estimation par l'interrogatoire (en mètres)         | 300 (163–500)                                                | 0,52 (0,13–0,77); 0,038                                                                                                |
| Walking impairment questionnaire (WIQ) (en %)       | 28 (15–47)                                                   | 0,53 (0,13–0,77); 0,033                                                                                                |
| Test de 6 minutes (en mètres)                       | 405 (338–441)                                                | 0,74 (0,47–0,88); <0,001                                                                                               |
| GPS (en mètres)                                     | 609 (283–1287)                                               | 0,81 (0,60–0,92); <0,001                                                                                               |

**Tableau 4 : Médianes obtenues par les différents modes d'estimation de la distance maximale de marche et corrélations entre la distance maximale de marche mesurée sur le tapis motorisé et les autres modes d'évaluation (Le Faucheur et al., 2008).**

Cette technique présente l'immense intérêt de pouvoir étudier la marche des patients dans leur environnement sans aucune contrainte de vitesse ou de pente imposée. En outre, elle ne nécessite pas la présence de personnel lors de sa réalisation.

Nous avons voulu étudier à l'aide de cette technique la variabilité à court terme de la capacité de marche chez les patients artériopathes au cours d'une promenade. En effet, la distance maximale de marche est reconnue comme étant peu variable (Hirsch et al., 2006). Cependant, la variabilité à court terme de cette distance maximale de marche n'a jamais été étudiée. Seule la reproductibilité de la distance maximale de marche lors de tests a été étudiée (Berglund and Eklund, 1981; Degischer et al., 2002; Nicolai et al., 2009b). De plus, la vitesse de marche est-elle modifiée au cours d'une promenade, la durée d'arrêt entre 2 marches est elle modifiée ? Ces différentes modifications au cours d'une promenade pourraient être à l'origine de la difficulté des patients à rapporter à l'interrogatoire leur distance maximale de marche et expliquer la faible concordance avec les tests sur tapis notamment (Watson et al., 1997).

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Variability and short-term determinants of walking capacity in patients with intermittent claudication.

Le Faucheur A, Noury-Desvaux B, **Mahé G**, Sauvaget T, Saumet JL, Lefthériotis G, Abraham P.

Nous avons réalisé une étude transversale chez 71 patients présentant une claudication intermittente. Ces 71 patients sont allés marcher avec un GPS lors d'une promenade dans un parc public d'Angers. Sur ces 71 patients, 14 ont été exclus de la post-analyse du signal GPS en raison soit d'arrêt non lié à des douleurs de jambes (n=11) soit à cause de divers problèmes rencontrés au début de l'enregistrement (non respect de la durée de repos avant le début de la promenade) (n=3). L'analyse du signal GPS chez les 57 patients restant a permis de mettre en évidence que la distance maximale de marche au cours d'une promenade était variable et que cette variation de distance maximale de marche était de l'ordre de 43%. De plus, chez les 36 patients ayant eu cinq arrêts et plus au cours de leur promenade, la variable dominante associée à cette variation était la durée de l'arrêt précédent cette marche chez 44% des patients. Il n'est pas étonnant de retrouver cette variable comme dominante. En effet, lorsque le patient est en ischémie, un certain temps est nécessaire pour revenir à l'état sans ischémie. Si le patient se remet à marcher sans attendre un certain délai, la douleur liée à l'ischémie réapparaîtra pour une distance moindre. Ce concept est bien illustré par « la double épreuve physiologique de marche » (Boissier et al., 1997). Le temps cumulé de marche au cours de cette promenade apparaissait aussi comme une variable associée à la variation de la distance maximale de marche chez seulement 14% des patients. Ce temps cumulé peut correspondre à la fatigue présentée par le patient. Cet effet n'avait jamais été mis en évidence auparavant chez les patients artériopathes. De façon plus surprenante, chez aucun des patients, la vitesse de marche n'était une variable explicative de la variabilité de la distance maximale de marche entre deux arrêts induits par la douleur.

En définitive, il existe une variabilité à court terme de la distance maximale de marche au cours d'une même promenade et celle-ci dépend pour l'essentiel de la durée de l'arrêt précédent cette marche. L'intérêt de la variabilité de cette durée d'arrêt sur l'évolution de l'AOMI chez un patient artériopathe reste à explorer. En effet, est-ce plus judicieux d'inciter le patient à se remettre rapidement à marcher après un arrêt ou est-il préférable que la phase de repos soit plus longue afin de remarcher plus longtemps ? Les réponses à ces questions pourraient permettre de développer des programmes individualisés de réadaptation spécifique à chaque patient et d'améliorer ainsi le pronostic fonctionnel chez ces patients.

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## 4 ISCHÉMIE DES MEMBRES INFÉRIEURS ET CONSIDÉRATIONS PHYSIOPATHOLOGIQUES

La limitation de la capacité de marche chez les patients artériopathes est liée en majeure partie à l'ischémie engendrée par la réduction partielle ou complète de l'apport en oxygène aux tissus au cours de l'effort dans la phase aigue mais aussi aux possibles conséquences de l'ischémie répétée notamment sur le système nerveux périphérique (Evans et al., 2011; Stewart et al., 2002). Il est important de rappeler, que compte tenu de la définition suscitée de l'appareil cardiovasculaire, ce manque d'apport en oxygène peut être lié soit à l'atteinte de la « pompe », soit du contenant (les vaisseaux), soit du contenu (le sang) (Abraham et al., 2010). L'atteinte de la pompe et/ou du contenu peuvent être des causes de diagnostics différentiels. L'atteinte du contenant à savoir des vaisseaux peut avoir lieu à différentes localisations de l'arbre artériel allant du cœur à la distalité des membres inférieurs. La douleur classiquement décrite par le patient est une douleur du ou des mollets. Lorsque la douleur est située au mollet, la lésion se situe en amont. Cet amont peut être aussi bien à l'étage poplitée par exemple qu'aux étages iliaques ou aortique. Ces douleurs de mollets sont alors accompagnées d'une chute de l'IPS de repos ou au moins de l'IPS post-effort. Cependant, il ne faut pas méconnaître d'autres localisations de la douleur artérielle comme la douleur de cuisse, de fesse et lombaire. Ces douleurs peuvent être en rapport avec des lésions de l'artère iliaque interne et être ainsi difficile à diagnostiquer en raison de la normalité des IPS de repos et d'effort en cas d'atteinte isolée de l'artère iliaque interne (Jaquinandi et al., 2004). La localisation distale (sous poplitée) ne pose généralement que peu de problèmes diagnostiques, ce qui n'est pas le cas pour la localisation proximale (Picquet et al., 2005). Pour aider le clinicien notamment à l'étage proximal, une méthode clinique, la mesure de la pression péniennne et deux méthodes de mesures de l'oxygénation tissulaire couplée au test rectangulaire sur tapis motorisé ont été proposées. L'une est la mesure transcutanée de la pression partielle en oxygène (TcPO<sub>2</sub>) largement développée dans le laboratoire et l'autre est la spectroscopie proche infra-rouge (NIRS) (Abraham et al., 2003; Bouye et al., 2005; Sugano et al., 2003) (ANNEXES 4 et 5). Au cours d'une même

étude, ces deux techniques ont été comparées. La performance diagnostique<sup>9</sup> de la NIRS était de 55% (intervalle de confiance à 95% : 41,6% à 67,9%) et celle de la TcPO<sub>2</sub> était de 82% (69,6% to 90,5%) pour prédire la présence de lésions artériographiquement prouvées au niveau de l'aorte, ou de l'artère iliaque primitive ou de l'artère iliaque interne (Bouye et al., 2005).

## **4.1 Localisations de l'ischémie à la marche**

### **4.1.1 L'ischémie proximale à la marche**

L'ischémie proximale à la marche entraîne des douleurs à type de claudication mais de localisation atypique au niveau de la cuisse, de la fesse, de la hanche et de la région lombaire, rendant ainsi difficile le diagnostic (Jaquinandi et al., 2004). Le diagnostic est d'ailleurs souvent retardé puisqu'il est en moyenne de deux ans (Picquet et al., 2005). Cette ischémie proximale est fréquemment liée à des lésions artérielles localisées au niveau de l'artère iliaque interne ou à des lésions sus-jacentes (Jaquinandi et al., 2007). Les artères iliaques internes vascularisent le pelvis. Des lésions isolées à ce niveau n'entraînent pas de modification de l'IPS. Pour palier à ce problème, la mesure de la pression pénienne et le calcul de l'index de pression pénienne-bras (IPPB = pression pénienne divisée par la pression humérale la plus haute) peuvent être utilisés pour le diagnostic de claudication proximale chez l'homme. Bien qu'un seuil d'IPPB à 0,60 soit défini pour caractériser une origine vasculaire d'une impuissance dans la population générale masculine (Chiu et al., 1986) et dans une population de patients vasculaires (Gossetti et al., 1991), aucun seuil n'est défini pour la claudication vasculaire. Notre travail a donc consisté à comparer les valeurs d'IPPB aux mesures de sténoses artériographiques chez des patients souffrant de claudication. Le but de l'étude n'était pas d'étudier l'impuissance, mais de définir si la limite de l'IPPB utilisée pour l'impuissance (0,60) dans la population générale masculine était précise dans la détection des lésions artériographiquement prouvées sur les artères alimentant le lit vasculaire hypogastrique chez les patients se plaignant de claudication. Notre second objectif était de rechercher la valeur seuil optimale à utiliser dans cette population de claudicants.

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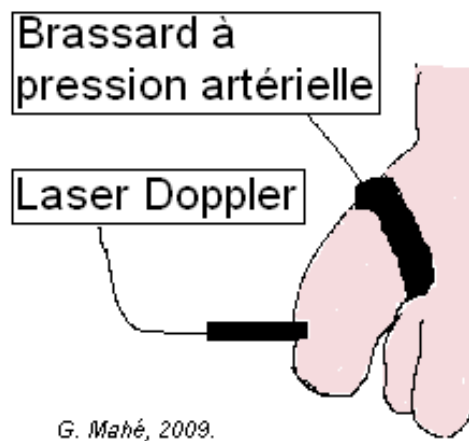
<sup>9</sup> Performance diagnostique : est calculée en divisant le nombre de vrais positifs et de vrais négatifs) par le nombre de sujets malades et le nombre de sujets sains évalués.

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A normal penile pressure cannot rule out the presence of lesions on the arteries supplying the hypogastric circulation in patients with arterial claudication.

**Mahé G**, Leftheriotis G, Picquet J, Jaquinandi V, Saumet JL, Abraham P.

Nous avons réalisé une étude prospective chez des patients en stade II de Leriche et Fontaine. Aucun patient inclus n'avait eu de traitement chirurgical ou de geste endovasculaire préalable. La mesure de la pression pénienne était réalisée par un opérateur ne connaissant pas le résultat de l'artériographie (figure 10).



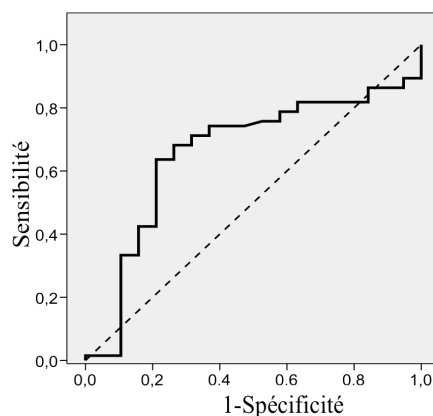
**Figure 10 : Mesure de la pression pénienne.**

Quatre-vingt huit patients ont été inclus. Parmi ces 88 patients, 3 n'ont pas eu la mesure de la pression pénienne : un patient en raison d'une obésité majeure, au autre en raison d'une instabilité de signal laser et le dernier en raison d'une prothèse pénienne. Les résultats de sensibilité et de spécificité pour la détection d'une sténose ou occlusion de l'artère iliaque interne (uni- ou bilatérale) sont présentés dans le tableau 5.

|                                                          | Sténose ou occlusion iliaque<br>interne (uni- ou bilatérale) |
|----------------------------------------------------------|--------------------------------------------------------------|
| <b>Index de pression pénienne <math>\leq 0,60</math></b> |                                                              |
| Sensibilité                                              | 80%                                                          |
| Spécificité                                              | 42%                                                          |
| <b>Index de pression pénienne <math>\leq 0,45</math></b> |                                                              |
| Sensibilité                                              | 74%                                                          |
| Spécificité                                              | 68%                                                          |

**Tableau 5 : Sensibilité et spécificité en fonction de l'index de pression pénienne.**

La figure 11 présente la courbe ROC (Receiver Operating Characteristics) pour un IPPB  $\leq 0,45$  pour détecter des occlusions bilatérales des iliaques internes.



**Figure 11 : Courbe ROC (Receiver Operating Characteristics) pour un IPPB  $\leq 0,45$  pour détecter des occlusions bilatérales des iliaques internes.**

Un index de pression pénienne  $\leq 0,45$  détecte 19 occlusions iliaques internes bilatérales sur 20 soit une performance diagnostique de 95%.

En définitive, cette étude a montré qu'une pression pénienne normale ou qu'un IPPB normal ne permet pas d'exclure une lésion au niveau des artères iliaques internes et par extension que cela ne permet pas d'exclure une origine vasculaire à une claudication proximale. D'autres approches doivent être préférées pour faire le diagnostic d'une claudication vasculaire proximale.

## A normal penile pressure cannot rule out the presence of lesions on the arteries supplying the hypogastric circulation in patients with arterial claudication

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**Abstract:** Proximal claudication remains a difficult diagnosis. The ankle to brachial index may be insensitive in the case of isolated hypogastric lesions. Penile pressure represents an alternative method for proximal arteries. Surprisingly, the accuracy of penile pressure measurement in detecting lesions on the arteries supplying pelvic circulation in patients suffering claudication has rarely been studied. We aimed to evaluate the diagnostic accuracy of the penile brachial index  $< 0.60$  (penile over brachial systolic pressure ratio) to non-invasively investigate arteriographic lesions on arteries supplying the hypogastric circulation in 88 male patients referred for Fontaine stage II. The receiver operating characteristic (ROC) curve was used to define the diagnostic performance of the penile brachial index and search for a specific cut-off point in this population. Accuracy was 69.3% (95% confidence interval: 58.6–78.7) for the detection of an arterial stenosis or occlusion on at least one side. The penile brachial index  $\leq 0.45$  was 74% sensitive and 68% specific to discriminate the 19 patients with bilateral arterial occlusion from the other 66 patients. In conclusion, the penile brachial index is relatively insensitive for the detection of proximal abnormal blood flow impairment except in the case of bilateral occlusion of arteries supplying the hypogastric circulation in patients with claudication. A normal penile pressure is probably not efficient enough to rule out the presence of lesions on the arteries towards the hypogastric circulation in patients with arterial claudication.

**Keywords:** arterial pressure, diagnosis, pelvis, peripheral vascular disease

### Introduction

The recent use of claudication questionnaires,<sup>1,2</sup> including proximal localizations (lower back, buttock, hip) of pain and the development of endovascular interventions at the iliac level, have increased the number of observations of isolated proximal claudication. The hypogastric arteries are often difficult to analyze during ultrasound investigations due to gaseous interposition or obesity.

The other most widely used non-invasive functional investigation of peripheral artery disease (PAD) is lower limb arterial pressure measurement. The measurement can be performed at different levels of the arterial tree: thigh, calf,

ankle and toe. Values are generally expressed as pressure indices defined as the ratio of limb systolic to brachial systolic pressure value. The ankle to brachial index (ABI) is used to estimate the hemodynamic consequences of arterial lesions in the lower limbs.<sup>3,4</sup>

Nevertheless, ABI is not accurate enough to estimate the blood flow supply towards the pelvic circulation. The ABI may even be abnormal despite normal pelvic blood flow supply if distal arteries are occluded. Inversely, ABI will remain in the normal range in the case of an isolated lesion of the hypogastric artery.

The measurement of arterial pressure at the penile level appears preferable to ABI to detect lesions on arteries supplying the hypogastric circulation, but it is rarely used in routine investigations.

Owing to the limitations with ABI and ultrasound, in most reported cases of isolated proximal

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claudication, diagnosis of the arterial origin of pain was only confirmed through invasive arterial imaging, although imaging cannot be proposed as a primary diagnostic tool.

The measurement of penile pressure and calculation of the penile brachial index (PBI) is used to diagnose subjects with impotence of potential vascular origin in the general population. Surprisingly enough, the accuracy of penile pressure measurement in detecting lesions on the arteries supplying pelvic circulation in patients suffering claudication has rarely been studied. One possible reason may be that, as for toe pressure, recording of penile pressure is technically more challenging than ABI and may be difficult in the lower-pressure ranges.<sup>5</sup>

The cut-off point used as a normal limit for penile pressure is usually defined arbitrarily as the same one used in the general population for impotence.

We aimed to compare the PBI (penile pressure over systolic brachial pressure ratio) to 'gold standard' arteriography in patients with claudication. The purpose was not to study impotence, but to define whether the limits for PBI used for impotence in the general population are accurate in detecting angiographically proved lesions on the arteries supplying the hypogastric vascular bed in patients complaining of claudication. Our secondary goal was to search for the optimal cut-off point to be used in this population.

## Methods

### Population

A prospective analysis was undertaken on consecutive male patients referred to the department for stable Fontaine stage II claudication and who previously had undergone, or were scheduled to have, an arteriogram within 3 months of their visit to our department. Although few patients reported impotence, the primary indication for the visit was claudication. A high proportion of patients reported either proximal ( $n = 36$ ) or proximo-distal ( $n = 27$ ) claudication as a result of the specific interest of our laboratory for proximal claudication. Twenty-five patients reported distal claudication. Patients undergoing any surgical or endovascular procedure between penile pressure measurements and arteriography were excluded from the study.

The study was performed as a part of the EOIP (Evaluation objective des ischémies proximales) study. The EOIP study is registered in the American National Institute of Health database under reference NCT-00152737.

## Methods

All patients underwent a penile and arm pressure measurement at rest. Results for ABI measurements at rest were obtained from the patients' files and not specifically measured for this study since it was not the parameter to be analyzed.

As a routine for each patient visit, we used a standard questionnaire requesting information concerning previous vascular interventions for cardiac or PAD. Age, weight, height, sex, diabetes, usual treatments and self-reported maximal walking distance were noted during the history.

### Arterial imaging

Arterial imaging consisted of digitized diagnostic arteriograms. All arteriograms were performed by catheterization through a femoral artery via the Seldinger technique using 4-French pigtail catheters. All arteriograms included at least a frontal view centered on the lower aorta, a left oblique anterior view and a right oblique anterior view for the analysis of internal iliac trunks.

Arteriograms were analyzed blinded to the results of penile pressure measurements. On each side, arteries towards the hypogastric circulation were divided into the following segments: the aorta, the ipsilateral common iliac artery, and the ipsilateral internal iliac artery to its first major branch of division. On each side, arterial imaging was evaluated for the presence of an occlusion or a diameter stenosis ( $\geq 75\%$  diameter reduction) of at least one of the pre-defined segments. In all distal end-to-side aorto-bi-femoral patent bypasses, the perfusion was sometimes retrograde through the external iliac arteries towards the hypogastric system. Then, in these patients, the external iliac artery was used for the analysis instead of the common iliac artery. Diameter measurements were made using the advantage Workstation 4.1-6 (General Electric, Buc/Yvette, France). For each arterial segment, the maximal and minimal arterial external diameters of each studied segment were measured as the number of pixels, and diameter stenosis was calculated as the ratio maximal-minus-minimal diameter to maximal diameter. If an artery was completely occluded its minimal diameter was noted as 0 mm. Variability of diameter measurement within the study between two observers was previously reported to be lower than 10%.<sup>6</sup>

### Pressure measurements

After a 20-minute resting period, patients were installed recumbent in a room with a temperature of  $21 \pm 2^\circ\text{C}$ . Systolic pressure at both arms was measured with automated devices (Dynamap1846; Johnson & Johnson, USA). Systolic perfusion pressure at the penile level was measured using

disposable pediatric cuffs (M1870A; Philips, France) connected to an electronic pressure device (Monitor 120; Roche, UK) and a laser Doppler flowmeter (PF 5000; Perimed, Sweden). Data were recorded on a computer via an analogue output to digital converter (Biopac System, Inc., California, USA) with a sample rate of 3 Hz. Once the laser Doppler was fixed to the skin, the pediatric cuff was inflated to supra-systolic systemic pressure and slowly deflated by approximately 3 mmHg/second. The reappearance of the laser Doppler signal was used to determine penile perfusion pressure (in mmHg). The laser Doppler flowmetry (LDF) technique is widely used at the toe level to measure perfusion pressure. Laser Doppler flowmetry is used routinely for toe pressure measurements and is advantageous compared to the manual Doppler recordings in case of low-pressure values. This technique greatly facilitates toe pressure recordings and results are highly correlated to the conventional strain-gauge technique.<sup>7</sup> The PBI was calculated as the ratio of penile perfusion pressure (PPP) to the highest brachial systolic pressure. The test was repeated three times and the recorded value was the mean of the three measurements. This procedure lasted for approximately 4–5 minutes. Results from arterial imaging were not made known at the time of pressure measurement. Penile pressure was reported impossible if the cuff could not be positioned as a result of major obesity, in the presence of a penile prosthesis, or if no signal reappearance could be found on the recordings.

#### Analysis of the results

Four different classifications of the arteriograms were tested. Arteriograms were considered positive: for unilateral or bilateral stenosis or occlusion, for bilateral stenosis or occlusion, for unilateral or bilateral occlusion only, or for bilateral occlusion only.

We first used PBI = 0.60 as a cut-off value according to the value used in detecting an arterial origin of impotence in both the general<sup>8</sup> and the vascular<sup>9</sup> population. Impossible recordings were considered negative: non-contributive for the presence of arterial lesions. The risk/chance of a positive arteriogram according to the results of penile pressure and PBI were analyzed with Yates-corrected chi-squared tests and expressed as relative risk (RR; Taylor series 95% confidence interval) for the four different angiographic classifications. Sensitivity, specificity and accuracy are presented by 95% confidence intervals<sup>10</sup> and differences between tests studied with the MacNemar test (SPSS V12.0F; SPSS Inc.).

A second analysis was performed with the receiver operating characteristics (ROC) curve

approach described by Hanley and McNeil<sup>11</sup> to determine the specific cut-off points issued from penile pressure recordings on available data, for either absolute penile pressure or PBI. This technique is based on calculating the sensitivity and specificity of a test for each value of the studied variable in the diagnosis of a disease. This approach has two advantages. First, it enables the objective determination of the performance of a test through the calculation of the area under the sensitivity/specificity relationship curve. Areas under ROC curves were tested against the null hypothesis of an area of 0.50 (SPSS V12.0F; SPSS Inc). A perfect test would provide an area of 1.00, whereas an area of 0.50 would be the result of a random choice. Second, ROC-curve analysis allows for the objective determination of the cut-off point to be proposed for clinical use. The value of the variable resulting in the lowest distance to this angle is considered to be the best compromise of sensitivity and specificity for an arbitrarily defined equal 'cost' of false positive or false negative tests. Using this cut-off point we calculated the optimal sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the parameter studied for each of the four angiographic classifications.

We estimated that at least 80% of patients with a positive test would have a stenosis or occlusion of one or both pathways to the hypogastric vascular bed and that 40% of patients with normal tests would have a stenosis or occlusion of one or both pathways to the hypogastric vascular bed (RR for a positive angiogram in case of a positive test  $\geq 2$ ) and that the test would be positive in 75% of the studied patients.

The minimal number of subjects to be included to reach significance with 5% risk and 85% power was 80. Results are expressed as mean  $\pm$  SD. For all statistical tests, a two-tailed probability level of  $p < 0.05$  was used to indicate statistical significance.

## Results

#### Population studied

The patients included were 88 males (among which seven were diabetics),  $170 \pm 7$  cm in height, weighing  $74 \pm 13$  kg and aged  $58 \pm 9$  years old. Humeral pressure was  $142 \pm 21$  mmHg on the right side and  $141 \pm 23$  mmHg on the left side. Minimal ABI at rest was  $0.68 \pm 0.30$  and contra-lateral ABI was  $0.86 \pm 0.27$ . Thirty-eight of the patients had undergone peripheral vascular surgery and eight coronary bypasses in the past. Their self-reported maximal walking distance was  $279 \pm 285$  m. Of the 88 patients, 73 were being treated with anti-platelet drugs, eight with vitamin K inhibitors, 42 received

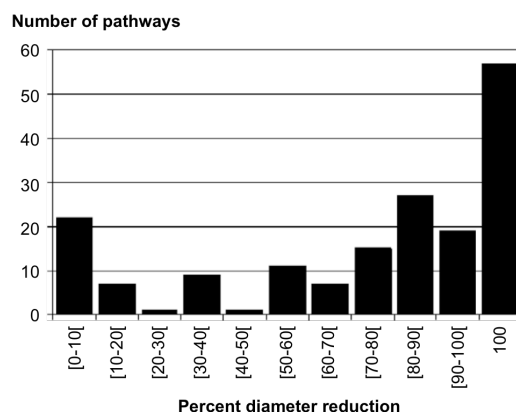
HMG-CoA-reductase inhibitors and 37 received conversion enzyme inhibitors. No patient was receiving sildenafil.

### Arterial imaging

The distribution of the degree of arterial reduction observed in the 88 patients is presented in Figure 1. Imaging revealed 26 stenoses and 26 occlusions on the right side and 25 stenoses and 31 occlusions on the left side, resulting in 24 patients showing no significant lesions on the arteries toward the hypogastric vascular bed, 20 patients having unilateral stenosis or occlusion and 44 having bilateral stenosis or occlusion of the aorta common or internal iliac arteries. Thus, according to the different classifications defining angiographic positivity, the number of positive tests was 64 when a positive arteriography was defined as a unilateral or bilateral stenosis or occlusion, 44 when a positive arteriography was defined as a bilateral stenosis or occlusion, 37 when a positive arteriography was defined as a unilateral or bilateral occlusion, and 20 when a positive arteriography was defined as a bilateral occlusion.

### Penile pressure

Penile pressure was measurable in 85 of the 88 patients. The three missing values were because of major obesity, LDF signal instability, and the presence of a penile prosthesis. In the 85 measured patients, penile pressure was  $72 \pm 27$  mmHg. The resulting average PBI was  $0.50 \pm 0.18$ . Thus, the PBI was lower or equal to 0.60 in 65 patients and either normal ( $n = 20$ ) or not measurable ( $n = 3$ ) in 23 patients. The average values for PBI are presented in Table 1 according to the presence of stenosis or occlusions seen in arteriography.



**Figure 1** Distribution of the maximal percentage of diameter reduction observed in the 176 studied pathways. A 100% stenosis is an occlusion of the pathway.

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**Table 1** Penile perfusion pressure (PPP)-index expressed as mean  $\pm$  SD in the 85 patients with measurable penile perfusion pressure

|                                                                | PPP index       | No. of patients |
|----------------------------------------------------------------|-----------------|-----------------|
| No stenosis or occlusion                                       | $0.54 \pm 0.22$ | 23              |
| Unilateral stenosis                                            | $0.49 \pm 0.14$ | 13              |
| Bilateral stenosis                                             | $0.47 \pm 0.15$ | 14              |
| Unilateral occlusion (with or without contra-lateral stenosis) | $0.52 \pm 0.17$ | 16              |
| Bilateral occlusion                                            | $0.45 \pm 0.18$ | 19              |

Table 2 summarizes the results of PBI for the prediction of underlying arterial lesions according to the definition for arterial positive imaging. In brief, the positive and negative predictive values were: 78.5% and 43.5% for unilateral or bilateral stenosis or occlusion, 49.3% and 47.8% for bilateral stenosis or occlusion, 41.5% and 56.5% for unilateral or bilateral occlusion, and 26.1% and 87.0% for bilateral occlusion only. Thus, the 0.60 limit was unable to discriminate normal from abnormal angiographic results, whatever the classification used to define a positive angiography.

Using the ROC curve analysis in the 85 patients with measurable penile pressure values, as shown in Table 3, the only area significantly different from the random choice was for the detection of bilateral occlusions with the PBI. The optimal cut-off point defined from the ROC curve analysis was a PBI lower than or equal to 0.45, providing 74% sensitivity and 68% specificity to discriminate the 19 patients with bilateral arterial occlusion from the other 66 patients (Figure 2). The other cut-off points (e.g. those to be used for the absolute value of penile pressure or to search for unilateral occlusion) have not been calculated since the area for the ROC curve was not statistically different from the area that would result from a random choice.

### Discussion

Evaluation of the pelvic circulation remains difficult with ultrasound imaging, especially in obese patients or in the case of gaseous interposition. Penile pressure measurement appears as the most 'intuitive' technique for the study of the hemodynamic consequences of aorto-iliac lesions, but it can hardly be used routinely. This could explain why epidemiological studies analyzing the concordance of non-calf claudication to arterial pressure changes,<sup>3</sup> or studies of the effect of iliac angioplasty<sup>4</sup> have used the ABI, but this is probably not the best technique for the detection of proximal lower limb arterial disease or

**Table 2** Number of true and false positive (+) and true and false negative (–) tests and diagnostic performance of the penile perfusion pressure (PPP)-index = or <0.60 against arterial imaging

|                 | Arterial stenosis or occlusion |           |                |           | Arterial occlusion only |           |                |           |
|-----------------|--------------------------------|-----------|----------------|-----------|-------------------------|-----------|----------------|-----------|
|                 | Unilateral or bilateral        |           | Bilateral only |           | Unilateral or bilateral |           | Bilateral only |           |
|                 | Value                          | 95% CI    | Value          | 95% CI    | Value                   | 95% CI    | Value          | 95% CI    |
| True (+)        | 51                             |           | 32             |           | 27                      |           | 17             |           |
| True (–)        | 10                             |           | 11             |           | 13                      |           | 20             |           |
| False (+)       | 14                             |           | 33             |           | 38                      |           | 48             |           |
| False (–)       | 13                             |           | 12             |           | 10                      |           | 3              |           |
| RR              | 1.4                            | 0.9–2.0   | 0.9            | 0.6–1.5   | 1.0                     | 0.6–1.7   | 2.0            | 0.7–6.2   |
| $\chi^2/p$      | 3.09/0.08                      |           | 0.00/1.00      |           | 0.01/0.93               |           | 1.00/0.31      |           |
| Sensitivity (%) | 79.7                           | 67.8–88.7 | 72.7           | 57.2–85.0 | 77.1                    | 59.9–89.6 | 85.0           | 62.1–96.8 |
| Specificity (%) | 41.7                           | 22.1–63.4 | 25.0           | 13.2–40.4 | 25.5                    | 14.3–39.6 | 29.4           | 19.0–41.7 |
| Accuracy (%)    | 69.3                           | 58.6–78.7 | 48.9           | 38.1–59.7 | 45.5                    | 34.8–57.5 | 42.1           | 31.6–53.1 |

95% CI is the 95% confidence interval for the determinations.

RR is the relative risk of a positive arteriogram in case of a positive test.

for the effect of treatment at the proximal level. Upper thigh pressure index with large cuffs could be proposed to study only proximal arteries. It was shown to correlate well with intra-arterial femoral pressure.<sup>12</sup> It seems as sensitive as ABI for the detection of pressure improvement after aorto-femoral reconstruction in patients with multilevel disease (i.e. aorto-iliac and femoro-popliteal occlusive disease).<sup>13</sup> Nevertheless, while Baur et al. found an 89% accuracy in the detection of iliac stenosis when used together with Doppler waveform analysis,<sup>14</sup> other authors have reported a much lower accuracy.<sup>15</sup> It has been suggested that pressure measurements above the ankle may be neither cost effective, nor have clinical interest.<sup>16</sup>

Contrary to thigh pressure, femoral lesions should not influence penile pressure measurement. The penile to brachial pressure index has been used largely for the detection of the vascular origin of impotence although the cut-off points used range from 0.60<sup>8</sup> to 0.91.<sup>17</sup> During acute occlusion of arteries supplying the hypogastric territory, the pressure decrease is more pronounced with bilateral than with unilateral occlusion, both with non-invasive (penile pressure) techniques<sup>18,19</sup> and

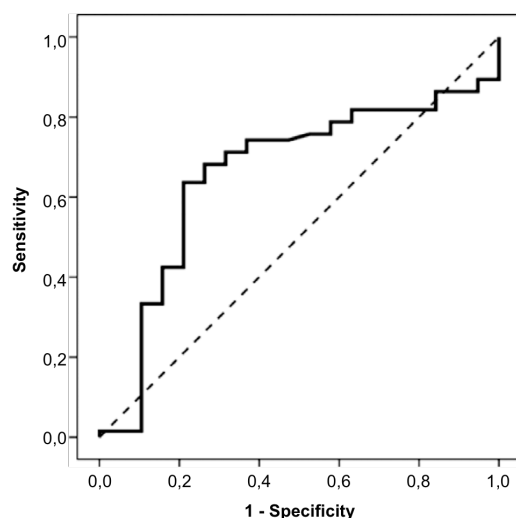
with invasive (hypogastric artery stump pressure) techniques.<sup>20</sup> Furthermore, the penile pressure index is significantly lower when the lesions are located on the main (aorto-iliac) rather than on distal (internal pudendal) arteries,<sup>21,22</sup> although this appears contradictory to the observation of a significantly higher incidence of symptoms of pelvic ischemia with more distal placement of coils for hypogastric artery embolization.<sup>23</sup> The differences shown between these studies are likely to be as a result of the time lapse between the occlusion and the measurement and development of the collateral circulation.<sup>24</sup> Collateral circulation development is also the underlying mechanism of clinical improvement of hip/buttock claudication observed in the first 6 months following bilateral hypogastric artery embolization,<sup>25</sup> whereas severe colonic and spinal ischemia are associated with high morbidity and mortality early on after endovascular abdominal aortic aneurysm repair.<sup>26</sup> The pelvic circulation is a complex network and many pathways may participate in the blood flow supply in the case of hypogastric chronic occlusion.<sup>6</sup>

It is likely that penile pressure is maintained within normal ranges if one hypogastric artery is

**Table 3** Area under the ROC curve for penile perfusion pressure (PPP) and PPP-index in the detection of angiographically proved lesions among the 85 patients with determinable penile perfusion pressure

|                       |                         |           | Area under the ROC curve | P-Value for the area |
|-----------------------|-------------------------|-----------|--------------------------|----------------------|
| Stenosis or occlusion | Unilateral or bilateral | PPP       | 0.58 ± 0.08              | 0.27                 |
|                       |                         | PPP-index | 0.60 ± 0.08              | 0.16                 |
|                       | Bilateral only          | PPP       | 0.53 ± 0.06              | 0.61                 |
|                       |                         | PPP-index | 0.54 ± 0.06              | 0.55                 |
| Occlusion only        | Unilateral or bilateral | PPP       | 0.56 ± 0.06              | 0.38                 |
|                       |                         | PPP-index | 0.56 ± 0.06              | 0.39                 |
|                       | Bilateral only          | PPP       | 0.62 ± 0.07              | 0.11                 |
|                       |                         | PPP-index | 0.66 ± 0.07              | 0.04                 |





**Figure 2** ROC curve for penile perfusion index in the prediction of the presence of a bilateral occlusion of the arterial pathway towards the hypogastric vascular bed.

chronically occluded and that pressure falls only when lesions are present bilaterally, whereas unilateral acute occlusion might be detected better.

This is probably why previous studies have shown a significant difference in penile to brachial pressure index between normal arteriograms and bilateral, but not unilateral, lesions.<sup>21</sup> This might also explain why an important overlap exists in impotent patients with normal versus abnormal angiography.<sup>27</sup> The present study using the ROC curve analysis shows that PBI cannot differentiate patients with unilateral lesions from normal subjects in the chronic setting of occlusion. This latter observation seems consistent with previous results.

In addition to the complex arterial anatomy and numerous potential anastomoses, technical problems may interfere with measurements, thereby increasing the intra- and inter-observer variability of penile pressure determination.<sup>28</sup>

As underlined by Doyle and Yu, Doppler penile-pressure determinations 'require an experienced technician, can be time-consuming, yield inconsistent results and require much penile manipulation'.<sup>5</sup> Using laser Doppler flowmetry in the present study facilitates the measurements and decreases the time required for the determination from 20 minutes to only 4 minutes, as strain-gauge plethysmography did in previous studies.<sup>5</sup> Nevertheless, it no longer enables the measurement of pressure in the dorsal and cavernous penile arteries, but these differential measurements are rarely used in clinical routine. Whether the results reported here could be comparable if penile pressures were to be

obtained by Doppler detection of cavernous penial arteries remains to be studied.

Another limitation of this study relies on the choice of the arteries used to define positive arteriograms. Since only proximal trunks were studied, it cannot be excluded that the relative inaccuracy observed results from a high rate of apparently false positive penile pressure values due to distal lesions on gluteal and pudendal arteries. Nevertheless, as previously underlined, penile pressures seem more sensitive to proximal than distal lesions<sup>21,22</sup> and a precise analysis of distal arteries would have required specific late timing for the arteriography at the pelvic level which is not done in routine investigations.

The choice of 75% as a limit for arterial stenosis could also be criticized. We have used a 50% stenosis limit (results not shown) and this has resulted in a comparable inaccuracy.

Finally, it cannot be excluded that some patients' conditions may have improved or been aggravated in the months between penile pressure measurement and arterial imaging. The fact that we studied only patients with stable claudication was aimed to limit such a possibility, although it does not exclude it.

As a conclusion, the normal limit used for PBI for impotence in the general population is not accurate enough to detect the presence of lesions on arteries supplying the hypogastric vascular bed in vascular patients with claudication. Further, the ROC curve analysis shows that penile pressure measurements performed at rest are relatively insensitive for the detection of chronic proximal arterial lesions in patients with arterial claudication.

Exercise-related changes in penile pressure have been shown to improve the accuracy of penile pressure measurements in the detection of proximal ischemia.<sup>29</sup> It cannot be excluded that post-exercise PBI could demonstrate a good correlation with arteriography in patients with claudication. This could be tested in future experiments, but remains difficult for clinical routine. The low sensitivity of resting values does not mean that penile pressure measurements are unreliable, since very low PBI provided a good positive predictive value for bilateral occlusion. It is possible that penile pressure or PBI at rest could be done as an easy first approach in selecting patients suffering unexplained proximal claudication. Then patients with vascular-type proximal claudication, but with a normal ankle and penile pressure, might be better referred to laboratories using one of the other techniques that have been proposed to study the blood flow supply to the pelvic circulation, such as in near infra-red spectroscopy,<sup>30,31</sup> whole body scintigraphy<sup>32</sup> or transcutaneous oxygen pressure.<sup>33</sup>

As a general rule, if ultrasound imaging is not conclusive for a diagnosis, we suggest that a normal

penile pressure or normal PBI should not exclude the presence of vascular lesions on the arteries supplying the hypogastric vascular bed (and, by extension, should not exclude a vascular origin of unexplained proximal exercise-induced pain).

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#### 4.1.2 L'ischémie distale à la marche

L'ischémie distale à la marche se manifeste par des douleurs distales des membres inférieurs, le plus souvent aux mollets et de façon uni- ou bilatérales. Les patients diabétiques sont connus pour avoir une claudication à la marche plutôt distale. Cependant, le diabète engendre une atteinte athéromateuse diffuse. Il a été montré que les patients diabétiques avaient une forte prévalence de lésions proximales et que ces patients présentaient davantage d'ischémie silencieuse probablement liée à la neuropathie périphérique (Cosson et al., 2001; Dolan et al., 2002; Haltmayer et al., 2001). Malheureusement, les données hémodynamiques à l'exercice sont manquantes. La TcPO<sub>2</sub> d'effort par l'intermédiaire des valeurs de DROP<sup>10</sup> permet une évaluation indirecte « hémodynamique » à l'effort de plusieurs sites au niveau des membres inférieurs (Abraham et al., 2005; Abraham et al., 2003) :

- 2 sites au niveau proximal, fesse droite et fesse gauche,
- 2 sites au niveau distal, mollet droit et mollet gauche.

A chaque site est mesurée une valeur de DROP, reflet de l'ischémie locale.

Dans une population de patients diabétiques lors d'un exercice de marche, nous avons ainsi voulu répondre à plusieurs questions :

Existe-t-il des différences de distances maximales de marche chez des patients diabétiques comparés à des patients non diabétiques ?

Existe-t-il des différences dans l'importance de l'ischémie (évaluée par la valeur de DROP des sondes de TcPO<sub>2</sub>) chez des patients diabétiques comparés à des patients non diabétiques ? En d'autres termes, les valeurs de DROP de TcPO<sub>2</sub> sont-elles différentes entre les deux groupes ?

Est ce que les patients diabétiques ont une ischémie plus diffuse (davantage de site avec des valeurs pathologiques) à l'exercice que des patients non diabétiques ?

Existe-t-il des différences dans la localisation de l'ischémie (proximale ou distale) entre les patients diabétiques et les patients non diabétiques ?

L'ischémie asymptomatique appelée aussi ischémie silencieuse<sup>11</sup> est elle plus présente chez les patients diabétiques que chez les patients non diabétiques ?

<sup>10</sup> DROP: Une valeur de DROP (Delta from Rest of Oxygen Pressure) < -15 mmHg est pathologique et traduit une ischémie de la zone, où est positionnée la sonde de mesure. Voir Annexe 4.

<sup>11</sup> Ischémie silencieuse : Elle est définie par une valeur de DROP de TcPO<sub>2</sub> inférieure à -15 mmHg au niveau d'un site de mesure alors que le patient ne présente pas de douleur au niveau de ce site de mesure.



Y a-t-il plus de symptômes aux membres inférieurs d'origine non vasculaire chez les patients diabétiques que chez ceux non diabétiques et y a-t-il plus de symptômes qui ne sont pas localisés aux membres inférieurs chez les patients diabétiques que chez ceux non diabétiques ?

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Exercise treadmill testing in patients with claudication, with and without diabetes.

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Pour répondre à ces différentes questions, nous avons réalisés une étude rétrospective entre 2000 et 2008 incluant 1212 patients, qui ont eu un test de marche sur tapis (3,2km/h et 10% de pente) associée à une TcPO<sub>2</sub> mettant en évidence une ischémie au niveau des membres inférieurs (Abraham et al., 2003). Un patient était classé comme diabétique si le patient déclarait un antécédent de diabète et/ou s'il prenait un traitement antidiabétique (oral ou insuline). Sur ces 1212 patients, 982 ont été classés comme non diabétiques et 230 comme diabétiques. Les patients diabétiques étaient statistiquement plus âgés, avaient un indice de masse corporelle plus élevé que les patients non diabétiques et prenaient davantage d'inhibiteurs de l'enzyme de conversion.

Il n'a pas été retrouvé de différence au niveau de la distance maximale déclarée à l'interrogatoire entre les deux groupes (376+/-330m chez les patients diabétiques versus 415+/-344m chez les patients non diabétiques ; P=0,11) alors que la distance maximale de marche sur tapis étaient statistiquement moindre chez les patients diabétiques (261+/-257 versus 339+/-326 ; P ajusté=0,04) et ce même après ajustements pour l'âge, l'indice de masse corporelle (IMC) et les traitements. Ces données mettent bien en valeur la discordance que l'on retrouve entre l'évaluation de la distance maximale de marche par l'interrogatoire et par un test de laboratoire.

La diffusion de l'ischémie évaluée par le nombre de sites ischémiques (1, 2, 3 ou 4) n'était pas différente entre les 2 groupes.

Par contre, les patients diabétiques présentaient davantage de lésions distales que les patients non diabétiques (38% versus 29%,  $P < 0,01$  après ajustements pour l'âge et l'IMC).

Il n'y avait pas de différence au niveau des ischémies silencieuses entre les 2 groupes ni au niveau des autres symptômes non ischémiques au niveau des membres inférieurs. Les patients diabétiques présentaient néanmoins davantage de symptômes non localisés aux membres inférieurs (dyspnée, douleur angineuse) (27,8% versus 18,3%,  $P < 0,01$ ).

En conclusion, cette étude a montré que la capacité de marche sur tapis était plus faible chez les diabétiques que chez les non-diabétiques, alors que la capacité de marche déclarée à l'interrogatoire et les IPS de repos étaient comparables entre les groupes. Cette différence significative observée sur le tapis ne semble pas s'expliquer par la différence d'IMC. D'autres facteurs pourraient expliquer cette différence comme des différences de sensibilité à la douleur, de prévalence de co-morbidités associées et de voies métaboliques utilisées lors de l'exercice. Notre étude confirme que les patients atteints de diabète ont plus fréquemment une ischémie distale que les patients sans diabète. Nous montrons pour la première fois que les patients atteints de diabète et d'AOMI ont une prévalence similaire de l'ischémie asymptomatique pendant le test sur tapis roulant et une prévalence comparable de douleurs des membres d'origine non-vasculaire, comparativement à des patients artériopathes sans diabète. Enfin, les patients artériopathes diabétiques présentent plus fréquemment des symptômes qui ne sont pas localisés aux membres inférieurs, en particulier au niveau cardiaque (anomalies électrocardiographiques). Ces observations soulignent l'intérêt spécifique de l'épreuve d'effort sur tapis chez les patients diabétiques artériopathes qui rapportent une claudication de type vasculaire.

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## Article: Complications

# Exercise treadmill testing in patients with claudication, with and without diabetes

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### Abstract

**Aim** To compare symptoms and walking capacities of patients with and without diabetes reporting vascular-type claudication.

**Methods** We recorded self-reported maximal walking distance, maximal walking distance on treadmill test ( $3.2 \text{ km h}^{-1}$ , 10% slope), exercise transcutaneous oxygen pressure DROP index [limb transcutaneous oxygen pressure (TcPO<sub>2</sub>) changes from rest minus chest TcPO<sub>2</sub> changes from rest] and symptoms on treadmill in 230 patients with diabetes and 982 patients without diabetes. Exercise-induced proximal and distal symptoms were analysed in the perspective of underlying proximal and distal ischaemia (DROP value < negative 15 mmHg).

**Results** Self-reported maximal walking distance did not differ between groups, whereas maximal walking distance on treadmill test was lower in patients with diabetes vs. patients without diabetes ( $261 \pm 257$  and  $339 \pm 326$  m, respectively;  $P < 0.05$  when adjusted for potential confounders). In patients with ischaemia, the number of ischaemic areas (proximal and/or distal on right and/or left) was comparable between the two groups. Patients with diabetes had more distal ischaemia than patients without diabetes (38 vs. 29%, respectively;  $P < 0.01$ ), whereas proximal ischaemia was similar between groups. The prevalence of lower-limb exercise-related symptoms without ischaemia was comparable between groups. There were more symptoms other than lower-limb pain in patients with diabetes than patients without diabetes (29.6 vs. 18.3%, respectively;  $P < 0.01$ ).

**Conclusions** Patients with diabetes show more severe limitation on the treadmill and more non-limb symptoms than patients without diabetes, although self-reported walking capacity is comparable between the two groups. Using TcPO<sub>2</sub>, we confirm that patients with diabetes reporting claudication show more distal ischaemia than patients without diabetes, with no difference at the buttock level. Treadmill testing is of interest in patients with peripheral artery disease and diabetes.

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**Keywords** buttock claudication, ischemia, pain, peripheral artery disease, treadmill test

**Abbreviations** DROP, delta from rest of oxygen pressure; TcPO<sub>2</sub>, transcutaneous oxygen pressure

### Introduction

Although it is generally accepted that patients with diabetes have more distal (infrapopliteal) than proximal (aorto-iliac) arteriographic lesions, the proximal arteries might still be affected because diabetes is associated with diffuse atherosclerotic disease. For example, previous studies have shown a high prevalence of buttock-level defects in asymptomatic patients with diabetes [1,2]. Secondly, as a result of diabetic peripheral neuropathy, it is generally suggested that patients

with diabetes have more 'silent' ischaemia, both centrally and peripherally, than their counterparts without diabetes [3]. Lastly, self-reported exercise-related symptoms of a non-vascular origin are reported to be more frequent in patients with diabetes than in patients without diabetes [3,4], although direct correlation with exercise haemodynamic data from the lower limb is lacking.

In our laboratory, we routinely use the transcutaneous oxygen pressure technique during treadmill exercise testing to simultaneously evaluate the presence of proximal (buttocks) and distal (calves) ischaemia on both sides in patients with stage 2 claudication, atypical claudication or claudication of suspected but questionable arterial origin [5–7]. We

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retrospectively analysed the data recorded for all new patients investigated between 2000 and 2008 to address the following questions of clinical interest. (i) Are there measurable differences in the objective measurement of walking capacity and in the magnitude of ischaemia between patients with and without diabetes? (ii) Do patients with diabetes have more diffuse exercise-induced ischaemia than patients without diabetes? (iii) Is there a difference in the localization of ischaemia (proximal or distal) between patients with and without diabetes? (iv) Do patients with diabetes have more asymptomatic ischaemia than patients without diabetes during treadmill tests? (v) During treadmill testing, are lower-limb symptoms without underlying exercise-induced ischaemia (and thus suspected of non-vascular origin), and non-lower-limb symptoms, more prevalent in patients with and without diabetes?

## Subjects and methods

### Populations

By 1 December 2008 (database closure), 1874 treadmill exercise tests with *TcpO2* recordings for 1333 different patients had been performed. For patients with multiple visits, only their first test was included. From these 1333 different patients, a retrospective study was conducted with the patients who had a history of vascular-type exercise-induced lower-limb pain (no pain at rest, exercise-induced pain or discomfort improving or disappearing within 10 min of exercise ending). Patients were included only if they were proved to have peripheral artery disease, at least on one side, within 6 months of the treadmill test. Peripheral artery disease was defined as stenoses  $\geq 75\%$  diameter on invasive investigations (magnetic resonance angiography or computed tomography angiography), an abnormal Doppler waveform analysis and/or an ankle-brachial systolic pressure index  $\leq 0.90$  at rest.

### Classification of diabetes mellitus

On admission, the patients' self-reported medical history and treatments and self-reported maximal walking distance were recorded. Specifically, clinical history of diabetes mellitus (yes/no/unknown) and anti-diabetic therapy such as oral agent or insulin (yes/no/unknown) were recorded. Diabetes was defined as a history of diabetes mellitus and/or the administration of anti-diabetic treatment. Patients with neither a history of diabetes mellitus nor anti-diabetic treatment constituted the group without diabetes. All other patients (i.e. patients unable to know about diabetes or report their treatment) were excluded from the analysis. Almost all patients with diabetes had Type 2 diabetes.

### Exercise procedure

All treadmill tests ( $3.2 \text{ km h}^{-1}$ ; 10% slope; maximized to 20 min) were performed as previously described [8]. A 12-lead

electrocardiogram (ECG) was used to measure heart rate and to detect any severe arrhythmia (e.g. sustained or repeated ventricular arrhythmia, occurrence of atrial fibrillation) or abnormal depolarization (e.g. left bundle branch block) or repolarization (e.g. horizontal or descending ST depression  $\geq 2 \text{ mm}$ ) events during the whole exercise test procedure. Patients were asked to exercise until when the pain became intolerable. At this point, the treadmill was stopped and we recorded the maximum walking distance.

### *TcpO2* measurements

All exercise tests were performed in a temperature-controlled room ( $21 \pm 2^\circ \text{C}$ ) after an acclimatization period of  $\geq 20 \text{ min}$ . Measurements were performed using five *TcpO2* probes with TINA-TCM3 or TINA-TCM400 devices (Radiometer, Copenhagen, Denmark) [9]. Calibration and preparation of the skin was performed as previously reported [8]. In brief, electrodes were positioned on the chest and each calf and buttock. Once the electrodes were in position, a pretest heating period of at least 15 min in the standing position was required to allow stable resting values to be reached. *TcpO2* values were recorded for 2 min in the standing position before the treadmill was started, during the walking period and for at least 10 min in the standing position following the end of the exercise test. The data were recorded with 5-s intervals until 2003 and 2-s intervals since then.

From the start of the exercise test, we calculated the delta from rest of oxygen pressure (DROP) index as previously reported [8,10]. The DROP index is the absolute change in *TcpO2* from rest in each of the four limb probes, corrected with the corresponding absolute change in *TcpO2* from rest in the chest electrode. This DROP index is a negative value expressed in mmHg. The minimum DROP value during exercise is highly accurate and reliable in predicting the presence/absence and severity of angiographically proved lesions at both the buttock and ankle levels [8,10]. Analyses of *TcpO2* were performed blinded to the results of the questionnaires. Consistent with our previous results at the buttock [8] and distal level [10], the presence of ischaemia on each of the four limb *TcpO2* probes during exercise was defined as a DROP value less than negative 15 mmHg.

Our aim was not to search for a threshold of *TcpO2* vs. symptoms, but to use *TcpO2* as an objective test for the presence of ischaemia and analyse the concordance between symptoms and ischaemia. Consequently, each patient could report pain at history and/or on treadmill and/or show significant ischaemia on *TcpO2* recording in one or more of the following four sites: proximal right, proximal left, distal right or distal left. The number of sites with exercise-induced ischaemia on *TcpO2* was used as an estimation of the diffusion of arterial lesions. Diffusion of symptoms was not used to estimate the diffusion of the arterial disease, because a patient with ischaemia on all four sites can be symptomatic only at the most severe ischaemic site.

### Symptoms on treadmill

During the test, subjects were repeatedly asked about the presence, location and severity of symptoms in their limbs and about non-limb symptoms. Immediately after the end of the walking period, they completed a French translation of the San Diego Claudication Questionnaire (SDCQ) [11]. Only exercise-related symptoms that were absent at rest, occurred during exercise and disappeared within 10 min after exercise (i.e. those presumed to be of vascular origin) were considered for the analysis. Proximal/distal symptoms were then classified according to answers to the question dealing with symptom localization.

### Statistical and ethical considerations

Differences between groups were studied with and without adjustment for age, BMI and treatments with Student's *t*-tests and ANCOVA for continuous variables and with a  $\chi^2$ -test and logistic regression for categorical variables. All tests were performed bilaterally, with  $P < 0.05$  used as the cut-off to indicate statistical significance, using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The study was performed according to the principles outlined in the Declaration of Helsinki.

### Results

Among the 1228 patients fulfilling the inclusion criteria, 16 (1.3%) could not be classified as having diabetes or not having diabetes because they were unable to give their treatment and medical history; these patients were excluded from the analysis. These 16 patients had an age, stature and body mass of  $64 \pm 14$  years,  $168 \pm 8$  cm and  $71 \pm 14$  kg, respectively, and 13 (81%) of them were male. Their self-reported maximal walking distance and maximal walking distance on treadmill test were  $284 \pm 255$  and  $296 \pm 162$  m, respectively.

### Characteristics of included patients

Data reported here are for 1212 patients who were referred to the vascular laboratory for symptoms of claudication or suspected claudication and who all tested positive for lower-limb peripheral artery disease. These patients had an age, stature and body mass of  $63 \pm 11$  years,  $168 \pm 9$  cm and  $76 \pm 14$  kg, respectively, and 1036 (85%) of them were male. Of the 1212 studied patients, 230 (19%) had a clinical history of diabetes mellitus or were taking either insulin or oral hypoglycaemic agents (group with diabetes). Therefore, 982 patients were classified in the group without diabetes (Table 1). Patients with diabetes were older (65 vs. 62 years;  $P < 0.01$ ) and heavier (BMI

**Table 1** Characteristics and treatments of patients with and without diabetes\*

|                                                                     | Patients with diabetes | Patients without diabetes | P      |
|---------------------------------------------------------------------|------------------------|---------------------------|--------|
| Total number ( <i>n</i> )                                           | 230                    | 982                       |        |
| Males, <i>n</i> (%)                                                 | 195 (84.8)             | 841 (85.6)                | NS     |
| Age (years)                                                         | $65 \pm 10$            | $62 \pm 12$               | 0.002  |
| Stature (cm)                                                        | $168 \pm 7$            | $169 \pm 8$               | 0.78   |
| Body mass (kg)                                                      | $81 \pm 14$            | $74 \pm 14$               | 0.0001 |
| Body mass index ( $\text{kg}/\text{m}^2$ )                          | $26.1 \pm 4.4$         | $28.7 \pm 4.4$            | 0.0001 |
| Self-reported maximal walking distance (m)                          | $376 \pm 330$          | $415 \pm 344$             | 0.11   |
| Self-reported inability to walk 1 km without stopping, <i>n</i> (%) | 183 (79.6)             | 740 (75.4)                | NS     |
| Arm systolic blood pressure (mmHg)                                  | $150 \pm 21$           | $147 \pm 23$              | 0.12   |
| Ankle-brachial index at rest                                        | $0.86 \pm 0.23$        | $0.87 \pm 0.23$           | 0.06   |
| Platelet inhibitors                                                 | 170 (74)               | 718 (73)                  | NS     |
| Statins                                                             | 113 (49)               | 427(43)                   | NS     |
| Other lipid-lowering agents                                         | 14 (6)                 | 63 (6)                    | NS     |
| Angiotensin-converting enzyme inhibitors                            | 67 (29)                | 223 (23)                  | 0.04   |
| Angiotensin II receptor blockers                                    | 42 (18)                | 106 (11)                  | 0.002  |
| Arterial vasodilator medications                                    | 54 (23)                | 302 (31)                  | 0.003  |
| Beta-blockers                                                       | 52 (23)                | 198 (20)                  | NS     |
| Diuretics                                                           | 36 (16)                | 134 (14)                  | NS     |
| Anticoagulants                                                      | 11 (4)                 | 71 (8)                    | NS     |
| Non-steroid anti-inflammatory drugs                                 | 2 (1)                  | 26 (3)                    | NS     |
| Analgesic or anxiolytic drugs                                       | 12 (5)                 | 59 (6)                    | NS     |
| Other anti-hypertensive                                             | 11 (5)                 | 53 (5)                    | NS     |
| Calcium-channel inhibitors                                          | 22 (10)                | 94 (10)                   | NS     |
| Nitroglycerin                                                       | 5 (2)                  | 39 (4)                    | NS     |
| Oral anti-diabetic                                                  | 153 (67)               | —                         | —      |
| Insulin                                                             | 81 (35)                | —                         | —      |

\*Mean  $\pm$  SD or number (%).

28.7 ± 4.4 vs. 26.1 ± 4.4 kg/m<sup>2</sup>;  $P < 0.01$ ) than patients without diabetes. Inhibitors of the renin-angiotensin system were used more frequently in patients with diabetes than in patients without diabetes, whereas arterial vasodilators were used less commonly in patients with diabetes than in patients without diabetes.

#### Walking capacity

Self-reported walking ability and ankle-brachial index did not differ between patients with and without diabetes (Table 1), whereas maximal walking distance on treadmill test was lower in patients with diabetes than patients without diabetes (Table 2), both before and after adjustment for age, BMI and treatment differences. Maximal heart rate during the treadmill test was 116 ± 22 and 117 ± 22 b min<sup>-1</sup> in patients with and without diabetes, respectively ( $P = \text{NS}$ ).

#### Symptoms and lower-limb ischaemia

The prevalence of lower-limb symptoms during treadmill testing did not differ between the two groups (Table 2).

The absolute resting TcpO<sub>2</sub> values were approximately 3 mmHg lower at all probe sites in the subjects with diabetes (Table 2); however, no group differences were found on DROP

indices during exercise (Table 2), apart from at the calf level when adjustments were made for age and BMI.

The TcpO<sub>2</sub> results showed the presence of ischaemia (TcpO<sub>2</sub> < -15 mmHg) in one or more of the lower-limb probes in 175 patients with diabetes (76%) and 690 (70%) patients without diabetes ( $P = \text{NS}$  between groups). Patients showing 1, 2, 3 and 4 ischaemic sites were 51 (29%), 51 (29%), 37 (21%) and 36 (21%), respectively, in the patients with diabetes and 178 (26%), 199 (29%), 140 (20%) and 173 (25%), respectively, in the patients without diabetes ( $P = \text{NS}$  between groups).

The localization of ischaemia was different in the patients showing at least one ischaemic area. Patients with diabetes had more distal ischaemia than patients without diabetes (38 vs. 29%;  $P < 0.01$  before and after adjustment for age, BMI and treatments). There were also trends towards less proximo-distal ischaemia (51 vs. 57%;  $P = \text{NS}$ ) and isolated proximal ischaemia (11 vs. 14%;  $P = \text{NS}$ ) in the patients with diabetes.

Asymptomatic ischaemia was found on one or more site in 91 of the 175 (52%) patients with diabetes and in 380 of the 690 (55%) patients without diabetes showing ischaemia ( $P = \text{NS}$ ).

Exercise-related lower-limb symptoms without underlying ischaemia were relatively common in our patients and were equally frequent in subjects with and without diabetes (38% in both groups). Exercise-related lower-limb symptoms with no

**Table 2** Maximal walking distance (MWD) on treadmill, maximal heart rate on treadmill\* and transcutaneous pressure results† on treadmill at rest and during exercise in subjects with and without diabetes

|                                                  |               | Patients with diabetes | Patients without diabetes | <i>P</i> | <i>P</i> adjusted‡ |
|--------------------------------------------------|---------------|------------------------|---------------------------|----------|--------------------|
| MWD on treadmill (m)                             |               | 261 ± 257              | 339 ± 326                 | 0.002    | 0.04               |
| Maximal heart rate (b min <sup>-1</sup> )        |               | 116 ± 22               | 117 ± 22                  | 0.63     | 0.79               |
| Limb pain symptoms                               |               | 205 (89.1)             | 853 (86.9)                | NS       | NS                 |
| Non-limb pain symptoms                           |               | 44 (64.7)              | 112 (62.2)                | 0.001    | NS                 |
| (% of the total non-limb symptoms)               |               |                        |                           |          |                    |
|                                                  | Dyspnoea      | 19 (27.9)              | 38 (21.1)                 | 0.001    | 0.04               |
|                                                  | Cardiac§      | 4 (5.9)                | 21 (11.7)                 | NS       | —                  |
|                                                  | Fatigue       | 1 (1.5)                | 9 (5.0)                   | NS       | —                  |
| TcpO <sub>2</sub> absolute values at rest (mmHg) |               |                        |                           |          |                    |
|                                                  | Chest         | 68 ± 15                | 71 ± 14                   | 0.005    | 0.059              |
|                                                  | Right buttock | 69 ± 12                | 72 ± 13                   | 0.001    | 0.183              |
|                                                  | Right leg     | 71 ± 14                | 74 ± 14                   | 0.004    | 0.047              |
|                                                  | Left buttock  | 70 ± 13                | 73 ± 13                   | 0.011    | 0.426              |
|                                                  | Left leg      | 71 ± 13                | 74 ± 14                   | 0.012    | 0.258              |
| Minimal DROP (mmHg)                              |               |                        |                           |          |                    |
|                                                  | Right buttock | -15 ± 11               | -16 ± 13                  | 0.27     | —                  |
|                                                  | Left buttock  | -15 ± 12               | -16 ± 13                  | 0.22     | —                  |
|                                                  | Right leg     | -20 ± 17               | -20 ± 16                  | 0.99     | —                  |
|                                                  | Left leg      | -21 ± 16               | -19 ± 15                  | 0.06     | —                  |
| Number (%) meeting criteria for ischaemia        |               |                        |                           |          |                    |
|                                                  | Right buttock | 85 (37)                | 374 (38.1)                | NS       | —                  |
|                                                  | Left buttock  | 111 (37.8)             | 394 (40.1)                | NS       | —                  |
|                                                  | Right leg     | 125 (48.3)             | 461 (46.9)                | NS       | —                  |
|                                                  | Left leg      | 87 (54.3)              | 459 (46.7)                | 0.04     | —                  |

\*Symptoms expressed as number (%).

†Mean ± SD.

‡For *P*, adjustment is for age, BMI and treatments.

§Cardiac symptoms account for suspected angina or severe arrhythmia.

DROP, delta from rest of oxygen pressure; TcpO<sub>2</sub>, transcutaneous oxygen pressure.



significant ischaemia on any of the TcpO<sub>2</sub> probes occurred in 39 of the 55 (71%) patients with diabetes and in 200 of the 292 (68%) subjects without diabetes ( $P = \text{NS}$ ). In patients that were ischaemic at least on one site, exercise-related lower-limb symptoms without underlying ischaemia at the same site were also present in one or more site in 49 of the 175 (28%) patients with diabetes and in 171 of the 690 (25%) patients without diabetes ( $P = \text{NS}$ ).

Last, as shown in Table 2, there were more symptoms other than lower-limb pain in subjects with diabetes (27.9%) than in subjects without diabetes (18.3%) (values are proportions within each group;  $P < 0.01$  before and after adjustment for age, BMI and treatment differences). Among these non-lower-limb symptoms, dyspnoea was the most frequently reported, representing almost two-thirds of all the symptoms reported. Suspected angina or an abnormal electrocardiogram was more frequent ( $P < 0.01$  before and  $P < 0.05$  after adjustment for age, BMI and treatment differences) among patients with diabetes than among subjects without diabetes (Table 2).

## Discussion

We found the maximal walking distance on the treadmill test to be lower in patients with diabetes than those without diabetes, although the self-reported maximal walking distances were comparable between groups. This suggests that objectively measured exercise tolerance is lower in patients with diabetes than patients without diabetes with claudication, as previously observed [3]. This finding appears not to be solely explained by group differences in BMI, as previously suggested [12], because statistical significance persisted after adjustment for this variable. The fact that self-reported walking capacity did not differ between the two groups does not exclude the possibility that patients with diabetes have slightly more severe symptoms in everyday life compared with patients without diabetes. Another hypothesis is that symptoms could be masked by a slower walking velocity in patients with diabetes than in patients without diabetes. This is an interesting question for future studies.

The higher prevalence of distal ischaemia in patients with diabetes is consistent with previous results [13]. Distal lesions are of particularly high prevalence in patients with diabetes [14], whereas proximal lesions were suspected to be equally frequent but less severe in patients with diabetes than those without diabetes with critical limb ischaemia [14]. In patients with peripheral artery disease, the prevalence of non-calf (proximal) claudication has been reported to be 3.8–5.0% [15]. As for distal peripheral artery disease, estimation of proximal peripheral artery disease from symptoms likely underestimates its prevalence as compared with imaging. Specifically, the prevalence of proximal ischaemia is high in our patients, but consistent with previous findings in patients with diabetes using Thallium scintigraphy [1]. Blood flow supply impairment is easily estimated at the distal level through Doppler and/or ankle systolic pressure measurements, but both techniques scarcely

account for proximal ischaemia. Penile pressure can only be measured in men and does not accurately differentiate right to left lesions, and near infrared spectroscopy during exercise shows a lower diagnostic performance than that of TcpO<sub>2</sub> at the buttock level [16]. TcpO<sub>2</sub> is an interesting research tool: (i) it allows for the detection of regional blood flow impairment during exercise, assumed to reflect regional ischaemia, simultaneously and independently at the proximal and distal level on both sides [8,10]; (ii) its results are proportional to the severity of angiographically proven arterial lesions [10]; (iii) it can detect exercise-induced ischaemia at the buttock level as a result of proximal arterial lesions [8,17]; and (iv) it is insensitive to arterial stiffness, which is advantageous, specifically in patients with diabetes. The fact that tcpO<sub>2</sub> at rest was slightly lower in patients with and without diabetes is consistent with a recent report in patients without peripheral artery disease [18]. Interestingly, the DROP indices, which are independent of absolute starting values and local skin diffusion differences, did not differ between the two groups, despite the lower treadmill walking capacity of the patients with diabetes. It would be of great interest to compare the DROP values at identical times in both groups and see whether the decrease in the DROP index along time is slower in normal subjects than in patients with diabetes. We did not do this because, to date, the only validated analysis of the DROP index is its lowest value throughout exercise testing.

In peripheral artery disease, patients may remain asymptomatic whilst sharing the same adverse evolution as symptomatic patients [19]. The prevalence of asymptomatic peripheral artery disease is 4.7–5.2 times higher than that of intermittent claudication [19,20]. Therefore, the fact that, in addition to symptomatic ischaemia, half of our patients had one or more asymptomatic ischaemic sites is not surprising. The interest here is that the presence of asymptomatic sites was not more frequent in patients with diabetes, which had never been shown previously. It is also likely that the more severe ischaemic sites result in symptoms early in walking and that exercise is stopped before symptoms at less severely ischaemic locations appear.

McDermott *et al.* reported that, in patients with peripheral artery disease, the prevalence of exertional leg symptoms other than intermittent claudication was almost two times that of intermittent claudication [21]. The difference with the present study is that the patients studied here were referred for lower-limb symptoms, whereas the patients in the study of McDermott *et al.* were issued from a screening programme in a general population. Exercise-induced hypoxaemia and lumbar spine syndrome can both induce limb pain of non-vascular origin and can both be apparent concomitantly with peripheral artery disease [3,4]. Last, neuropathic pain in diabetes is not expected to be exacerbated by walking, but the mechanical stimulation may worsen the chronic pain in these patients. The specific interest of the present study is the use of TcpO<sub>2</sub> to account for proximal ischaemia and confront proximal symptoms to the presence of buttock ischaemia.



Atherosclerosis is inherently a systemic disease and myocardial ischaemia can be observed in up to one third of patients with intermittent claudication [22]. Other co-morbid conditions, aside from arterial diseases, are frequent in patients with peripheral artery disease. For example, McDermott *et al.* found prevalence for angina, congestive heart failure and pulmonary disease to be 35.5, 25.9 and 32%, respectively [23]. Furthermore, Hertzner *et al.* observed that 5% of patients undergoing aorto-iliac interventions had severe chronic obstructive pulmonary disease [24]. Direct comparisons with the present finding are not possible as many of these conditions can remain asymptomatic and we focused only on exercise-induced symptoms. Nevertheless, the high prevalence of symptoms other than lower-limb pain in our patients is not surprising when considering the frequency of co-morbid conditions in patients with peripheral artery disease. It is an interesting issue to consider whether or not the fact that cardiac symptoms were more frequent among patients with diabetes results from under treatment of cardiac disease because of a higher prevalence of silent ischaemia in patients with diabetes.

There are several limitations to the present study. First, our classification in the groups with and without diabetes was based on medical history and treatment. Therefore, it could be suggested that some patients were not aware that they had diabetes and so were falsely classified as patients without diabetes. This is quite unlikely as all patients had peripheral artery disease and diabetes mellitus is one of the first risk factors to be searched for in such patients. Further, our patients were not referred for primary care. The 19% prevalence of diabetes in our population is also consistent with previous results in cardiovascular patients [25]. Secondly, it could be suggested that our patients are not representative of those who are optimally treated. Nevertheless, our treatment data are consistent with what is known about the usual under treatment of patients with cardiovascular disease specifically in the lower-limb [26], except the unusually low percentage of lipid-lowering agent use in the present population. An explanation for this low use is not readily apparent, specifically in patients with an established diagnosis of peripheral artery disease. Thirdly, the physician performing the treadmill test was not blinded to the presence or not of diabetes; however, the DROP measurement is operator-independent. Fourthly, as patients with diabetes might receive more frequent medical care, they might be more likely to be assessed for peripheral artery disease and referred for exercise treadmill testing earlier in the disease process. Fifth, it could be suggested that the accuracy of TcpO<sub>2</sub> is lower in obese patients with diabetes than in lean patients without diabetes, specifically within the perspective of the reported difference in resting TcpO<sub>2</sub> values between patients with and without diabetes [18]. By construction, the DROP index is relatively insensitive to local differences in resting values and our unpublished observations suggest its accuracy is comparable between lean and obese patients. However, the DROP is highly sensitive to exercise-induced changes in chest TcpO<sub>2</sub>. For example, the DROP might

remain within normal limits if the chest TcpO<sub>2</sub> decreases during walking because of exercise-induced hypoxaemia, falsely leading to the conclusion that no blood flow impairment is present in the lower limb. Sixth, although we questioned participants about their health status, we did not assess potentially important cardiovascular risk factors (e.g. smoking, hypertension) or biological values (e.g. blood cell count, dyslipidaemia). Therefore, it is possible that these variables might have confounded the TcpO<sub>2</sub> results. Finally, our results might only be generalizable to the treadmill protocol and inclusion criteria we used.

In conclusion, treadmill walking capacity was lower in patients with diabetes than those without diabetes, whereas self-reported walking capacity and ankle-brachial systolic pressure index were comparable between groups. This treadmill difference appears not to be solely explained by group differences in BMI. Other potential factors could include differences in the sensitivity to pain, the prevalence of co-morbid conditions and the metabolic pathways supporting exercise. Our study confirms that patients with diabetes have more frequent distal ischaemia than patients without patients. We show for the first time that patients with diabetes and peripheral artery disease have a similar prevalence of asymptomatic ischaemia during treadmill testing, and a comparable prevalence of limb pain of non-vascular origin, than do patients with peripheral artery disease without diabetes. Last, non-limb symptoms were more frequent among patients with diabetes, particularly at the cardiac level. These observations underline the specific interest of exercise testing in patients with diabetes with peripheral artery disease reporting vascular-type claudication.

### Competing interests

PA has been reimbursed by the radiometer company for attending the 2010 French Society of Physiology Congress, but the company was not involved in any points, conception, design, collection, interpretation, etc., of the present study.

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## 4.2 Une modification physiopathologique de l'ischémie à la marche

Dans les travaux précédents, nous avons montré que la  $TcPO_2$  d'effort est un moyen original d'évaluer l'ischémie des membres inférieurs à l'effort (Abraham et al., 2005; Abraham et al., 2003). Celle-ci permet en effet de localiser le lieu de l'ischémie (proximale ou distale, droite ou gauche) en fonction du positionnement des différentes sondes, mais cette technique permet aussi de quantifier l'importance de l'ischémie au niveau de la zone étudiée (lieu, où est placée la sonde de mesure). En effet, la valeur de DROP de  $TcPO_2$  obtenue au niveau d'un site de mesure est proportionnelle à la sévérité des lésions artérielles irriguant ce territoire (Abraham et al., 2003). Nous postulons que la somme des sites de mesures (fesse droite, fesse gauche, mollet droit et mollet gauche) est le reflet de l'importance (sévérité et diffusion) de l'ischémie aux membres inférieurs. C'est-à-dire que si sur quatre sondes positionnées sur un patient une seule présente une valeur pathologique alors l'ischémie sera moindre que si deux sondes avaient eu des valeurs de DROP pathologiques.

L'augmentation du débit cardiaque grâce à l'augmentation de la fréquence cardiaque est un moyen pour répondre à la demande en oxygène pendant l'effort. De plus, la fréquence cardiaque reste d'autant plus élevée après l'effort que la dette en oxygène est importante. L'ischémie est la conséquence d'un manque d'apport en oxygène aux tissus (Levick, 2000). Il a été montré que la différence entre la fréquence cardiaque de fin d'exercice et celle de post exercice à 1 minute était diminuée chez les patients présentant une athérosclérose carotidienne et chez les sujets présentant une ischémie myocardique (Georgoulas et al., 2003; Jae et al., 2008). Cette différence entre la fréquence cardiaque de fin d'exercice et celle de post exercice à 1 minute est appelée la variation de la fréquence cardiaque post-effort à 1 minute. Aucune donnée n'est actuellement disponible dans la littérature sur l'influence de l'ischémie des membres inférieurs sur la variation de la fréquence cardiaque post-effort à 1 minute. Nous supposons que lorsqu'un patient artériopathe claudicant atteint sa distance maximale de marche, la durée pour le retour à sa fréquence cardiaque de repos est d'autant plus importante que l'ischémie au niveau des membres inférieurs a été importante. En d'autres termes la différence entre la fréquence cardiaque de fin d'exercice et celle de post exercice à 1 minute est d'autant plus faible que l'ischémie des membres inférieurs est sévère.

Nous avons donc étudié la relation entre l'importance (sévérité et diffusion) de l'ischémie des membres inférieurs mesurée lors d'une TcPO<sub>2</sub> d'effort (ANNEXE 4) durant un test sur tapis à charge constante et la variation de la fréquence cardiaque post effort à 1 minute chez des patients artériopathes.

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Pour ce faire nous avons réalisé une étude rétrospective chez des patients artériopathes venus dans le service entre 2003 et 2009 et ne prenant pas de bêta-bloquants (effet chronotrope négatif<sup>12</sup>).

Quatre groupes de patients ont été formés en fonction de l'importance de l'ischémie des membres inférieurs. Les patients dans le quartile de moindre ischémie sont ceux qui ont eu la plus grande distance de marche sur le tapis ( $481 \pm 391$ ) et la plus grande diminution de la variation de la fréquence cardiaque post-effort à 1 minute ( $23 \pm 11$  battements par minute (bpm)). A contrario, les patients dans le quartile de plus sévère ischémie sont ceux qui ont marché le moins loin ( $228 \pm 234$ ) et qui ont eu la plus faible diminution de la variation de fréquence cardiaque post effort à 1 minute ( $14 \pm 11$  bpm). La variation de la fréquence cardiaque post-effort à 1 minute est directement liée à l'intensité de l'exercice lors des tests incrémentiels (Cole et al., 1999). Compte tenu de l'utilisation dans cette étude d'un test à charge constante, cette différence significative observée entre les groupes ne peut pas être liée au test sur tapis.

En définitive, cette étude a confirmé que la diminution de la variation de la fréquence cardiaque post-effort à 1 minute était associée à l'importance de l'ischémie retrouvée au cours d'un test de marche sur tapis à charge constante. Cette moindre diminution de la variation de la fréquence cardiaque post-effort à 1 minute, chez les

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<sup>12</sup> Effet chronotrope négatif : diminution de la fréquence cardiaque.

patients ayant une ischémie plus importante, peut s'expliquer par une dette en oxygène plus importante au niveau des tissus ischémiques (Depairon and Zicot, 1996). Une durée plus importante de resynthèse de la créatine phosphate (source immédiate d'énergie pour le muscle) pourrait constituer une explication supplémentaire (Kramer, 2007). La modification de cette variation après un geste de revascularisation artérielle ou une prise en charge médicale optimale serait un argument supplémentaire en faveur d'un lien de causalité entre l'importance de l'ischémie des membres inférieurs et la variation de la fréquence cardiaque post-effort à 1 minute.

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# Heart rate recovery after constant-load exercise tests is decreased in proportion to the importance (severity and diffusion) of exercise-induced lower-limb ischaemia

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## Summary

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### Key words

cardiac rhythm; exercise; ischaemia; peripheral artery disease; regional blood flow; treadmill

**Background:** Conditions that may influence heart rate recovery at 1 min of recovery from exercise (HRR1: end-exercise heart rate minus heart rate 1 min after exercise) are not fully understood. We hypothesized that the 'importance' (both local severity and regional diffusion) of peripheral skeletal muscle ischaemia is associated with low HRR1.

**Design and Methods:** In 529 patients with suspected or confirmed peripheral vascular disease not receiving beta-blockers ( $61.4 \pm 11.3$  years old), we retrospectively studied the relationship of HRR1 to exercise-induced changes in transcutaneous oxygen DROP index (limb changes minus chest changes from rest). The sum of DROP indices observed on both calves and both buttocks (DROP<sub>tot</sub>) provides the unique opportunity to estimate both the severity and the diffusion of exercise-induced ischaemia on the right and left side simultaneously. It was used during a constant-load treadmill test ( $3.2 \text{ km h}^{-1}$ ; 10% grade) to classify patients in quartiles, the fourth quartile representing the more 'important' ischaemias.

**Results:** There was an inverse relationship between quartiles of DROP<sub>tot</sub> and HRR1, even after adjustment for heart rate reserve (Delta HR: end-exercise minus resting heart rate), age ( $\leq$  or  $>60$  years), gender, body mass index, treadmill maximal walking distance and ankle brachial index: adjusted  $R = 0.629$ ;  $P < 0.0001$ .

**Conclusions:** During constant-load treadmill testing, DROP<sub>tot</sub>, an index of the 'importance' of exercise-induced lower-limb ischaemia, correlates with HRR1. Whether HRR1 is improved in proportion of DROP<sub>tot</sub> improvement in patients undergoing surgery or rehabilitation for peripheral artery disease is a fascinating issue for future studies.

## Introduction

Conditions that may influence the reduction in heart rate recovery (HRR) 1 min after exercise (HRR1) are still incompletely defined. Specifically, a reduced HRR is associated with carotid atherosclerosis (Jae et al., 2008) and a high rate of scintigraphic images of myocardial ischaemia (Georgoulas et al., 2003), but little information is available about the effect of lower-limb ischaemia. To date, the only evidence reported is the relationship between HRR and arterial stiffness, aortic wave velocity with the decrease in HRR following maximal exercise testing in apparently healthy adults (Fei et al., 2005). In peripheral artery disease (PAD), HRR1 could be decreased as a

function of the 'importance' of lower-limb ischaemia, which means not only as a function of the local severity of exercise-induced muscle ischaemia in the lower limbs, but also as a function of the regional diffusion of ischaemia (quantity of muscle mass affected by ischaemia). Changes in transcutaneous oxygen pressure (TcPO<sub>2</sub>) during exercise are proportional to the local severity of arterial lesions (Abraham et al., 2003, 2005; Bouye et al., 2004) and may allow for the recording of regional blood flow impairment on both limbs and at both proximal and distal levels simultaneously (Jacquinandi et al., 2004). As such, exercise TcPO<sub>2</sub>, although a time-consuming and not a primary care technique, is a unique research tool to estimate not only the local severity but also the regional diffusion of ischaemia during

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exercise. Our aim was to estimate the relationship between peripheral regional blood flow impairment, as assessed through proximal (buttocks) and distal (calves) exercise-induced TcpO<sub>2</sub> changes on both lower limbs, and HRR1 after constant-load exercise.

## Methods

### Population

The study cohort consisted of the 674 consecutive new patients referred for cardiovascular risk evaluation, vascular-type claudication or seemingly patients with asymptomatic peripheral artery (PAD) (very sedentary subjects) who underwent constant-load treadmill exercise testing at the laboratory of exercise investigation at the University Hospital in Angers between 2003 and 2009. As a retrospective observational study, no patient's consent was required under French legislation.

### Clinical history

As part of their routine clinical evaluation, a detailed history including medication was taken. Height and weight were measured on arrival. As a routine selection, only the patients able to walk 10 m in <12 s were included in the study group. This was to ensure that all patients would be able to walk at the required speed on the treadmill. Patients with atrial fibrillation, those with a history of osteo-articular disease limiting walking capacity, permanent pacemaker implantation, or patients treated with beta-blockers were excluded from the study (Arena et al., 2008). No patient had previously undergone cardiac transplantation. Ankle and brachial pressures to calculate ankle-brachial systolic pressure index (ABI) were retrieved from patient's file. If not available in the last 3 months or if any clinical event occurred since ABI report, ABI was measured de novo at patient's arrival. ABI was calculated as the ratio of the lowest (right or left) ankle values to the higher of the two brachial values, each side value being the higher of the posterior tibial and dorsalis pedis arteries (Greenland et al., 2000; Norgren et al., 2007).

### Exercise procedure

All patients underwent constant-load exercise testing on a computer-controlled treadmill ergometer (Gymrol 1800, Tech-machine, Fr) while continuing their medication. The test started with a resting period of 2 min. Then, the 3.2 km h<sup>-1</sup> speed and 10% grade were progressively attained within 1 min and maintained constant until muscle fatigue or pain forced the subjects to terminate the test. The choice of the constant-load test was based on our previously published standard (Abraham et al., 2003, 2005) and was used on purpose to allow the future comparison of pre-to-postsurgery HRR despite the slightly lower reliability of this procedure

when compared to incremental testing (Chaudhry et al., 1997). Because of the well-known low concordance between self-reported and treadmill-measured walking distance (Watson et al., 1997), it was expected that few patients reporting claudication would remain asymptomatic or would experience non-limiting symptoms on treadmill. In these patients, the test was stopped after 20 min in the absence of limiting symptoms. At end-exercise, maximal walking distance (MWD) was recorded; treadmill speed and grade were returned to zero within 5 s and patients were asked to remain standing.

### Heart rate recording

A continuous 12-lead electrocardiogram recording was taken during the whole exercise procedure (Ergocard; Medisoft, Sorinnes, Belgium). Heart rate (beats per min: bpm) was recorded at rest (HR rest) and immediately before exercise termination (HR end). Heart rate increase (Delta HR) was calculated as the difference between end-exercise heart rate and HR rest. For the calculation of HRR1, heart rate at 1 min postexercise was subtracted from HR end. Last, estimated maximal HR was calculated as  $208 - 0.7 \times \text{age}$  in years (Tanaka et al., 2001).

### TcpO<sub>2</sub> recording

Patients were placed in an air-conditioned room:  $21 \pm 2^\circ\text{C}$ . Calibration, skin preparation and measurements were performed as previously reported (Jaquinandi et al., 2008). We used 5 TcpO<sub>2</sub> probes (TINA; Radiometer, Copenhagen, Denmark), with probes heated to  $44.5^\circ\text{C}$ . In brief, electrodes were positioned on each calf, on each buttock and on the chest. Once the electrodes were in position, a pretest period of at least 15 min was required in the standing position to allow stable resting values to be reached. TcpO<sub>2</sub> values were then recorded for 2 min in the standing position before the treadmill was started, during the walking period and for at least 10 min in the standing position following the end of the exercise test. From the start of the exercise test, on each recorded value we calculated the delta from rest of oxygen pressure (DROP) index as previously described (Jaquinandi et al., 2008). The DROP index is the absolute tcpO<sub>2</sub> change from rest in each of the four limb probes corrected with the corresponding absolute value of the chest electrode tcpO<sub>2</sub> change. This DROP index is a negative value. It is expressed in mmHg and is accurate and reliable in predicting the presence/absence and severity of angiographically proved lesions at both buttocks and ankles (Abraham et al., 2003, 2005). The 'importance' (severity and diffusion) of ischaemia was estimated by the sum of the four minimal DROP values recorded on each of the four limb tcpO<sub>2</sub> probes during the test (DROP<sub>tot</sub>). Results for DROP<sub>tot</sub> (negative values) were converted into absolute (positive) values. Values of zero (or close to zero) are found in the absence of ischaemia; the highest values are for the more important (severe and/or diffuse) ischaemia.

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### Statistical analysis

Continuous variables are presented as the means  $\pm$  SD, except for MWD which is expected to follow a non-normal distribution in constant-load treadmill tests (Mahe et al., 2010) and is presented in median [25–75 centiles]. DROptot values were categorized into quartiles. The fourth quartile (highest values) represented more severe ischaemia. Differences between groups were estimated using the chi-square test for binomial variables or ANOVA with Bonferroni post hoc test as appropriate. To explore the role of limb ischaemia as assessed by DROptot on HRR1 while adjusted for other clinical and exercise test characteristics, we used a general lineal model with DROptot alone and then including DROptot and all the following potential confounding factors: age, gender, body mass index, Delta HR, treadmill maximal walking distance and ABI (Desai et al., 2001; Dimkpa & Ibhezhebo, 2009; Dimkpa & Oji, 2009; Arena et al., 2010). Male gender and age  $>60$  are quoted '1' whereas female gender and age  $\leq 60$  are quoted '0' in the model. ECG suggestive of myocardial ischaemia at exercise was not included in the model because of its low prevalence in the studied group. We tested the interaction between DROptot and the adjustment variables. Statistical analyses were carried out using the *SPSS v.15.0* (SPSS, Chicago, IL, USA). The level of statistical significance was set at 0.05.

### Results

The study groups included 529 patients,  $61.4 \pm 11.3$  years old,  $168.8 \pm 8.1$  cm,  $76.0 \pm 14.3$  kg, among which 448 (84.7%) were men. Treatment included antiplatelet or anticoagulant ( $n = 381$ ; 72.0%), hypolipemic ( $n = 225$ ; 42.5%), antidiabetic ( $n = 92$ ; 17.4%) and antihypertensive ( $n = 225$ ; 42.5%) drugs. Ankle to brachial index was  $0.95 \pm 0.21$ , HR rest was  $83.5 \pm 16.8$  bpm, HR end was  $121.3 \pm 20.7$  bpm, HRR1 was  $18.5 \pm 11.6$  bpm and DROptot was  $70.0 \pm 45.6$  mmHg for the whole group. On treadmill, 92 (17.4%) among 529 patients could complete the 20 min of the test. Among the other 437 patients, the median walking distance was 161 m [103–250]. No patient had to stop the treadmill test for symptomatic angina although asymptomatic abnormal repolarization suggesting exercise-induced myocardial ischaemia was observed in four patients. For most patients, the exercise procedure used was likely submaximal on a cardiac point of view, because only 89 (16.8%) patients had HR end in excess of 85% of estimated maximal HR.

A typical example of DROP changes over time and of the resulting DROptot calculation is presented in Fig. 1. As shown, although the decrease in values was of moderate amplitude at each site for the second patient (lower panel), it was found on all the four sites and resulted in a DROptot higher (more important ischaemia) than that of the first patient.

Characteristics of the patients stratified by the severity of ischaemia, as assessed with TcpO<sub>2</sub>, are reported in Table 1. As shown, there was a significant trend for more male subjects and

for shorter walking distance in the two higher quartile groups. Resting heart rate was increased in quartile 3 when compared to quartile 1 and 2, and maximal heart rate was increased in quartile 3 when compared to quartile 4. However, no difference was found between other groups for these two parameters.

Finally, there was an inverse relationship between quartile of DROptot and HRR1 (Table 2). Beta coefficient for the lineal model analysis was  $-2.70$ ,  $R = 0.635$ ,  $P < 0.0001$  and power  $>95\%$ . The relationship between quartile of DROptot and HRR1 persisted after adjustment for potential confounding factors including age, gender, body mass index, Delta HR, treadmill maximal walking distance and ABI: adjusted beta  $-2.07$  (95% CI:  $-2.88/-1.26$ ), adjusted  $R = 0.629$ ;  $P < 0.0001$ , power  $>95\%$ .

### Discussion

To the best of our knowledge, this is the first study providing evidence for a relationship between an estimation of the importance (local severity and regional diffusion) of exercise-induced peripheral muscle ischaemia and decreased HRR1 following exercise in patients with atherosclerosis.

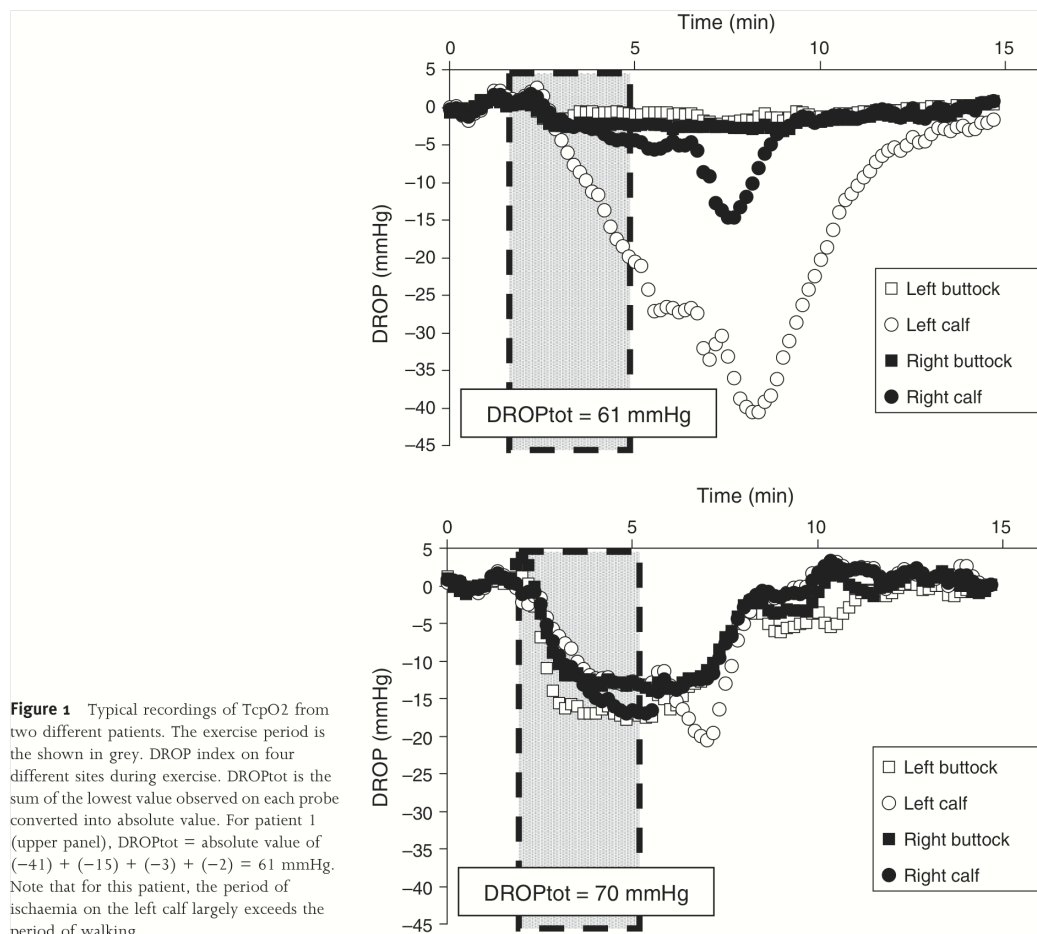
It was previously shown that during the recovery from a walk test, the delayed increase in oxygen uptake is proportional to the delayed hyperaemia in the ischaemic muscles (Depairon & Zicot, 1996); recovery time constant of phosphocreatine following peak exercise was increased in patients with mild-to-moderate symptomatic PAD when compared to normal control subjects (Kramer, 2007). Nevertheless, to date, no study had studied such a large group of patients and evaluated proximal exercise-induced and distal exercise-induced ischaemia on both limbs.

The influence of Delta HR on HRR1 (Desai et al., 2001) or HRR1 changes after training (Myers et al., 2007) is well known. Then, if one aims at studying potential underlying mechanisms influencing HRR, it is of particular interest to get rid of the differences in exercise intensity and use constant-load exercise to attain comparable end-exercise heart rate between groups. Given the relationship between peak VO<sub>2</sub> and HRR1 (Cole et al., 1999), the HRR response to incremental exercise may depend on the level of exercise reached and would have influenced HRR1. The specific interest is that it could not be the case here, because constant-load tests were used. This constant-load procedure avoid that this HRR1-DROptot relationship could result from the more severe patients with PAD achieving lower work loads, as could have been the case if we had used incremental tests. It should be also noted that although the test was of constant load and submaximal on a cardiac point of view in most patients, Delta HR was still found to be both significantly and positively associated with HRR1 in the model. This probably relies on inter-individual differences in fitness level. However, the relationship of HRR1 to DROptot persisted after the adjustment for Delta HR.

For simplification, our initial arbitrary decision was to apply a simple addition of the four DROP values, although it might be possible that a coefficient of proportionality should be applied to

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proximal and to distal ischaemia, respectively. It is not surprising that the patients with the more severe DROPtot results had the lowest ABI resting values; nevertheless, the relationship of HRR1 and DROPtot persisted after the adjustment for ABI. This likely reflects the inability of ABI to account for the presence or absence of ischaemia in the hypogastric vascular bed if it results from lesions of hypogastric arteries.

### Study limitations

There are limitations to this study. First, control for all proposed confounding factors that were reported to influence HRR1 such as waist circumference and dietary intake (Nilsson et al., 2007; Ba et al., 2008) was not made. Second, extension of our results to all exercise procedure cannot be made because the HRR1 response depends on the exercise mode (Maeder et al., 2009).

A technical limitation of this study is the lack of direct evidence of sympathetic nervous system activity, either through

muscle sympathetic nerve activation or through plasma catecholamine measurements. Acute pain enhances sympathetic tone, resulting in an increase in the cardiac rate (Terkelsen et al., 2005); nevertheless, previous reports have underlined the absence of relationship between pain disappearance and the normalization of hemodynamic parameters in patients with PAD after exercise (Gardner, 1993).

It could be suggested that ABI would be an easier tool to estimate PAD severity. Indeed, ankle brachial index (ABI) cannot discriminate distal from proximo-distal lesions or detect a perfusion impairment resulting from lesions of the hypogastric vascular bed. Last, neither penile pressure (Mahe et al., 2009) nor near infrared spectrometry (Bouye et al., 2005) satisfactorily estimates exercise-induced ischaemia at the buttock level. Our aim here was not to promote the use of tcpO<sub>2</sub> in patients with PAD but to use the technique as a unique tool allowing for the estimation of both local severity and regional diffusion of exercise-induced ischaemia. Thallium scintigraphy could have

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**Table 1** Characteristics of 529 patients according to the quartile of DROPot value observed during exercise.

|                                       | Quartile 1  | Quartile 2   | Quartile 3    | Quartile 4    |        |
|---------------------------------------|-------------|--------------|---------------|---------------|--------|
| DROPot (mmHg)                         | [0–34]      | [34–60]      | [60–95]       | [95–246]      |        |
| Number of subjects                    | 136         | 129          | 134           | 130           | P      |
| Ankle to brachial index               | 1.07 ± 0.15 | 0.98 ± 0.17* | 0.92 ± 0.21*† | 0.83 ± 0.15*† | <0.001 |
| Males n (%)                           | 101 (74.3)  | 105 (81.4)   | 121 (90.3)    | 121 (93.1)    | <0.001 |
| Age (years)                           | 62.4 ± 12.9 | 61.0 ± 11.8  | 61.4 ± 10.4   | 60.7 ± 9.6    | 0.63   |
| Height (cm)                           | 167 ± 9     | 168 ± 15     | 170 ± 8*      | 170 ± 7*      | <0.001 |
| Weight (kg)                           | 75.2 ± 15.3 | 76.7 ± 14.8  | 78.1 ± 13.4   | 73.8 ± 13.2   | 0.08   |
| Body mass index (kg m <sup>-2</sup> ) | 27.0 ± 4.4  | 27.0 ± 4.7   | 27.0 ± 4.3    | 25.4 ± 4.2*†‡ | <0.01  |
| Resting heart rate (bpm)              | 80 ± 16     | 82 ± 15      | 88 ± 18*†     | 84 ± 17       | <0.001 |
| End-exercise heart rate (bpm)         | 120 ± 20    | 119 ± 21     | 127 ± 22      | 119 ± 20‡     | 0.02   |
| Delta HR (bpm)                        | 40 ± 16     | 38 ± 15      | 38 ± 18       | 35 ± 15       | 0.10   |
| HRR1 (bpm)                            | 22.7 ± 11.1 | 19.3 ± 11.4  | 17.7 ± 12.0*  | 14.1 ± 10.5*† | <0.001 |
| Treadmill MWD                         | 481 ± 391   | 380 ± 341*   | 274 ± 254*†   | 228 ± 234*†   | <0.001 |

HR, heart rate; MWD, maximal walking distance; DROP, delta from rest of oxygen pressure; HRR, heart rate recovery.

\*P<0.05 from quartile 1.

†P<0.05 from quartile 2.

‡P<0.05 from quartile 3.

**Table 2** Multivariate general lineal model analysis for the different studied factors with 95% CI values for quartile of HRR1.

| Parameter                                  | Beta (95% CI)       | P      |
|--------------------------------------------|---------------------|--------|
| Quartile of DROPot                         | -2.07 (-2.88/-1.26) | <0.001 |
| Heart rate reserve (bpm)                   | 0.41 (0.36/0.46)    | <0.001 |
| Age (≤60 years old = 0; >60 years old = 1) | -0.33 (-1.91/1.26)  | 0.69   |
| Gender (males = 1; females = 0)            | 1.39 (-0.89/3.66)   | 0.23   |
| Body mass index (kg m <sup>-2</sup> )      | 0.04 (-0.15/0.22)   | 0.70   |
| Maximal walking distance on treadmill (m)  | -0.002 (-0.01/0.00) | 0.11   |
| Ankle to brachial index                    | 2.36 (-2.10/6.82)   | 0.30   |

DROP, delta from rest of oxygen pressure; HRR, heart rate recovery.

been a satisfactorily alternative approach (Segall et al., 1990; Tellier et al., 2000), but the technique is relatively expensive and invasive.

Overall, causation cannot be determined because of the cross-sectional nature of this study. Nevertheless, our method provides a unique opportunity to address this question in future studies prospectively evaluating the differences in HRR1 observed before and after treatment in patients

undergoing lower-limb revascularization or re-education. In this perspective, the use of constant-load exercise is of particular interest because of the close relationship of HHR1 to work load and HRR1 to Delta HR as previously discussed.

## Conclusion

The 'importance' of peripheral ischaemia during constant-load walking tests contributes to the decrease in HRR 1 min after constant-load exercise. Whether HRR1 is improved in proportion of improvement in exercise-induced lower-limb ischaemia resulting from arterial revascularization would be an interesting observation to support or exclude causation of the 'importance' of peripheral ischaemia as a cause of a reduced HRR1. This requires future prospective experiments.

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## Conflicts of interest

None.

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### 4.3 Diagnostic différentiel : l'hypoxémie d'effort

Les douleurs à la marche peuvent être liées à une anomalie du contenant (les vaisseaux), mais ils ne faut pas oublier le rôle important de la pompe cardiaque et du sang, notamment de la quantité d'hémoglobine oxygénée transportée (Abraham et al., 2010). La TcPO<sub>2</sub> d'effort permet de mesurer l'oxygénation tissulaire à différents sites en même temps et paraît mieux adaptée pour les mesures à l'effort que la saturométrie. En effet, compte tenu de la relation sigmoïde entre la pression partielle en oxygène artérielle et la saturation de l'hémoglobine en oxygène, une diminution de la pression partielle en oxygène artérielle peut ne pas entraîner de modification notable de la saturation de l'hémoglobine surtout si la saturation est normale au repos.

Plusieurs travaux ont montré que les changements observés au niveau des sondes de TcPO<sub>2</sub> miment les variations de la pression en oxygène artérielle (Brudin et al., 1994; Hutchison et al., 1987; McDowell and Thiede, 1980). Les différentes sondes de TcPO<sub>2</sub> permettent d'étudier l'oxygénation tissulaire au niveau de différents sites. Les sondes situées au niveau des membres inférieurs permettent de détecter des anomalies au niveau des membres inférieurs. Une sonde thoracique placée sur la face dorsale du thorax au niveau de la 4<sup>ème</sup> vertèbre thoracique environ permet d'étudier les modifications de pression en oxygène systémique (étude initial VHS<sup>13</sup> en cours). L'ensemble des valeurs mesurées au niveau d'une sonde de TcPO<sub>2</sub> au cours d'une épreuve de marche peut être représenté sous la forme d'un tracé appelé profil. L'étude des variations de cette sonde thoracique pourrait permettre de mettre en évidence des profils particuliers d'évolution de la pression partielle en oxygène artérielle au cours d'un exercice modéré sur un tapis motorisé à charge constante. Ces profils thoraciques, reflets de l'oxygénation systémique, pourraient peut-être, quand ils sont particuliers, expliquer les douleurs à la marche présentées par certains patients. En effet, un manque d'apport en oxygène aux membres inférieurs lié à un trouble de l'oxygénation autre que celui liée à une sténose pourrait aussi entraîner une ischémie locale et ainsi induire une douleur.

Nous avons réalisé une étude afin de répondre aux questions suivantes : Peut-on classer les profils thoraciques de pression en oxygène des patients ? Cette distribution retrouvée dans une population de validation des profils est-elle retrouvée dans une

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<sup>13</sup> Etude initial VHS : Cette étude cherche à montrer que les variations de TcPO<sub>2</sub> enregistrées au niveau de la sonde thoracique sont le reflet la pression partielle en oxygène artérielle mesurée par gaz du sang

population différente ? Ces profils retrouvés dépendent-ils de la position de la sonde thoracique ? Le profil thoracique trouvé lors d'un examen est-il retrouvé lors d'un second examen ? En d'autres termes la mesure du profil thoracique est-elle reproductible ?

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Chest TcPO<sub>2</sub> changes during constant-load treadmill walking tests in patients with claudication.

Ouedraogo N, Feuilloy M, ***Mahé G***, Leftheriotis G, Saumet JL, Abraham P.

Quatre expérimentations différentes ont été réalisées afin de répondre à ces quatre questions. Lors de la première expérimentation, nous avons étudié rétrospectivement 485 patients adressés dans notre laboratoire pour suspicion de claudication vasculaire. Chaque patient a eu une TcPO<sub>2</sub> d'effort sur tapis à charge constante. Les profils de sonde thoracique obtenus ont alors été comparés à 9 différents modèles mathématiques (figure 12). Les modèles ont été créés à partir d'études préliminaires par une méthode de cross-corrélation qui permet d'évaluer si deux tracés (deux profils) présentent ou non les mêmes variations au cours du temps en s'affranchissant des valeurs absolues. Ainsi, un coefficient « r » de cross-corrélation (qui est le coefficient de Pearson) égal à 1 traduit une ressemblance parfaite des tracés et donc des profils alors qu'une valeur proche de 0 traduit des différences majeures entre les tracés et donc des profils.

Lors de la deuxième expérimentation, nous avons voulu étudier dans une nouvelle population si la proportion de profils classés dans chaque catégorie était superposable à celle retrouvée lors de la première expérimentation.

Lors de la troisième expérimentation, nous avons testé si la valeur absolue de la sonde thoracique influençait le profil obtenu.

Lors de la quatrième expérimentation, la reproductibilité de la classification des profils thoraciques dans un des 9 modèles mathématiques a été étudiée.

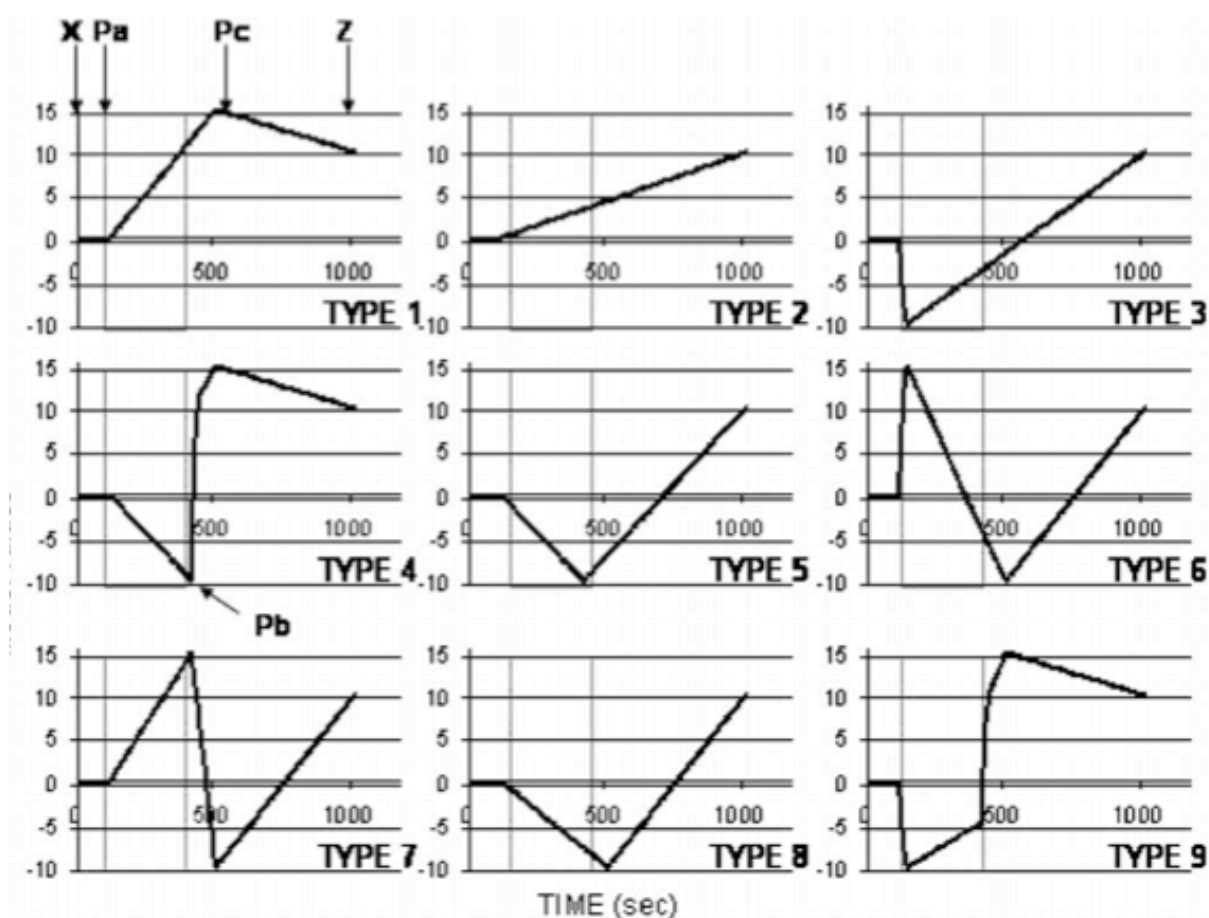


Figure 12 : Les 9 différents modèles mathématiques d'évolution des valeurs obtenues par la sonde thoracique. Les points X, Pa, Pc et Z sont des points d'intérêts permettant de générer les courbes. Merci de se référer à l'article pour de plus amples informations.

La première expérimentation a permis de déterminer quatre profils prédominants dans une population de 485 patients (figure 13).

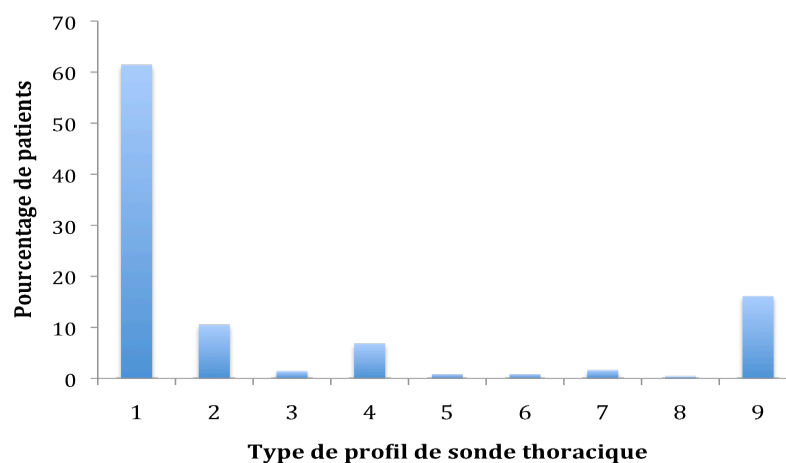
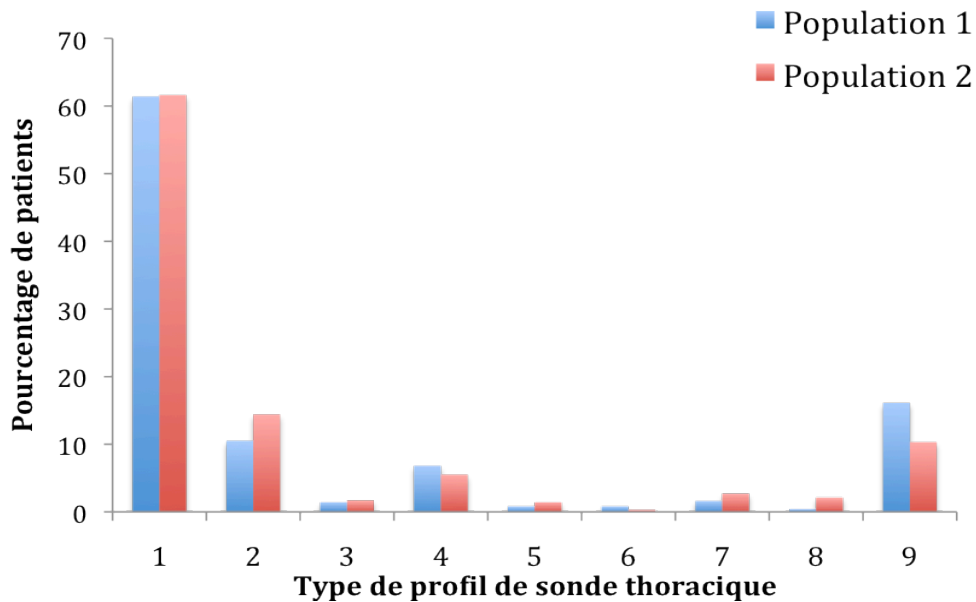


Figure 13 : Distribution des 9 profils thoraciques dans une population de 485 patients.



La deuxième expérimentation a permis de comparer les distributions trouvées dans 2 populations différentes (figure 14).



**Figure 14 : Distribution des 9 profils thoraciques dans une population de 485 patients (population 1) et dans une population de 292 patients (population 2).**

Lors de la troisième expérimentation, une excellente cross-corrélation a été retrouvée ( $r = 0,919 \pm 0,091$ ) entre les tracés obtenus à partir de deux sondes thoraciques placées à deux endroits différents du thorax enregistrant simultanément la  $TcPO_2$  au cours de l'effort.

La quatrième expérimentation a montré une bonne reproductibilité de la classification des profils thoraciques parmi les 9 modèles mathématiques pour un même patient. Vingt patients ont eu une excellente reproductibilité ( $r > 0,80$ ), neuf patients ont eu une reproductibilité satisfaisante ( $0,50 < r \leq 0,80$ ) et deux ont eu une mauvaise reproductibilité ( $r \leq 0,50$ ) en raison des faibles modifications des valeurs absolues de la sonde thoracique au cours de l'effort.

Les profils thoraciques des patients peuvent donc être aisément classés. Quatre profils sont majoritaires (type 1, type 2, type 4 et type 9). Ces profils sont retrouvés en proportion similaires dans deux populations différentes. Ces profils sont indépendants des sondes utilisées et ils sont reproductibles.

Les profils de type 1 et 2 peuvent être considérés comme normaux car ils traduisent une augmentation de l'oxygénation tissulaire enregistrée au niveau thoracique. Cette augmentation de l'oxygénation tissulaire au cours d'un effort modéré de marche peut résulter de l'augmentation de la ventilation totale, de l'augmentation du volume courant<sup>14</sup> et de l'augmentation du rapport de ventilation-perfusion (Rubin et al., 1982). Le profil le plus représenté ensuite est le type 9 qui se traduit par une chute au début de l'effort suivie d'une légère augmentation jusqu'à la fin de l'effort, où une rapide augmentation se produit pour atteindre des valeurs supérieures à celles de repos. Enfin, apparaît une diminution progressive jusqu'au retour à la normale (valeur de repos avant le début de l'effort). Cette augmentation très rapide de fin d'effort est appelée « overshoot ». Ce profil de type 9 est appelé le « coup de hache de l'oxygénation transcutanée liée à la marche » ou « walking-induced transcutaneous hack » (WITH). Ce profil est très certainement pathologique et pourrait traduire une mauvaise adaptation de l'organisme à l'effort dont l'origine reste à préciser.

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<sup>14</sup> Volume courant : Volume d'air inspiré et expiré à chaque cycle respiratoire.

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## 5 CONCLUSION ET PERSPECTIVES

L'ischémie des membres inférieurs à l'effort peut être la cause d'une limitation de la capacité de marche au cours de l'artériopathie oblitérante des membres inférieurs. Différentes méthodes de mesures ont été développées pour évaluer indirectement ou directement cette ischémie et de façon plus ou moins objective. Les questionnaires présentent l'avantage d'être facilement disponibles et peu coûteux. Malheureusement, comme nous l'avons montré, l'un des plus utilisés, le Walking Impairment Questionnaire, est souvent mal rempli et sa corrélation est limitée avec l'examen de référence à savoir le test sur tapis et ce même après correction des erreurs de remplissage. Nous avons développé un autre questionnaire (EACH-Q) plus court ne comprenant que quatre questions. L'originalité de ce questionnaire réside dans le fait qu'il demande au patient de quantifier sa durée de marche à différentes allures. De plus, celui-ci est tout aussi bien corrélé que le WIQ au test sur tapis et, de surcroît, il a permis de considérablement réduire les erreurs de remplissage. En outre la prise en compte de la vitesse de marche du patient dans ces deux questionnaires (WIQ et EACH-Q) a amélioré la corrélation avec le test sur tapis qui reste toutefois autour de 0,65. Cette corrélation « moyenne » pourrait être expliquée par les difficultés présentées par les patients à répondre à des questions ne correspondant pas toujours à leurs activités. D'autre part, la quantification de la capacité maximale de marche peut être réalisée soit sur une échelle spatiale soit sur une échelle temporelle. Or, cette échelle spatiale est une notion difficile à appréhender aujourd'hui alors que l'échelle temporelle fait partie intégrante du quotidien des patients. Une journée est découpée en une échelle temporelle. Le trajet pour aller d'un point A à un point B est le plus souvent aussi estimé en échelle temporelle. Cet élément pourrait donc également expliquer les difficultés d'auto-évaluation du patient vis-à-vis de sa capacité maximale de marche estimée en distance. Cependant, une autre méthode originale d'évaluation de la limitation de la capacité de marche et développée dans le laboratoire peut en partie expliquer cette corrélation. En effet, l'évaluation ambulatoire par géo-positionnement satellitaire a mis en évidence qu'il existait une variabilité à court terme de la distance maximale marche des patients artériopathes. La durée d'arrêt entre deux périodes de marche semble être un facteur explicatif de cette variabilité de la distance maximale de marche dans notre

étude. Cela n'est pas étonnant car cet arrêt entre deux marches permet à la zone ischémisée de se ré-oxygéner, c'est-à-dire de combler sa dette d'oxygène. Il est probable que plus la ré-oxygénation tissulaire est importante, plus la distance de marche suivante est grande. Cette hypothèse serait facile à confirmer en laboratoire en faisant marcher plusieurs fois de suite des patients sur un tapis tout en mesurant l'oxygénation tissulaire par  $TcPO_2$  au niveau des zones ischémisées. A chaque arrêt, les valeurs de  $TcPO_2$  permettront d'évaluer l'ischémie locale tissulaire. Ainsi la relation entre la valeur de  $TcPO_2$  de fin d'arrêt et la distance de marche suivant cet arrêt pourra être analysée. L'idéal serait néanmoins de coupler l'évaluation ambulatoire par GPS à une  $TcPO_2$  d'effort ambulatoire afin d'être réellement dans les mêmes conditions.

En plus de s'être attaché à développer des méthodes originales d'évaluation de la limitation de la capacité de marche (EACH-Questionnaire et GPS), ce travail a précisé les durées optimales (minimale et maximale) du test de référence, à savoir le test sur tapis à charge constante. Les résultats de ce travail permettront d'optimiser le temps d'évaluation nécessaire lors de ce test, particulièrement coûteux et chronophage, afin d'éviter de mal diagnostiquer une limitation de la capacité de marche chez un patient en cas de durée trop courte de test.

Associé à ces différentes méthodes d'évaluation de la distance maximale de marche, ce travail a aussi mis en évidence les différentes localisations (proximale(s) ou distale(s), droite ou gauche) de l'ischémie des membres inférieurs rencontrées au cours de cette limitation. La mesure de la pression péniennne censée être un bon reflet de l'ischémie proximale est en fait peu sensible et il convient de préférer d'autres méthodes pour affirmer l'ischémie proximale comme la  $TcPO_2$  d'effort. La  $TcPO_2$  nous a aussi permis de mettre en évidence que la sévérité et la diffusion ischémiques périphériques (nombre de sites de mesures à avoir une valeur pathologique) étaient associées à une plus faible différence entre la fréquence cardiaque de fin d'exercice et celle de post exercice à 1 minute. Une plus faible variation de cette fréquence cardiaque est associée à une ischémie des membres inférieurs plus sévère. En outre, la  $TcPO_2$  d'effort présente l'avantage de pouvoir étudier en même temps le niveau d'oxygénation systémique par le biais de la sonde thoracique. Il semblerait que certains patients ayant une limitation de leur capacité de marche présentent un profil d'oxygénation systémique particulier au cours d'un effort de marche. Ainsi, la claudication présentée par certains de ces patients ne serait pas simplement liée à une atteinte vasculaire mais pourrait être aussi liée à une

hypoxémie d'effort mise en évidence par ce profil thoracique particulier, reflet de l'oxygénation systémique.

Les perspectives sont nombreuses et sont principalement de trois ordres, physiopathologique, diagnostique et thérapeutique.

Ce travail a mis en évidence que l'ischémie entraînait une limitation de la capacité de marche. Cependant, les phénomènes physiopathologiques conduisant à la douleur demeurent mal connus actuellement, même si plusieurs hypothèses sont émises. Lors de l'effort, les apports en oxygène sont réduits chez les artériopathes, les cellules utilisent alors préférentiellement la voie anaérobie conduisant ainsi à la formation d'acide lactique pouvant ainsi induire une douleur (Levick, 2009). L'accumulation des déchets cellulaires peut aussi être une explication tout comme l'atteinte neurologique par le biais d'un manque chronique d'apport en nutriments aux cellules nerveuses. D'ailleurs, plusieurs travaux ont montré que l'artériopathie était associée à des troubles neurologiques et notamment de conduction nerveuse et de troubles de la sensibilité nerveuse (Evans et al., 2011; Tew et al., 2011). Les mécanismes douloureux mis en jeu restent donc à préciser. L'autre point physiopathologique important à clarifier est ce profil particulier d'oxygénation thoracique, reflet de l'oxygénation systémique. Pourquoi certains patients ont-ils ce « coup de hache » d'oxygénation tissulaire thoracique alors que la plupart des patients présentent une augmentation de leur oxygénation thoracique à la marche ? Ce coup de hache est-il visualisé par d'autres systèmes de mesure d'oxygénation tissulaire comme la saturométrie ou par la spectroscopie en proche infra-rouge ? Quelle est l'origine de ce profil ? Ce profil particulier est-il modifié dans certaines conditions ou lors d'effort incrémentiel ? Ces patients n'ont-ils pas d'autres comorbidités associées pouvant expliquer ce profil ? Si ce profil est pathologique peut-on le corriger ? Si oui, sa correction entraîne-t-elle une disparition de la limitation de la capacité de marche ?

Sur le plan diagnostique, il apparaît important de continuer le développement d'outils validés et faciles d'usage pour les cliniciens. A ce titre, le questionnaire EACH-Q peut probablement être amélioré. La question sur la course est-elle vraiment utile puisqu'en pratique peu d'artériopathes disent pouvoir courir ? Nous sommes d'ailleurs en cours de validation d'un nouveau questionnaire sans cette question. Il serait aussi intéressant de proposer un arbre décisionnel des examens diagnostiques de la limitation

de la capacité de marche à proposer pour le clinicien, situant chaque méthode d'évaluation face à une situation clinique donnée. En effet, est-il nécessaire de recourir à un test sur tapis lorsqu'un patient a un score au questionnaire WIQ ou au EACH-Q très faible ? N'est ce pas une perte de temps ? Dans la même optique, une étude multicentrique évaluant la faisabilité de la mesure ambulatoire par GPS est en cours. Elle permettra sans doute de valider la faisabilité de son utilisation en routine clinique pour évaluer la capacité de marche des patients comme un holter tensionnel ou électrocardiographique. Le clinicien n'aura alors plus qu'à remettre au patient un boîtier GPS afin d'objectiver sa distance de marche maximale. En outre, des mises au point technologiques notamment par l'ajout d'un bouton « marqueur d'événements » apparaissent utiles afin de bien différencier l'arrêt lié à la douleur de l'arrêt lié à une autre cause (rencontre d'un ami, ...).

Sur le plan thérapeutique, il faudra s'interroger sur la pertinence de ces nouveaux outils validés pour mettre en évidence les modifications (amélioration ou dégradation) de la capacité de marche consécutives à la mise en place de traitement(s) (médicamenteux, réadaptation, endovasculaire ou chirurgical) ? L'intérêt de l'utilisation de l'outil GPS comme monitoring au cours des séances de réadaptation mériterait d'être évalué ainsi que son association à un système de TcPO<sub>2</sub> ambulatoire (actuellement en développement).

Ce travail aura finalement permis d'améliorer la compréhension et la caractérisation de la limitation de la capacité de marche au cours de l'artériopathie oblitérante des membres inférieurs et contribuera, je l'espère, à l'optimisation de la prise en charge des patients.

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## ANNEXES

### Annexe 1 : Les maladies vasculaires

Les maladies vasculaires artérielles sont principalement liées à l'athérosclérose<sup>15</sup> et sont essentiellement représentées par la coronaropathie, les accidents vasculaires cérébraux ischémiques et l'artériopathie oblitérante des membres inférieurs. Ces maladies sont des pathologies qui peuvent entraîner d'une part des accidents aigus tels que l'infarctus du myocarde, l'ischémie cérébrale ou l'ischémie aiguë de membre, d'autre part des lésions chroniques lentes, insidieuses et asymptomatiques qu'il est nécessaire de détecter pour en éviter les conséquences parfois létales. Les maladies vasculaires ont parmi les maladies chroniques la prévalence la plus importante dans les pays développés (Leal et al., 2006; Murray and Lopez, 1997) et l'incidence est en forte augmentation (Ezzati et al., 2003; Yusuf et al., 2001). D'après l'organisation mondiale de la santé (OMS), les maladies vasculaires représentent la première cause de décès dans le monde. En effet, en 2005, un tiers des décès étaient dus à une pathologie vasculaire (17,5 millions) (Mackay J, 2004). En France, on estime entre 150000 et 180000 le nombre de décès annuels attribuables aux maladies vasculaires (Aouba et al., 2007). Elles représentent la deuxième cause de décès après les cancers avant 65 ans et la première cause après 65 ans (Aouba et al., 2007) et surviennent, quelque soit le territoire, vers l'âge de 72 ans comme l'a démontré l'étude OXVASC (Rothwell et al., 2005).

En outre, les maladies vasculaires représentent un coût économique important. Les dépenses liées à ces pathologies sont estimées à 169 milliards d'euros dans l'Union Européenne soit en moyenne 230 euros par habitant et par an (Leal et al., 2006). Cette somme englobe les coûts liés aux traitements, aux hospitalisations et à la perte de productivité des personnes malades.

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<sup>15</sup> Athérosclérose se définit depuis 1957 par l'OMS comme « une association variable de remaniements de l'intima des artères, consistant en une accumulation locale de lipides, de complexes glucidiques, de sang, de produits sanguins, de tissus fibreux et de dépôts calciques, l'ensemble associé à des remaniements de la média ».



## Annexe 2 : Walking Impairment Questionnaire (WIQ)

**Nom :**

**Prénom :**

**Date :**

**Distance de Marche :** Pour chacune des distances de marche qui vous sont proposées ci-dessous, reportez le degré de difficulté physique qui traduit le mieux votre difficulté à marcher sur terrain plat sans vous arrêter pour vous reposer.

| <i>Distance</i>                           | <i>Degré de difficulté</i> |                          |                          |                          |                          |
|-------------------------------------------|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                           | <i>Aucun</i>               | <i>Léger</i>             | <i>Moyen</i>             | <i>Important</i>         | <i>Infaisable</i>        |
| 1. Marcher chez soi (autour de la maison) | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Marcher 20 m                           | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Marcher 50 m (1 demi pâté de maisons)  | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Marcher 100 m (1 pâté de maisons)      | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Marcher 200 m (2 pâtés de maisons)     | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Marcher 300 m (3 pâtés de maisons)     | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Marcher 500 m (5 pâtés de maisons)     | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Vitesse de Marche :** Reportez le degré de difficulté physique qui décrit le mieux la difficulté que vous avez à parcourir, en fonction de différentes vitesses de marche, la distance correspondant à un pâté de maisons (sur terrain plat) et ce, sans vous arrêter pour vous reposer.

| <i>Vitesse</i>                                                  | <i>Degré de difficulté</i> |                          |                          |                          |                          |
|-----------------------------------------------------------------|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                                                 | <i>Aucun</i>               | <i>Léger</i>             | <i>Moyen</i>             | <i>Important</i>         | <i>Infaisable</i>        |
| 1. Parcourir un pâté de maisons (100 m) en marchant lentement ? | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Parcourir un pâté de maisons à une vitesse de marche normale | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Parcourir un pâté de maisons en marchant rapidement ?        | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Parcourir un pâté de maisons en courant (footing) ?          | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Montée d'escaliers :** Reportez le degré de difficulté physique qui décrit le mieux la difficulté que vous avez eu à monter des escaliers, sans vous arrêter pour vous reposer, au cours de la

dernière semaine.

| <i>Montée d'escaliers</i> | <i>Degré de difficulté</i> |                          |                          |                          |                          |
|---------------------------|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                           | <i>Aucun</i>               | <i>Léger</i>             | <i>Moyen</i>             | <i>Important</i>         | <i>Infaisable</i>        |
| 1. Monter 1 étage ?       | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Monter 2 étages ?      | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Monter 3 étages ?      | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

### **Annexe 3 : PADHOC (Peripheral Arterial Disease Holter Control)**

Le dispositif se compose d'une unité principale portée par le patient à la ceinture (Figure) (Boissier et al., 1997; Coughlin et al., 2001). Cette unité principale contient une carte amovible d'ordinateur qui enregistre les données. Cette unité est reliée à :

- deux capteurs à ultrasons (un capteur "émetteur" et un capteur "récepteur"), fixées chacune sur une malléole interne du patient par des sangles à la cheville,
- un module de contrôle possédant 3 boutons de couleurs différentes est tenu par le patient dans sa main.

Quand le patient commence à marcher, il appuie sur le bouton vert. Au début de la douleur claudication, le patient appuie sur le bouton jaune. Enfin, il appuie sur le bouton rouge lorsqu'il ne peut plus marcher. Le patient se repose alors debout pendant une minute, et le test est ensuite répété. Pour chaque essai, la distance, où la douleur apparaît, la distance maximale de marche, où le patient s'arrête et la vitesse de marche sont calculées. Cette procédure détermine ce que l'on appelle "Double physiological walking tests". L'unité principale contenue dans le sac à la ceinture reçoit et traite le signal et affiche les résultats sur un écran LED. Le dispositif comporte un certain nombre d'avantages :

- Le test ne nécessite pas d'être réalisé en milieu hospitalier,
- Le test mesure l'incapacité réelle vécue par le claudicant,
- Il n'y a pas de charge de travail constante prédéfinie contre laquelle le patient doit marcher.

Le principe de mesure du dispositif PADHOC est basé sur la télémétrie par ultrasons (figure 15). La distance de marche est calculée par la mesure en continu de la distance entre les malléoles internes du patient. Le capteur "émetteur" envoie un signal ultrasonore à un capteur "récepteur" 64 fois par seconde. L'unité centrale mesure le temps mis par le signal pour aller du capteur "émetteur" au capteur "récepteur". La distance entre les malléoles médiales est alors calculée en multipliant le temps mis par le signal pour aller d'un capteur à l'autre par la vitesse de propagation du son. Toutes les mesures de ces distances sont représentées par une courbe sinusoïdale. Chaque oscillation sur la courbe correspond à un pas. Les variations maximales de signal correspondent au moment, où les 2 pieds touchent le sol. Par conséquent, chaque

variation maximale représente la distance de marche réelle parcourue pendant un pas. La somme de toutes les distances maximales permet ainsi de calculer la distance de marche.



**Figure 15 : Système PADHOC porté par une patiente (Coughlin et al., 2001) .**

Le principe de « la double épreuve physiologique de marche » avec le système PADHOC (figure 16). Quand le patient marche, la douleur qui arrête le patient, est censée apparaître en même temps que la chute de pression de cheville. La vitesse à laquelle la pression de cheville retourne à sa valeur de pré-exercice dépend de l'état fonctionnel des collatérales. Après la période de repos de 1 minute debout, la douleur disparaît mais la valeur de pression de cheville peut rester inférieure à la pression initiale avant la marche. Plus la valeur de pression de cheville met du temps à retourner à la valeur initiale, plus la durée de marche suivante sera courte. En utilisant ce principe, la sévérité de l'AOMI peut être déterminée en calculant les rapports de distance d'apparition du début de la douleur et de distance maximale de marche entre le premier test et le second test de marche. Un rapport bas détermine une AOMI sévère.

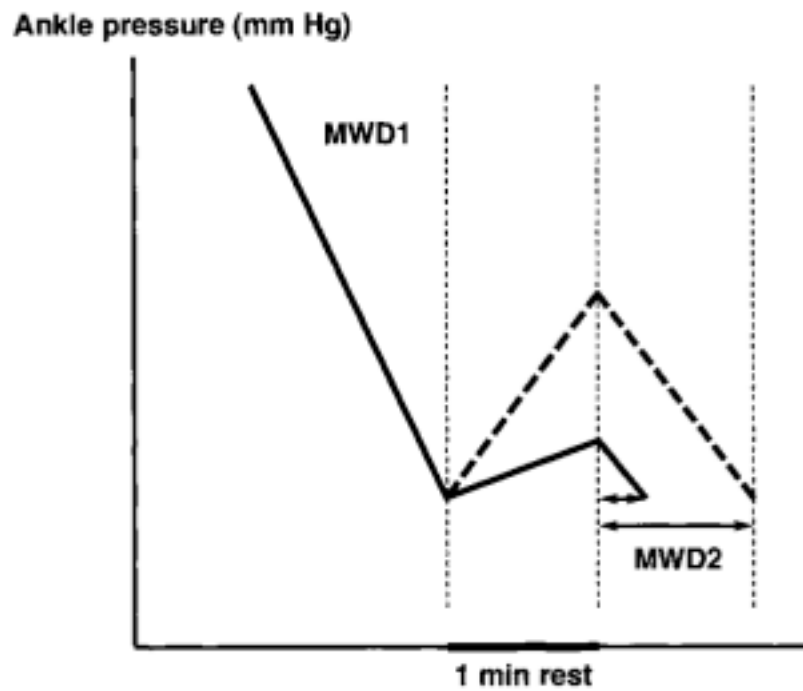
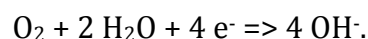


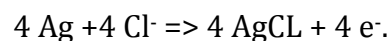
Figure 16 : Principe de « la double épreuve physiologique de marche » pour la distance maximale de marche. MWD1 : maximal walking distance signifie distance maximale de marche 1 ; MWD2 signifie distance maximale de marche 2. Ankle pressure signifie pression de cheville ; « 1 min rest » signifie 1 minute de repos.

## Annexe 4 : Mesure transcutanée de la pression partielle en oxygène

La mesure transcutanée de pression d'oxygène aussi appelée "transcutaneous oxygen pressure measurement" (TcPO<sub>2</sub>) est une mesure utilisée à l'origine pour l'exploration des troubles trophiques cutanés chez les artériopathes et permet de déterminer le niveau d'amputation (Dowd et al., 1983; Franzeck et al., 1982; Sarin et al., 1991). Le principe de la mesure est basé sur l'utilisation d'une électrode mise au point par Clark *et al.* en 1953 (Clark et al., 1953). La valeur de TcPO<sub>2</sub> exprimée en mmHg représente la pression partielle d'oxygène diffusant au niveau de la peau et dépend de la pression partielle artérielle en oxygène, du débit sanguin local et des conditions de diffusion de l'oxygène à travers la peau (Lubbers, 1987). Elle est mesurée à travers un capteur constitué d'une électrode polarographique recouverte d'une fine membrane de polyéthylène. Cette électrode contient une anode en argent et une cathode en platine. Avant fixation au niveau de la peau un liquide de conduction est déposé sur la membrane afin de favoriser la bonne diffusion de l'oxygène à la peau vers la membrane. Le capteur est chauffé à une température de 44°C afin d'obtenir une vasodilatation cutanée maximale et donc de favoriser une diffusion optimale d'oxygène. Les molécules d'oxygène traversent les tissus sous cutanées puis diffusent à travers le derme et l'épiderme pour atteindre la membrane du capteur. Au niveau de la cathode a alors lieu la réaction chimique de réduction suivante :



Les électrons nécessaires sont apportés par l'anode avec formation de chlorure d'argent (AgCl) suite à la réaction suivante :



Un courant électrique est alors produit entre l'anode et la cathode et celui-ci est directement proportionnel à la quantité d'oxygène disponible (Got, 1998). Ce courant électrique est converti par un ordinateur en une valeur numérique de TcPO<sub>2</sub> et exprimé en mmHg.

Compte tenu d'un gradient de diffusion de l'oxygène propre à chaque individu, la valeur de TcPO<sub>2</sub> n'est pas le reflet direct de la pression d'oxygène artériel. Ce gradient de diffusion est inconnu d'un patient à un autre et même chez un même patient d'un jour à l'autre ou d'un site de mesure à un autre. Afin de palier à ce problème de gradient une

sonde de référence dite thoracique est placée sur l'individu afin de prendre en compte non par les valeurs absolues mais le Delta from Rest of Oxygen Pressure (DROP) exprimé en mmHg. L'intérêt de l'utilisation du DROP est de rendre le calcul des variations temporelles de TcPO<sub>2</sub> indépendantes des valeurs absolues initiales de repos et ainsi de seulement tenir compte des variations des valeurs des sondes des membres inférieurs en fonction de l'évolution des valeurs de la sonde thoracique. Une valeur seuil de DROP de -15 mmHg a une sensibilité<sup>16</sup> de 79% et une spécificité<sup>17</sup> de 86%. Une valeur de DROP  $\leq$  15 mmHg est pathologique et traduit une ischémie de la zone, où est positionnée la sonde de mesure.

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<sup>16</sup> Sensibilité : C'est la probabilité d'avoir le signe de la maladie (test positif) lorsque l'on est malade.

<sup>17</sup> Spécificité : C'est la probabilité de ne pas avoir le signe de la maladie (test négatif) lorsque l'on n'est pas malade.

## **Annexe 5 : Spectroscopie proche infra-rouge**

La spectroscopie dans le proche infrarouge appelée aussi « Near Infra-Red Spectroscopy » (NIRS) a été proposée dans l'évaluation des artériopathies à l'effort (Sugano et al., 2003). Le principe de mesure est identique à celui des saturomètres pour connaître la saturation en oxygène dans le sang notamment pour l'exploration du cardio-respiratoire (Mancini et al., 1994). La mesure est supposée refléter la saturation tissulaire en oxygène des structures profondes comme les muscles. La spectroscopie proche infrarouge (NIRS) est une spectroscopie d'absorption dont le principe repose sur l'absorption du rayonnement proche infrarouge par la matière organique. Dans le muscle, le rayonnement infrarouge est absorbé principalement par l'oxyhémoglobine (HbO<sub>2</sub>), la désoxyhémoglobine (Hb), l'oxymyoglobine, la désoxymyoglobine et l'eau. Dans la bande passante infrarouge (715 nm à 825 nm) il a été montré que l'effet de l'absorption de l'eau dans la détermination de la concentration de l'hémoglobine est inférieur à 5% et que la contribution de la myoglobine dans le signal réfléchi est faible. Ainsi, l'absorption du rayonnement infrarouge est due de façon prépondérante à l'hémoglobine, ce qui conduit à l'expression du coefficient d'absorption de l'hémoglobine. Cette mesure couplée au test d'effort permet ainsi de connaître l'oxygénation tissulaire au cours de l'effort chez les patients artériopathes (Bouye et al., 2005).



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## Annexe 6 : Articles pour la thèse en deuxième et troisième auteurs

## ARTICLE IN PRESS

## Validation of a new simple questionnaire to “estimate ambulation capacity by history” (EACH) in patients with claudication

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**Objectives:** The assessment of walking limitation is important in determining the severity of many diseases, including peripheral artery disease. Questionnaires exist for estimating walking capacity, but these have limited use in routine clinical practice. We sought to establish the feasibility and validity of the estimating ambulation capacity by history questionnaire (EACH-Q), a self-administered, four-item questionnaire that estimates walking capacity in patients reporting vascular-type claudication.

**Background:** The EACH-Q estimates the maximal duration that can be attained (eight possibilities: from impossible to 3 hours or more) at four different displacement speeds (from slow walking to running). Scores can be obtained easily by multiplying the rank of each possible answer (impossible being zero) by a speed factor.

**Methods:** The Walking Impairment Questionnaire (WIQ) and the EACH-Q were completed by 218 patients with vascular-type claudication, undergoing treadmill exercise testing. We hypothesized that less errors (ie, missing, duplicated, or paradoxical answers) and missing final scores would be observed for the EACH-Q than the WIQ. Validity was assessed by calculating correlation coefficients ( $r$ ) between the questionnaire scores (both questionnaires, noncorrected and corrected) and treadmill maximal walking distance (MWD: 3.2 km/h, 10% slope, maximized to 15 minutes).

**Results:** Compared with the EACH-Qs, nearly twice as many WIQs had to be corrected for one or more errors (52% vs 28%;  $P < .0001$ ). This resulted in 37 (17%) WIQ versus 18 (8%) EACH-Q scores being missing on noncorrected questionnaires ( $P < .0001$ ). MWD was 162 m (25–75<sup>th</sup> percentiles: 91–390 m). The correlation coefficients of WIQ and EACH-Q to MWD were 0.59 and 0.52, respectively, before correction ( $P = .357$ ) and 0.60 and 0.51, respectively, after correction ( $P = .185$ ).

**Conclusions:** The EACH-Q is a simple and valid questionnaire for estimating walking capacity in patients with vascular-type claudication. It is easily scored. It might help standardize the reporting of how patients feel about their walking limitation. Further research is needed to validate the EACH-Q in other patient groups and against other treadmill protocols and to assess its reliability and sensitivity. (J Vasc Surg 2011;■■■■■)

The maximal walking distance (MWD), the distance at which pain forces the patient to stop walking, is of great importance for assessing the severity of claudication in patients with lower extremity arterial disease (LEAD). Patient interview is the most readily accessible way of estimating walking capacity in routine clinical practice, although patients suffering with LEAD typically estimate their walking capacity poorly.<sup>1</sup> Opened questions without guided answers about the distance estimated by the patient before limb pain or discomfort forces to stop walking, lack standardization. A question such as “Because of a health or physical problem, do you have any difficulty walking for

one mile?”<sup>2</sup> only allows for a yes/no response. The functional status component of the 86-item PAVK-86 questionnaire estimates MWD,<sup>3,4</sup> but the PAVK-86 is a time-consuming tool. The walking impairment questionnaire (WIQ)<sup>5-7</sup> was proposed a decade ago to standardize the estimation of walking capacity by patient interview and is largely used. Unfortunately, the WIQ is also relatively complex (14 items with five possible answers for each item: 70 boxes), which often results in a high number of errors when self-completed by the patient.<sup>8</sup> Furthermore, the WIQ score is difficult to obtain by mental calculation or without the use of a computer.

Our goal was to test the validity of a new simple four-item questionnaire, the EACH-Q, for “Estimating Ambulation Capacity by History” in patients complaining of vascular-type claudication. We hypothesized that: (1) a self-completed EACH-Q would have fewer errors than a self-completed WIQ; and, (2) these two questionnaires would show comparable concordances with treadmill MWD.

### METHODS

**Study population.** A prospective study on all new French language-speaking patients referred to our laboratory for vascular-type claudication was performed. Claudi-

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

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Please answer each of the following questions with one and only one « X » in the box that best describes your situation. If you never perform an activity, estimate what it would be to perform it. If you think you would not be able to perform the task or if you cannot physically perform a specified activity without stopping to rest because of symptoms such as leg pain or discomfort, please place a "X" in the box labelled "impossible".

For each of the following displacement speed, how long can you perform the task easily on level ground without stopping to rest.

|                                                                                                 | Impossible | 30 seconds | One minute | Three minutes | 10 minutes | 30 minutes | One hour | Three hours or more |
|-------------------------------------------------------------------------------------------------|------------|------------|------------|---------------|------------|------------|----------|---------------------|
| Walk slowly (slower than usual, or slower than friend, relatives or persons of your age)?       | 0          | 1          | 2          | 3             | 4          | 5          | 6        | 7                   |
| Walk at average speed (usual pace, or same pace as friend, relatives or persons of your age)?   | 0          | 2          | 4          | 6             | 8          | 10         | 12       | 14                  |
| Walk quickly (faster than usual, or faster pace than friend, relatives or persons of your age)? | 0          | 4          | 8          | 12            | 16         | 20         | 24       | 28                  |
| Run or jog?                                                                                     | 0          | 7          | 15         | 22            | 29         | 36         | 44       | 51                  |

IMPORTANT NOTE: The original table includes no number and no circles. Here, ticks have been changed to circles and boxes have been completed by the numbers resulting from the product of the coefficient by the item value to illustrate the scoring of the EACH-Q. The score is the sum of the numbers observed for each item divided by 100. In this example:  $(5+8+12+7)/100 = 32\%$ .

Fig 1. English translation of the EACH Questionnaire.

cation is of vascular type (ie, suspected of arterial origin) when pain or discomfort occurs at exercise and is improved within 10 minutes when exercise is stopped. Most patients had, or were suspected to have, peripheral artery disease (PAD). Evidence for PAD was based on the presence of at least one of the following criteria: a history of revascularization (surgery or angioplasty) for PAD; a previous ultrasound or radiological investigation showing stenosis/occlusion of the aortoiliac and/or lower-limb arteries; an ankle-to-brachial index (ABI) at rest < 0.90 on one or both legs. Patients who were referred more than once during the study period had only their first visit included. This study received local ethics committee approval and conforms to the Declaration of Helsinki. Written, informed consent was provided by patients prior to their participation. The study is accessible on the <http://clinicaltrials.gov> web site under reference NCT01114178. On arrival at the laboratory, patients were asked to complete (without help) the EACH-Q and WIQ using a black or blue pen. The patients were not aware of which was the new questionnaire.

**Design of the EACH-Q.** The EACH-Q was designed with the assumption that, since many patients have a watch and may have measured their true walking time, using maximal estimated time rather than maximal estimated distance would facilitate patients' reporting of their walking capacity and thereby reduce the number of missing answers. Furthermore, we used the three following observations:

- 1) Patients suffering claudication might show different walking capacities (in time or distance) if they walk fast or slow. Therefore, the new questionnaire was con-

structed to assess estimated maximum exercise duration for different displacement speeds.

- 2) At a constant load, the walking distance in claudicating patients follows a log-normal distribution.<sup>9</sup> Thus, the possible exercise durations proposed for each displacement speed were defined such that they follow an exponential increase.
- 3) There is an inverse exponential relationship between MWD and walking speed in patients with claudication.<sup>10</sup> Therefore, the values attributed to the different displacement speeds in the new questionnaire were defined so that they follow an exponential increase.

Last, our aim was that scoring of a questionnaire should be easy to remember and possible without the use of a computer program.

The original EACH-Q used in this study is in French, but an English translation is presented in Fig 1. The EACH-Q includes four items, each one representing a different displacement speed. For each item, the patient was asked to choose the longest duration that could be performed easily among the durations proposed. As shown for each item, if the answer was not "impossible," the durations followed an exponential increase from 30 seconds to 3 hours.

Each duration was attributed a value consistent with its position among the possible responses (eg, 0 for "impossible," 1 for "30 seconds," and 7 for "3 hours or more"). Each displacement speed was attributed a coefficient, and a score was calculated for each displacement speed by multiplying the corresponding coefficient by the value attributed to the duration response. These coefficients for each item

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were fixed “a priori” before the study, but the primary goal was to have a maximal possible EACH-Q score of 100 and an exponential increase of the coefficients. Since the maximal value of the answers to each item was 7, then the sum of coefficients had to be  $14.286: 7 \times 14.286 \sim 100$ . We then used the following coefficients: 1 for “slow walk,” 2 for “normal walk,” 4 for “fast walk,” and 7.286 for “run.” Although arbitrarily fixed, these coefficient fit an exponential increase ( $r = .999$ ). For the 7.286 speed coefficient, the eight possible products were rounded to the nearer whole number giving the following possible values: 0, 7, 15, 22, 29, 36, 44, and 51. The total EACH-Q score was the sum of the calculated scores for all displacement speeds divided by 100, since, by construction, the maximal possible score is  $100 (= [1 \times 7] + [2 \times 7] + [4 \times 7] + [7.286 \times 7])$ . For example, a patient reporting 30 minutes at a slow walking speed, 10 minutes at a normal walking speed, 1 minute at a fast walking speed, and impossible for running would score  $21\% (= [1 \times 5] + [2 \times 4] + [4 \times 2] + [7.286 \times 0])/100$ .

For noncomplete, noncorrected EACH-Qs, paradoxical answers (eg, higher duration at higher displacement speed) were left unchanged; for duplicate answers (two or more answers for the same question), the shorter duration was used; missing (no answer to a question) answers were considered “impossible” for the running question only and left unchanged for other items. Then, the score was calculated when at least two items were available (by dividing the sum of points of the available items by the maximum possible score for these items and multiplying by 100). Thereafter, the questionnaire was checked for completion and errors by a technician or nurse before the treadmill test. Missing, duplicate, and paradoxical answers were discussed with the patient and corrected. For a missing answer, if the patients were unable to predict what they could manage if they had to perform the task, the response was declared “impossible.” For duplicate answers, if the patient was unable to choose, the lower duration was arbitrarily kept. For paradoxical answers, the patient was asked to correct his or her answers after having it explained to him or her that the answers were expected to follow a logical order with unchanged or decreased maximal time for an increase in speed displacement. Corrections were made with a red pen to allow us to easily identify corrected and noncorrected questionnaires. Once corrections were made, a new scoring of the corrected questionnaire was done.

**WIQ.** We used the French version of the WIQ, as previously reported.<sup>11</sup> Self-completed WIQs were scored as previously described.<sup>7</sup> In brief, each response is attributed a value ranging from 0 (impossible) to 4 (no difficulty). For the distance subscale, each distance is attributed a weight ranging from 20 to 1500. For each distance proposed, the product of weight by the answer value is calculated, and the subscale score is the sum of these products divided by 14,080 (maximal possible result). For the speed subscale, each speed is attributed a weight (ranging from 1.5 to 5). The product of weight by the answer value is calculated for each question, and the speed subscale score is the sum of these products divided by 46 (maximal possible result). For

the stair climbing subscale, weights are 12 for one, 24 for two, and 36 for three flights of stairs. The product of weight by the answer value is calculated and the stair-climbing subscale score is the sum of these products divided by 288 (maximal possible result). For noncomplete, noncorrected WIQs, paradoxical answers were left unchanged; for duplicate answers, the highest difficulty was used; for missing answers, a subscale score was calculated when at least half of the answers were available (by dividing the sum of the points of available answers by the maximum possible point score for these answers); and the total WIQ score was calculated when at least two subscale scores were available. Thereafter, as for the EACH-Q, the WIQ was checked for completion and errors by a technician or nurse before the treadmill test. Missing, duplicate, and paradoxical (eg, lower difficulty for higher distance or higher number of stairs) answers were discussed with the patient and corrected. For a missing answer, if the reason was “I never perform such a task,” the response was declared “impossible.” For duplicate answers, if the patient was unable to choose, the higher level of difficulty was arbitrarily kept. For paradoxical answers, the patients were asked to correct their answers after being explained to that the answers within a subscale of the WIQ were expected to follow a logical order with unchanged or increasing difficulty for increase in task level (speed, distance, or number of stairs). Corrections were made with a red pen to allow us to easily identify corrected and noncorrected questionnaires. Thereafter, as for the EACH-Q, once corrections were made, a new scoring of corrected WIQs was done.

**Walking capacity on treadmill.** The treadmill gradient was set at 10%. The speed was increased from 0 to 3.2 km/hour within 1 minute (to allow the patient to adapt to treadmill walking) and then stabilized for a maximum duration of 15 minutes, which corresponds to a maximum distance of 750 meters. This maximal distance was chosen because we have previously shown that, after reaching the 750 meter mark, <10% of patients stop walking within the next 250 meters.<sup>9</sup> Before the treadmill test, each patient was informed that the test could be stopped whenever symptoms (eg, claudication, breathlessness, nonischemic leg pain) became intolerable. The MWD was recorded for each patient.

**Sample size calculation and statistical analyses.** Sample size calculation was based on the estimation that 25% of the WIQs and only 12.5% of EACH-Qs could not be scored as a result of missing answers. A minimal number of 155 participants was required to search for a significant difference between these two proportions for  $\alpha = 0.05$  and 90% power. For practical reasons, in perspective of the number of new patients that are referred to the laboratory, a 6-month study period was used.

Results are reported as mean  $\pm$  SD except for MWD, WIQ, and EACH-Q scores, which were nonnormally distributed and thus presented as median (25-75 percentiles). We used a McNemar test to identify if the proportion of questionnaires with errors or unavailable scores differed between the WIQ and the EACH-Q before correction.

Indeed, an error or a missing answer does not necessarily result in a missing score. We calculated the Spearman "r" coefficient of correlation between the questionnaire scores (both questionnaires, noncorrected and corrected) and MWD. Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, Ill). For all tests, a two-tailed  $P < .05$  was used to indicate statistical significance.

## RESULTS

**Population studied.** During the study period, as a result of an increased activity in the laboratory, 219 patients with claudication were referred for treadmill testing. One patient refused to participate. Of the remaining 218 patients, 178 (82%) were male, and the average age, body mass, height, and body mass index was  $62 \pm 11$  years,  $77 \pm 14$  kg,  $1.70 \pm 0.08$  meters, and  $26.6 \pm 4.5$  kg/m<sup>2</sup>, respectively. ABI was nonmeasurable on both sides in four patients. Brachial artery systolic and diastolic pressures were  $135 \pm 20$  mm Hg and  $78 \pm 9$  mm Hg, respectively. The ABI (lowest of left and right sides) was  $0.81 \pm 0.25$ . Among studied patients, 180 (82.6%) were proved to have PAD. Among the other 38 patients, nine were later proved to have isolated buttock exercise-induced ischemia. Treatments included antiplatelet or anticoagulant ( $n = 161$ ), beta blockers ( $n = 61$ ), antidiabetic drugs or insulin ( $n = 41$ ), cholesterol-lowering drugs ( $n = 134$ ), antihypertensive ( $n = 130$ ), analgesic or anxiolytic drugs ( $n = 58$ ), and other drugs ( $n = 130$ ).

**Completion of the questionnaires.** Sixty percent of the patients made at least one error in one or both questionnaires: 18 on the EACH-Q only, 71 on the WIQ only, and 42 on both the EACH-Q and the WIQ. As a result, the proportion of questionnaires with errors was 52% (range, 45%-58%; 113 out of 218) with the WIQ, and 28% (range, 22%-34%; 60 out of 218) with the EACH-Q ( $P < .0001$ ).

**Type of errors.** The number of EACH-Qs with missing, paradoxical, or duplicate answers was 41, 22, and 4, respectively. The total number of missing, paradoxical, or duplicate answers for the EACH-Q was 102, 26, and 5, respectively. The number of WIQs with missing, paradoxical, or duplicate answers was 94, 42, and 12, respectively. The total number of missing, paradoxical, or duplicate answers for the WIQ was 608, 77, and 13, respectively. Overall, considering the total number of questions that had to be completed and that multiple errors could be made within one item, we observed 133 errors of a possible 872 (15%) with the EACH-Q and 698 errors of a possible 3052 (23%) with the WIQ ( $P < .0001$ ). As a result of missing values, the distance, speed, and stair-climbing subscores for the WIQ could only be obtained in 173 (79%), 181 (83%), and 176 (81%) cases, respectively. This resulted, before correction of questionnaires, in 37 missing WIQ scores (17% of WIQ questionnaires), compared with only 18 missing EACH-Q scores: 8% of EACH-Qs ( $P < .0001$ ).

The distribution of questionnaire scores is presented in Fig 2. In both cases, scores were not normally distributed. As shown, the median score with the EACH-Q was 23%

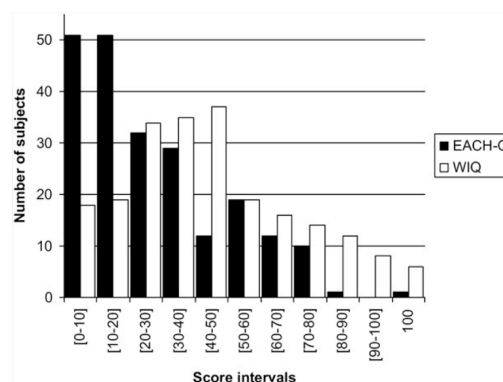


Fig 2. Distribution of the scores for the EACH-Q and the WIQ by intervals of 10%.

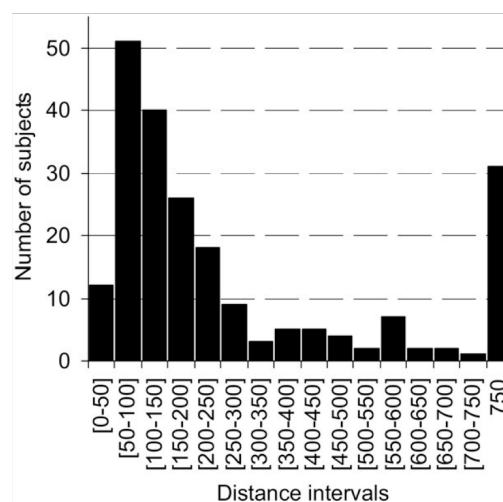


Fig 3. Distribution of the walking distances by intervals of 50 meters.

(range, 10%-40%). It was lower than the median score of the WIQ, which was 41% (range, 26%-61%;  $P < .001$ ).

**Treadmill MWD.** Treadmill median MWD was 162 meters (25°-75° percentiles: 91-390 meters). The distribution of MWD observed on treadmill is reported in Fig 3. Thirty-one (14%) of the patients completed the test. The treadmill test evoked lower-limb claudication in 184 of the 218 patients (84%), among which 17 completed the test despite claudication. Twenty (9%) patients had to stop the test for nonlimb symptoms, mainly dyspnea. Fourteen (6%) patients completed the test without claudication.

**Correlation of questionnaire scores to treadmill MWD.** The relationships between questionnaire scores and MWD were moderate, ranging from  $r = .51$  to  $r = .60$  (Table). There was no significant difference between the



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**Table.** Spearman rank coefficients of correlation with treadmill walking distance before and after correction

|              | Questionnaires              | R     | n   | P     |
|--------------|-----------------------------|-------|-----|-------|
| Noncorrected | WIQ distance subscore       | 0.553 | 173 | <.001 |
|              | WIQ speed subscore          | 0.515 | 181 | <.001 |
|              | WIQ stair climbing subscore | 0.520 | 176 | <.001 |
|              | Overall WIQ                 | 0.586 | 181 | <.001 |
|              | EACH-Q                      | 0.520 | 200 | <.001 |
| Corrected    | WIQ distance subscore       | 0.581 | 218 | <.001 |
|              | WIQ speed subscore          | 0.560 | 218 | <.001 |
|              | WIQ stair climbing subscore | 0.448 | 218 | <.001 |
|              | Overall WIQ                 | 0.601 | 218 | <.001 |
|              | EACH-Q                      | 0.513 | 218 | <.001 |

n is the number of available scores.

correlation coefficients of the questionnaire scores to MWD ( $P = .357$  and  $P = .185$ ) before and after correction, respectively.

## DISCUSSION

When validated against treadmill MWD, the EACH-Q compares favorably with the WIQ in patients complaining of vascular-type claudication. However, fewer errors were made on the EACH-Q, since it is easier to complete. The EACH-Q also has three other advantages over the WIQ. First, it includes only four items, thus the time needed for completion is very short (usually 1-2 minutes). Second, the EACH-Q integrates the concept that displacement speed and exercise capacity are inversely related in patients with LEAD. Third, the scoring is easy, without the need of a computer.

Our first goal when designing the EACH-Q was for it to be simple and short, to limit the number of errors made by patients during self-completion. The EACH-Q has four questions, each having eight possible answers (for a total of 32 boxes). The WIQ is relatively long in comparison, having 14 questions each with five possible answers (for a total of 70 boxes).<sup>7</sup> The findings of a meta-analysis of randomized control trials suggested that shorter questionnaires should be preferred and that reducing the length of relatively short questionnaires is more effective than reducing the length of longer questionnaires.<sup>12</sup> Reducing the length of the questionnaire reduces the time needed for completion and probably increases the response rate (ie, proportion of completed questionnaires).<sup>13</sup> The exponential-type increase in the durations proposed for each displacement speed seems to facilitate the decision of patients.<sup>14</sup> The lower number of errors of the EACH-Q might be explained by the use of exponential scales, the limited number of questions, and the use of maximal time rather than maximal distance.

Our second goal for the EACH-Q was for it to have a level of validity (ie, the relationship between the question-

naire score [estimated walking capacity] and treadmill MWD) comparable to that of the WIQ. Estimation of walking capacity by history is an easy and low-cost tool for epidemiologic studies. Furthermore, questionnaires facilitate the standardization of patients' answers in clinical routine. Previous studies have shown that the relationship between questionnaire-based estimates of walking capacity and objectively-determined walking capacity is generally fair, both in LEAD and non-LEAD patients.<sup>3-5,7,11,15-17</sup>

For example, the correlation coefficient ( $r$ ) between the overall WIQ score and constant-load treadmill MWD was shown to be 0.53 for 24 patients with arterial claudication.<sup>11</sup> In another study, Spearman rank correlation coefficients ( $\rho$ ) between the WIQ distance score and maximum 6-minute walking distance were 0.56 among 145 patients with LEAD ( $P < .001$ ) and 0.48 among 65 patients without LEAD ( $P < .001$ ).<sup>7</sup> In the same study, correlation coefficients ( $r$ ) between the WIQ speed score and the usual pace 4-meter walking time have also been shown to be 0.53 among patients with LEAD ( $P < .001$ ) and 0.52 among patients without LEAD ( $P < .001$ ).<sup>7</sup> Another study showed that, of the four WIQ subscales, treadmill MWD (1.5 mph and 10% grade) was only significantly correlated with distance ( $r = .41$ ) and speed ( $r = .39$ ).<sup>5</sup> The correlation coefficients between the EACH-Q scores and treadmill MWD were in the same range as the values stated above, although it cannot be excluded that the absence of difference has resulted from a type II error. Further study is needed to assess whether changes in the EACH-Q score correlate with changes in objectively measured MWD, as is the case for the WIQ.<sup>18</sup> A large prospective study is required to assess the sensitivity of the EACH-Q to changes in LEAD severity (as could be estimated through ABI changes).

There are some limitations to the present study. First, although many studies in vascular disease include more males than females, the proportion of males in our study is particularly high. The explanation for this is not readily apparent and might limit the generalization of our findings. Additional studies are needed in women, other socioeconomic groups, and other patient groups. Second, due to the specific interest of our laboratory being proximal and atypical claudication, a large proportion of our patients experienced claudication with an apparently normal ABI at rest. This might lead one to question whether some of our patients did suffer vascular claudication. Therefore, it is important to note that the description of claudication symptoms provided by patients was consistent with a vascular origin. Third, the reliability of the EACH-Q requires testing in a large group of patients. The reliability of the WIQ, as assessed using Cronbach's alpha, has been reported to be high, in the range 0.92 to 0.97<sup>15,19</sup>; however, the Cronbach's alpha value increases with the number of items in the scale,<sup>20,21</sup> and it is not robust against missing data.<sup>21</sup> These two points are of specific interest since the WIQ is longer and suffers a high range of missing data when self-completed, than the EACH-Q. Fourth, one could suggest that the 7.286 speed coefficient is not easy to

remember for a routine use. We found it easy to memorize this coefficient by using 22/3, which is 7 and one-third. The numbers of points obtained with 7.333, when rounded to the nearer whole number, are almost the same as with 7.286. Fifth, we have no information about the education, intelligence, socioeconomic status, or functional level of the patients. Nevertheless, this was expected to be of little influence since we compared the questionnaires in the same population. Last, we did not specifically assess for the presence of other conditions that may impair walking (such as osteoarthritis, prior stroke) and would likely impair running ability.

### CONCLUSION

The EACH-Q is short and easy to score, resulting in <10% missing scores when self-completed. Correlation of the EACH-Q-score with the objective measurement of MWD on treadmill is comparable to that observed previously for other questionnaires. Further research is needed to validate the EACH-Q in other patient groups and against other treadmill protocols and to assess its reliability and sensitivity.

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### AUTHOR CONTRIBUTIONS

Conception and design: PA  
 Analysis and interpretation: PA, GM, GL  
 Data collection: NO, GM, JM, KS, PA  
 Writing the article: GM, PA  
 Critical revision of the article: NO, JM, KS, GL  
 Final approval of the article: NO, GM, JM, KS, GL, PA  
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## Variability and short-term determinants of walking capacity in patients with intermittent claudication

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**Objective:** Global positioning system (GPS) recordings can provide valid information on walking capacity in patients with peripheral arterial disease (PAD) and intermittent claudication (IC) during community-based outdoor walking. This study used GPS to determine the variability of the free-living walking distance between two stops (WDBS), induced by lower-limb pain, which may exist within a single stroll in PAD patients with IC and the potential associated parameters obtained from GPS analysis.

**Methods:** This cross-sectional study of 57 PAD patients with IC was conducted in a university hospital. The intervention was a 1-hour free-living walking in a flat public park with GPS recording at 0.5 Hz. GPS-computed parameters for each patient were WDBS, previous stop duration (PSD), cumulated time from the beginning of the stroll, and average walking speed for each walking bout. The coefficient of variation of each parameter was calculated for patients with the number of walking bouts ( $N_{WB}$ )  $\geq 5$  during their stroll. A multivariate analysis was performed to correlate WDBS with the other parameters.

**Results:** Mean (SD) maximal individual WDBS was 1905 (1189) vs 550 (621) meters for patients with  $N_{WB} < 5$  vs  $N_{WB} \geq 5$ , respectively ( $P < .001$ ). In the 36 patients with  $N_{WB} \geq 5$ , the coefficient of variation for individual WDBS was 43%. Only PSD and cumulated time were statistically associated with WDBS in 16 and 5 patients, respectively.

**Conclusions:** A wide short-term variability of WDBS exists and likely contributes to the difficulties experienced by patients with IC to estimate their maximal walking distance at leisurely pace. Incomplete recovery from a preceding walk, as estimated through PSD, seems to dominantly account for the WDBS in patients with IC. (J Vasc Surg 2010;51:886-92.)

Claudication is generally one of the first symptoms in peripheral artery disease (PAD). It is frequently assumed that the different walking distances between two stops induced by lower-limb pain within a single stroll are relatively stable. In fact, to our knowledge, the variability of walking distance between two stops (WDBS) that may exist within a single stroll has never been measured. What is available is only the reproducibility of maximal walking distance (MWD) through test-rest experiments.<sup>1-6</sup>

The study of this short-term variability (changes in WDBS within a single stroll) could provide interesting information about some of the issues relating to functional assessment in PAD patients. Indeed, if such short-term variability exists, it may contribute to the difficulties experienced by patients with arterial claudication to estimate their MWD at usual pace, where MWD would be the highest WDBS within a stroll. This short-term variability could also at least partly explain the low concordance between estimated and measured MWD in PAD patients.<sup>7-9</sup>

We showed in a previous study<sup>10</sup> that global positioning system (GPS) recordings, an original approach for walking studies, could monitor community-based outdoor walking and provide valid information on walking capacity in PAD patients. The GPS technique provides useful data about actual walking in something approaching a real-world situation. It further allows for the investigations of new dimensions of walking, such as the short-term variability of walking distance, effect of walking speed, and importance of stop durations, which would hardly be done by using treadmill testing.

In the present study, we used the previous validated methodology of GPS data recording and processing<sup>10</sup> to record walking speed and distance for each walking bout, duration of the stop preceding each walking bout, and cumulated time from the onset of walking in PAD patients undergoing nonsupervised walking strolls. From these recordings and for patients showing multiple walking bouts, our first goal was to quantify the individual magnitude of the variability of WDBS within a single stroll. We hypothesized that the short-term variability would be high in most patients. A secondary goal was to provide insights into potential GPS-derived parameters that could be associated with this short-term variability.

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**Table I.** Inclusion criteria

- Age >18 years old
- Clinical stability of claudication  $\geq 3$  months
- Ankle-brachial index at rest  $< 0.95$
- Ability to walk on treadmill
- No systemic disease limiting exercise other than claudication
- No myocardial infarction  $\leq 6$  months
- No heart disease requiring surgery
- No angina pectoris
- No sustained ventricular arrhythmias
- No abdominal aortic aneurysm  $> 40$  mm
- No uncontrolled hypertension
- No inability to participate in the study for any logistic reason

## MATERIALS AND METHODS

This study was approved by the local scientific and ethics committees and registered in the American National Institute of Health database under reference No. NCT00485147 (<http://www.clinicaltrials.gov>).

**Studied population and inclusion criteria.** Volunteers were recruited from among the PAD patients referred to our laboratory for MWD evaluation on the treadmill. Criteria for inclusion are presented in Table I. Eligible patients were asked to provide signed, informed consent to participate.

**Definition of claudication.** The San Diego Claudication Questionnaire was used to characterize leg symptoms.<sup>11</sup> Intermittent claudication was defined as fatigue, discomfort, or pain that occurred in the calf, thigh, or buttock during effort due to exercise-induced ischemia and that resolved  $\leq 10$  minutes of rest.<sup>12,13</sup>

**Laboratory measurements.** The ankle-brachial index (ABI) was measured manually at rest. Self-reported MWD was noted before the treadmill test by patient interview. Thereafter, the treadmill test was performed with a 10% grade and 3.2 km/h speed under medical supervision.<sup>14,15</sup> Patients were blinded to the distance and time walked and were encouraged to perform the test for as long as possible. Treadmill MWD was noted at the end of each test.

**Recommendations for the outdoor stroll.** All experiments took place in a designated public park that was the same as in our previous study.<sup>10</sup> This public park is flat (no hills) and free of motorized vehicle traffic, buildings, and compact trees. During the postprocessing analysis, the use of a map projection of the patient's position during the tests (CartoExploreur, version 3.11.0 build 2.6.6.22, 2006, Bayo Ltd, France) allowed investigators to ensure that patients walked into the right place. The walking surface at the park is stable ground designed for leisure walking. Likelihood of crowding and distracting influences (eg, bicyclists, baby carriages) during the study was very limited because footpaths are sufficiently large and the park is sufficiently big to avoid crowding. Because experiments took place during the week, the park was not busy with too many people.

Recommendations for the stroll were extensively described in our previous study.<sup>10</sup> In brief, PAD patients were recommended to:

1. Rest for 10 minutes before starting to stroll when arriving at the park.
2. Walk at a leisurely pace for a minimum of 1 hour (including stops).
3. Stop when necessary in case of intense claudication pain rather than voluntarily slow down to avoid pain when walking discomfort occurred (onset of pain), with no recommendation about a minimal or maximal duration of the stops.

To ensure data recording quality, a short post-test questionnaire was given by the investigator when patients returned to the hospital. Each patient was asked to report any unexpected external (eg, dogs, bicycles) or personal (eg, urinating, answering a phone call) event(s) that may have led to a walking stop unrelated to limb pain.

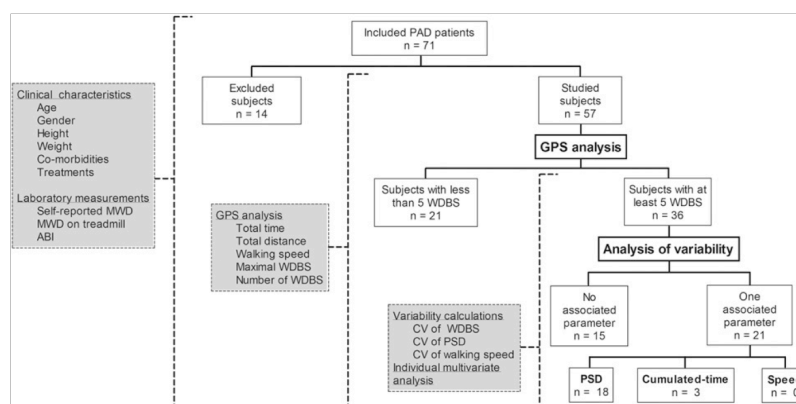
**GPS data recording and processing.** We used the Garmin GPS 60 (Garmin Ltd, Olathe, Kan) to record the stroll. Technical details, validation of the recording method, and data analysis have been previously reported.<sup>10,16</sup> In the present study, stops  $\leq 10$  seconds were removed and incorporated in walking bouts because they were not expected to induce a significant recovery and could artificially increase variability. The parameters recorded for each patient were the total walked distance, the whole duration of the outdoor stroll, the mean walking speed calculated over each walking bout, the number of walking bouts ( $N_{WB}$ ), the various WDBS over each walking bout, and the duration of the stop preceding each walking bout (or previous stop duration [PSD]).

The cumulated-time from the beginning of the stroll (including durations of walking and stopping) was calculated as an indirect estimation of fatigue. Because the final walking bout for the patients corresponded with the arrival to their cars and not necessarily to lower limb pain, both the last walking distance and the walking speed over the final walking bout, as well as the stop duration preceding this final walking bout, were not taken into account for subsequent analysis.

The expression WDBS was used to avoid possible confusion with the MWD observed on the GPS recording ( $MWD_{GPS}$ ).  $MWD_{GPS}$  was the maximal value among the different WDBS values.

**Exclusion criteria.** If any unexpected event was reported on the post-test questionnaire, the patient was excluded from the study. Furthermore, we expected that some patients would not strictly follow the required 10-minute pretest waiting period. After GPS data processing, patients who did not stop for a minimal resting time before the beginning of the stroll were excluded. This minimal resting time was a priori and arbitrarily fixed at 2 minutes.

**Statistical analysis.** All data are expressed as mean (standard deviation) or number and percentage. Between-groups differences were compared using the  $\chi^2$  test, and two-sample  $t$  tests for categoric and continuous variables, respectively. Although we included only patients reporting claudication, we expected that some patients would show a limited number of stops. A minimal  $N_{WB}$  of  $\geq 5$  was arbitrary.



**Fig 1.** Flow diagram of studied patients with peripheral arterial disease (PAD) shows included/excluded patients, subgroups of analyzed participants, and associated computed parameters. *ABI*, ankle-brachial index; *CV*, coefficient of variation; *GPS*, global positioning system; *MWD*, maximal walking distance; *PSD*, previous stop duration; *WDBS*, walking distance between two stops (induced by lower-limb pain).

trarily required to allow for the individual estimation of WDBS variability and further analysis. The magnitude of variability for each parameter was expressed as the coefficient of variation (CV).

A step-by-step multivariate linear regression analysis with stepwise selection was performed to search for a predictor parameter associated with WDBS. In our model, WDBS was the dependent variable. The value for predictor (independent) parameters to enter and stay in the model was set at  $P = .10$ . The predictor parameters included into the model were the negative exponential transformation of walking speed during each walking bout ( $\text{Exp}^{-Y}$ ), the logarithm transformation of PSD (log-PSD), and the cumulated time. The rationales for those choices are presented in the Discussion.

In a multivariate analysis, a positive or negative  $\beta$  value means a positive or inverse relationship between the dependent variable and a predictor (independent) parameter, respectively. The  $\beta$  coefficients were normalized to percentage values and, when significant, were an estimation of the relative participation of the predictor parameter to the variable to be explained by the model.

For all statistical tests, a two-tailed probability level of  $P < .05$  was used to indicate statistical significance. SPSS 15.0 software (SPSS Inc, Chicago, Ill) was used for all statistical analyses.

**Sample size estimation.** Sample size estimation was calculated according to our first goal, which was an estimation of WDBS variability. We hypothesized that the mean (SD) for the CV of WDBS was 50% (30%) and defined the absolute acceptable error for the estimation of mean to 10%. Sample size calculation showed that 36 recordings were required. There is low relationship between self-reported MWD and objective measurements of walking distance.<sup>7-9</sup> Further,  $\text{MWD}_{\text{GPS}}$  is an average of about three times higher than treadmill MWD.<sup>10</sup> Last, because tests

were performed in a public area and were not supervised, we expected that some patients would be excluded due to interfering events or to deviations from the recommendations for the walk. We therefore anticipated that many of the included patients would have  $<5 N_{\text{WB}}$ . Inclusions were performed until we had 36 patients with  $N_{\text{WB}} \geq 5$ .

## RESULTS

As expected, 71 inclusions were required to reach the 36 patients necessary to allow for WDBS variability estimation (Fig 1). Among these 71 PAD patients, 14 were excluded (Table II, right column): 11 for reported stops unrelated to leg pain during the walking stroll (urinating, dizziness, looking at birds) and 3 other patients did not stop for a minimum of 2 minutes before the beginning of the stroll. The remaining 57 studied PAD patients were 47 men and 10 women (Table II, left column). Characteristics of included patients were not significantly different from excluded patients.

**GPS results in included participants.** Table III presents patient characteristics as well as GPS computed results in two subgroups of PAD patients. After the analysis of GPS recordings, among the 57 studied PAD patients, 21 had  $N_{\text{WB}} < 5$  and 36 had  $N_{\text{WB}} \geq 5$ . As expected, the 36 patients with  $N_{\text{WB}} \geq 5$  were more severe in term of self-reported MWD, treadmill MWD, and ABI than the 21 patients with  $N_{\text{WB}} < 5$ . In agreement with these laboratory measurements of walking capacity, GPS computed results showed that  $\text{MWD}_{\text{GPS}}$  was higher in patients with  $N_{\text{WB}} < 5$  compared with patients with  $N_{\text{WB}} \geq 5$  (Table III).

**Variability result.** All further results are calculated only in the 36 patients with  $N_{\text{WB}} \geq 5$ . Table IV presents results for individual WDBS, walking speed, and PSD. The mean WDBS observed for each patient was 295 (226) meters. WDBS was variable within each stroll in all patients.

**Table II.** Characteristics of studied and excluded patients with peripheral arterial disease (PAD)

| Characteristic                       | Studied     | Excluded    | P <sup>a</sup> |
|--------------------------------------|-------------|-------------|----------------|
| PAD patients, No.                    | 57          | 14          |                |
| Age, mean (SD), y                    | 59 (11)     | 61 (11)     | .67            |
| Female sex, No. (%)                  | 10 (18)     | 13 (7)      | .34            |
| Height, mean (SD), cm                | 168 (6)     | 168 (7)     | .87            |
| Weight, mean (SD), kg                | 79 (14)     | 82 (14)     | .43            |
| Comorbidities, (history of), No. (%) |             |             |                |
| Coronary disease                     | 13 (23)     | 4 (29)      | .65            |
| Stroke                               | 2 (4)       | 0           | .48            |
| Chronic bronchitis                   | 9 (16)      | 0           | .11            |
| Vascular surgery                     | 21 (37)     | 2 (14)      | .11            |
| Medications, No. (%)                 |             |             |                |
| Anticholesterol                      | 45 (79)     | 11 (79)     | .87            |
| Oral antidiabetic                    | 11 (19)     | 3 (21)      | .87            |
| Insulin                              | 3 (5)       | 2 (14)      | .45            |
| Antihypertensive                     | 33 (58)     | 8 (57)      | .88            |
| -blocker                             | 19 (33)     | 5 (36)      | .88            |
| Antiplatelet                         | 53 (93)     | 13 (93)     | .85            |
| Anticoagulant                        | 1 (2)       | 1 (7)       | .49            |
| Vasodilator                          | 23 (40)     | 3 (21)      | .35            |
| Self-reported MWD, mean (SD), m      | 449 (517)   | 464 (535)   | .93            |
| MWD-TT, mean (SD), m                 | 174 (104)   | 168 (92)    | .85            |
| Lowest rest ABI, mean (SD)           | 0.66 (0.19) | 0.54 (0.20) | .06            |

ABI, Ankle-brachial index; MWD, maximal walking distance; SD, standard deviation; TT, treadmill test.

<sup>a</sup>P values represent <sup>2</sup> for categoric variables and two-sample *t* test for continuous variables.

Indeed, mean CV of WDBS was 43% (28%). Extreme individual values for WDBS variability were 10% and 123%.

The mean individual walking speed throughout the stroll was 3.79 (0.67) km/h. Contrary to WDBS, speed was relatively constant throughout the stroll for each patient. The mean individual CV of speed among the different bouts was 7% (range, 1%-17%).

The mean PSD in these 36 patients was 2.1 (1.8) minutes. Most patients had short stops (< 3 minutes), whereas one patient showed multiples stops that lasted almost 10 minutes each. The durations of stops widely varied during the stroll for each patient. The mean individual CV for PSD was 57% (35%) and superior to 22 in all the patients.

**Individual multivariate regression analysis.** Fig 2 presents individual results for the multivariate analysis in the 36 patients with  $N_{WB} \geq 5$ . As shown, log-PSD was found in 16 patients as the predictor parameter in the multivariate analysis. Cumulated time was associated to WDBS in five other patients. Walking speed was never found as a predictor parameter to WDBS. In the remaining 15 patients, no significant correlation was found, either as a result of low *r* values despite multiple walking bouts or of an insufficient number of bouts to reach significance despite a high *r* value (Fig 2). This is also why the multivariate analysis was not performed in patients with  $N_{WB} < 5$ .

An example of GPS recording with PSD as the predictor parameter is presented in Fig 3. As shown, the WDBS to

**Table III.** Characteristics of peripheral arterial disease patients (PAD) and global positioning system-computed results in the PAD patients showing < 5 walking bouts ( $N_{WB}$ ) and those showing at  $\geq 5$   $N_{WB}$  during the stroll

| Characteristic                       | $N_{WB}$ per patient, No. |             | P <sup>a</sup> |
|--------------------------------------|---------------------------|-------------|----------------|
|                                      | 5                         | $\geq 5$    |                |
| PAD patients, No.                    | 21                        | 36          |                |
| Age, mean (SD), y                    | 61 (11)                   | 58 (10)     | .23            |
| Female sex, No. (%)                  | 5 (24)                    | 5 (14)      | .34            |
| Height, mean (SD), cm                | 166 (5)                   | 168 (7)     | .23            |
| Weight, mean (SD), kg                | 74 (11)                   | 81 (15)     | .06            |
| Comorbidities, (history of), No. (%) |                           |             |                |
| Coronary disease                     | 5 (24)                    | 8 (22)      | .89            |
| Stroke                               | 1 (5)                     | 1 (3)       | .70            |
| Chronic bronchitis                   | 4 (19)                    | 5 (14)      | .61            |
| Vascular surgery                     | 6 (29)                    | 14 (39)     | .43            |
| Treatments, No. (%)                  |                           |             |                |
| Anticholesterol                      | 16 (76)                   | 29 (81)     | .70            |
| Oral antidiabetic                    | 4 (19)                    | 7 (19)      | .97            |
| Insulin                              | 2 (10)                    | 1 (3)       | .27            |
| Antihypertensive                     | 11 (52)                   | 23 (64)     | .39            |
| -blocker                             | 7 (33)                    | 12 (33)     | 1.00           |
| Antiplatelet                         | 20 (95)                   | 34 (94)     | .90            |
| Anticoagulant                        | 0                         | 1 (3)       | .44            |
| Vasodilator                          | 9 (43)                    | 15 (42)     | .93            |
| Self-reported MWD, mean (SD), m      | 690 (649)                 | 315 (374)   | .01            |
| MWD by TT, mean (SD), m              | 223 (150)                 | 145 (48)    | .01            |
| Lowest rest ABI, mean (SD)           | 0.73 (0.13)               | 0.62 (0.20) | .03            |
| GPS computed results, mean (SD)      |                           |             |                |
| $N_{WB}$                             | 3 (2)                     | 13 (7)      | .001           |
| Stroll duration, min                 | 59.0 (8.6)                | 65.5 (11.1) | .02            |
| Stroll total distance, m             | 3408 (824)                | 2819 (1036) | .02            |
| Walking speed, km/h                  | 3.79 (0.51)               | 3.78 (0.65) | .92            |
| MWD by GPS, m                        | 1905 (1189)               | 550 (621)   | .001           |

ABI, Ankle-brachial index; GPS, global positioning system; MWD, maximal walking distance; TT, treadmill test.

<sup>a</sup>P values represent <sup>2</sup> test for categoric variables and two-sample *t* test for continuous variables.

PSD relationship is clearly not linear, underlying the interest of the logarithm transformation.

## DISCUSSION

To our knowledge, this is the first application study using GPS to approach new insights (walking speed, cumulated time, PSD) into walking impairment in PAD patients during a free-living, community-based outdoor walking. The 43% CV found for the short-term variability of WDBS during each stroll is larger than the 15% to 30% test-retest CV generally reported for MWD in PAD patients.<sup>1-6</sup> We believe this is also the first study to report PSD as the dominant parameter associated to WDBS.

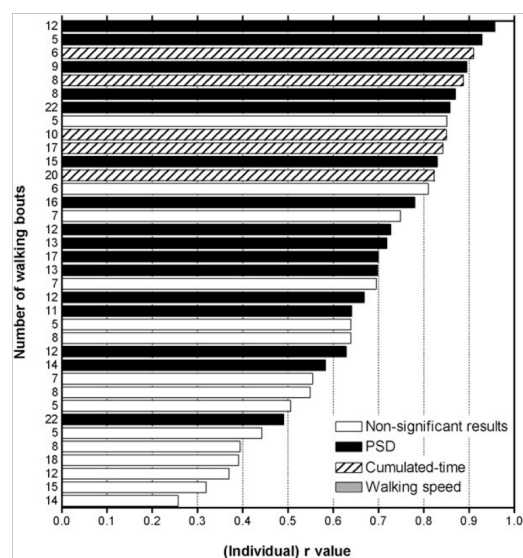
Previous studies have shown the GPS technique is an accurate tool to detect walking and stopping bouts and estimate the walking speed and the distance between two stops in healthy participants.<sup>16</sup> Afterward, we showed that



**Table IV.** Results from global positioning system recording in the 36 peripheral arterial disease patients showing  $\geq 5$  walking bouts during the stroll

| Variable                      | Mean (SD)   | Range     |
|-------------------------------|-------------|-----------|
| WD between pain-induced stops |             |           |
| Individual means, m           | 295 (226)   | 78-1158   |
| Individual CV, %              | 43 (28)     | 10-123    |
| Walking speed over each bout  |             |           |
| Individual means, km/h        | 3.79 (0.67) | 2.54-5.39 |
| Individual CV, %              | 7 (4)       | 1-17      |
| Previous stop duration        |             |           |
| Individual means, min         | 2.1 (1.8)   | 0.4-9.2   |
| Individual CV, %              | 57 (35)     | 22-209    |

CV, Coefficient of variation; SD, standard deviation; WD, walking distance.

**Fig 2.** Individual results from the multivariate analysis are shown for the 36 participants with  $\geq 5$   $N_{WB}$ . One bar represents one participant, bars are presented in decreasing values of absolute  $r$ . PSD, Previous stop duration. The absolute  $r$  value is presented for each individual ( $r$  is negative for cumulated time) and the explanatory parameter found in the multivariate analysis (specific color or pattern). Facing each bar is the number of walking bouts during the stroll. Note that white bars represent nonsignificant results and that walking speed was never found as an explanatory parameter to WDBS.

$MWD_{GPS}$  is significantly correlated with the MWD measured on treadmill ( $r = 0.81$ ) in PAD patients with intermittent claudication.<sup>10</sup>

The log-PSD in most patients was the predictor parameter for WDBS. Although the time required for physiologic parameters to recover is longer if workload is increased,<sup>17,18</sup> when PAD patients walk to maximal claudication pain on a treadmill, dissipation of pain during recovery is similar whether the preceding treadmill exercise is

performed at relatively low or high intensities.<sup>19</sup> Inversely, a plateau of forthcoming WDBS is expected when PSD is increased, hence the use of log-PSD in the analysis. It is expected that if patients start walking immediately after pain relief, physiologic parameters are not normalized and that the next walking bout will have to be stopped sooner. This is consistent with the observations that the distance walked at usual speed until a predefined 1-minute stop is higher than the second distance performed after the stop.<sup>20,21</sup>

In the present study, a negative relationship was observed in 5 patients between WDBS and cumulated time. Assuming that cumulated time is an acceptable tool for fatigue estimation, our interpretation is that fatigue was interfering with the walking capacities in these patients. More than half of PAD patients walk 3.2 km/w;<sup>22</sup> therefore, a 1-hour stroll for most PAD patients, even at a leisurely pace, represents an unusually long walk in itself. Longer walks (eg, 2 hours) would probably have decreased the proportion of patients with  $N_{WB} = 5$ , but we estimated that many patients would not have completed such a long walk.

The underlying mechanisms of fatigue are still debated<sup>23-25</sup> and induce unstable and slowed gait rhythm.<sup>26</sup> PAD patients respond to claudication pain by reducing preferred walking speed and step length.<sup>27</sup> The effect of fatigue during prolonged walking has not been studied in PAD patients.

A negative exponential relationship exists between MWD and treadmill exercise intensity.<sup>3,19,28</sup> The average speed in our volunteers corresponded with the segment of this relationship where any small intensity (speed) change should result in a wide distance (WDBS) change.<sup>3</sup> Then, walking speed could be expected to be a dominant predictor parameter of WDBS, and walking speeds should show an inverse relationship to WDBS (positive value for  $\text{Exp}^{-V}$ ). This was not the case. The absence of a relationship between walking speed and WDBS does not mean that if our patients had voluntarily walked fast, their WDBS would not have decreased. We assume that the absence of negative relationship between WDBS and speed resulted from the patients' average speed being relatively stable throughout the stroll or from fatigue (and the potentially associated decreased speed) interfering with the inverse relationship searched between WDBS and speed.

**Study limitations.** From a statistical point of view, the number of walking bouts per participant was small and thus allowed at best for only one parameter per participant to be statistically associated with WDBS. Additional data for each volunteer could have been obtained by having the patients perform multiple strolls. However, this would have mixed two different concepts—short-term variability and test-retest variability—and would not have allowed for the analysis of the effect of cumulated time on walking capacity. It could be suggested that cumulated time is only a mediocre way of estimating fatigue and that there is no necessary, linear association between this and WDBS. Lastly, the statistical association of WDBS with the parameters studied

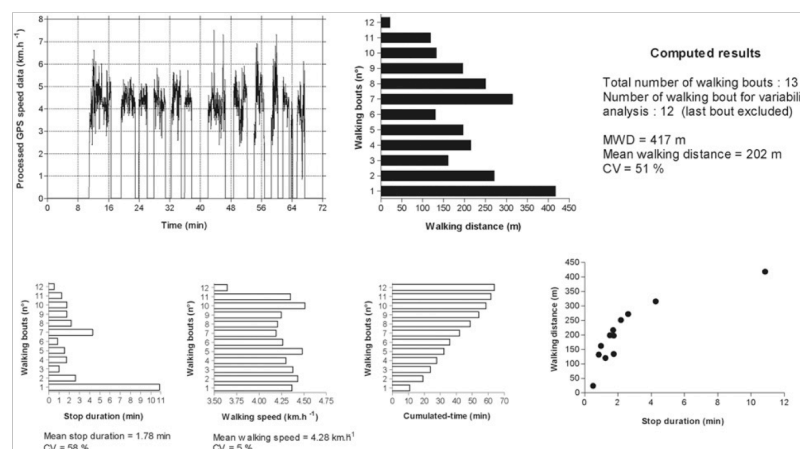


Fig 3. A typical example of a global positioning system (GPS) recording and computed results are shown for one patient with peripheral arterial disease. CV, Coefficient of variation; MWD, mean walking distance.

is not evidence for the causal relationship between the variables.

From a technical point of view, we only studied the distance to pain-induced stops and not the distance to the onset of limb discomfort. Nevertheless, walking distance at maximal leg pain is generally preferred to distance at the onset of pain.<sup>2,3,5</sup> Unexpected external events led to the exclusion of 3 patients. We cannot totally rule out that other patients did not report them, thereby amplifying their WDBS variability. At times, this might also be the reason for the absence of association between WDBS and studied parameters. Nevertheless it is unlikely that unreported events, if present, changed the dominant parameter observed because they would interfere in the same way over all the studied parameters. Many potential confounding parameters, including rain, wind, air temperature, and changes in the level of ground, were not studied. Nevertheless, rainy and windy days were avoided for the present study, which was performed in a flat park.

From a clinical point of view, there is no doubt that many pathophysiologic mechanisms could account for the short-term WDBS variability and remain to be studied. Lastly, our patients' WDBS variability, and potential determinants of WDBS, might not necessarily reflect that of less severe patients. This is true, but our goal was to have a sufficient number of stops for each patient to allow the CV calculation.

**Clinical perspectives.** Although the use of the GPS technique in medicine is embryonic, particularly for vascular practice, the present study, together with our previous study,<sup>10</sup> provides interesting clinical perspectives. A GPS recording could enable vascular specialists for whom treadmill testing is not readily accessible to have an objective evaluation of a patient's MWD, beyond the subjective estimation through patient interview. Further, a number of original parameters related to the walking capacity can be

processed, including walking speed (at the bout and stroll level) or stopping duration, which are not readily accessible even for physicians who do have a treadmill. Finally, the GPS technique could be used as a Holter monitor in PAD patients performing home-based exercise rehabilitation programs. GPS might be helpful in determining compliance during such programs and could be used to change and adapt the training load throughout the rehabilitation program.

## CONCLUSIONS

The MWD is an index of the severity of PAD and a key point for the therapeutic choices to be proposed to PAD patients. In addition to the well-known test-retest variability of MWD, we show here that a wide short-term variability of WDBS exists during a single stroll. This wide short-term variability of walking capacity may contribute to the difficulties experienced by patients with arterial claudication to estimate their so-called MWD at a usual pace and could at least partly explain the low concordance between estimated and measured MWD in PAD patients.<sup>7-9</sup>

In most patients, WDBS is inversely related to the duration of the stop that precedes each walking bout. This suggests that early restart of walking, after pain relief, leads to shortened walking capacity probably due to incomplete ischemic recovery from the preceding walk. Whether PAD patients with claudication should be asked to wait for a minimal duration after the time of pain relief is an interesting issue for future research studies.

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## AUTHOR CONTRIBUTIONS

Conception and design: ALF, BN, GM, JLS, GL, PA

Analysis and interpretation: ALF, BN, GM, PA

Data collection: ALF, BN, TS, PA

Writing the article: ALF, PA

Critical revision of the article: ALF, BN, GM, TS, JLS, GL, PA

Final approval of the article: ALF, BN, GM, TS, JLS, GL, PA

Statistical analysis: ALF, GM, PA

Obtained funding: BN, PA.

Overall responsibility: PA

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## Chest tcpO<sub>2</sub> changes during constant-load treadmill walking tests in patients with claudication

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### Abstract

Changes in chest transcutaneous-pO<sub>2</sub> at rest ( $\Delta\text{tcpO}_2$ ) mimic absolute changes in arterial-pO<sub>2</sub> during moderate exercise, although the absolute starting values may dramatically differ. We retrospectively studied 485 patients (group 1), prospectively studied 292 new patients (group 2) and estimated the intra-test and the test–retest reproducibility of  $\Delta\text{tcpO}_2$  during constant-load treadmill tests: 3.2 km h<sup>-1</sup>, 10% grade, using the cross correlation technique. Patients were classified into groups according to their best fit to nine pre-defined mathematic models. Respectively, 71% and 76% of patients of groups 1 and 2 fitted with a model showing a  $\Delta\text{tcpO}_2$  increase during and a decrease following exercise. Another 18% and 12% of the patients of groups 1 and 2 respectively fitted with a model that showed an abrupt decrease at exercise onset, a slow increase during walking and an overshoot in the recovery period, referred here as a walking-induced transcutaneous hack (WITH) profile. The mean  $r_{\text{max}}$  value for the cross-correlation analysis was  $0.919 \pm 0.091$  and  $0.800 \pm 0.129$  for intra-test and test–retest reproducibility. Most profiles show the expected  $\Delta\text{tcpO}_2$  exercise-induced increase. Future studies are needed to confirm and explain the WITH profiles that we found, and screen for potential-associated diseases.

Keywords: exercise testing, physiopathology, methods, exercise intolerance, classification

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## 1. Introduction

Lower limb claudication can result from various diseases such as peripheral artery disease, exercise-induced hypoxemia or lumbar spine stenosis. Hypoxemia can result in limb pain while walking sometimes without associated dyspnoea (Killian *et al* 1992). When occurring as a result of systemic exercise-related hypoxemia, limb pain is likely to fulfil vascular-type characteristics. Pulmonary disease and vascular disease share a number of common risk factors (age, overweight, tobacco). All patients with pulmonary disease do not have hypoxemia but 15% of patients with peripheral artery disease (PAD) (von Kemp *et al* 1997, Heidrich 2004) or undergoing cardiac surgery (Clough *et al* 2002) have pulmonary disease. Thus detecting abnormal arterial  $pO_2$  response to exercise might be of interest in patients with claudication as a potential patho-physiological mechanism mimicking or aggravating claudication of arterial origin.

The  $tcpO_2$  technique, although not a primary care technique, is used in patients with claudication to argue for a vascular origin of pain, detect buttock ischemia or estimate the effect of rehabilitation programmes (Caillard *et al* 1990, Abraham *et al* 2003, 2005). The transcutaneous oxygen pressure ( $tcpO_2$ ) technique is an old technique initially proposed in neonates to non-invasively estimate arterial  $pO_2$ . Although a complex and time-consuming technique as compared to pulse oxymetry (saturometry), it is expected of advantage as compared to saturometry to detect abnormal arterial oxygen changes at exercise. Indeed, keeping in mind the sigmoid relationship between oxygen pressure and oxygen saturation in human blood, arterial saturation may remain in normal limit despite a significant decrease in arterial  $pO_2$ , specifically in patients with normal arterial  $pO_2$  at rest. Further intra-arterial blood sampling cannot be proposed as a screening technique of eventual abnormal  $pO_2$  changes in all patients suffering exercise intolerance.

There is multiple evidence that chest  $tcpO_2$  changes at rest ( $\Delta tcpO_2$ ) mimic the changes in arterial  $pO_2$  at rest during mild or moderate exercise (McDowell and Thiede 1980, Hughes *et al* 1984, Hutchison *et al* 1987, Sridhar *et al* 1993, Brudin *et al* 1994, Carter and Banham 2000, Planes *et al* 2001) despite the presence of an unpredictable transcutaneous gradient and provided that the changes are relatively slow (90% time response of  $tcpO_2$  being  $\sim 20$  s). During constant-load exercise, if one aims at estimating only the absolute changes in arterial  $pO_2$  at rest overtime regardless of the initial starting absolute value, then the transcutaneous technique is accurate. When used during exercise in patients with claudication, limb  $tcpO_2$  changes are usually analysed in comparison to  $tcpO_2$  changes observed with a reference probe on the chest, either by dividing the limb  $tcpO_2$  value by the chest  $tcpO_2$  value (Osmundson *et al* 1988, Arnold *et al* 1993) or subtracting chest changes from limb changes (Abraham *et al* 2003, 2005, Gelis *et al* 2009). In both cases, the potential information available in the chest signal itself is lost. To the best of our knowledge, specific analysis of chest  $\Delta tcpO_2$  profiles in patients undergoing treadmill walking tests has never been reported. We hypothesized that analysing  $\Delta tcpO_2$  changes could provide new insights into the mechanisms of exercise intolerance in patients reporting claudication provided that an easy and observer-independent classification of  $\Delta tcpO_2$  changes can be performed, that the classification is reliable and that  $\Delta tcpO_2$  changes are specific of each patient's response to exercise.

We performed a series of experiments to: (1) propose a classification of  $\Delta tcpO_2$  profiles based on a cross-correlation observer-independent approach, using an excel spreadsheet, (2) test the reliability of the distribution of  $\Delta tcpO_2$  profiles types with this technique in a population different from the initially studied group, (3) evaluate the intra-test reproducibility of  $\Delta tcpO_2$  changes using two probes to ascertain that changes observed are independent of the probe position on the chest, and (4) analyse the reproducibility of  $\Delta tcpO_2$  profiles in test-retest

experiments to check whether or not each profile is a reproducible characteristic of each patient's response to the walking test.

## 2. Methods

### 2.1. Experiment 1

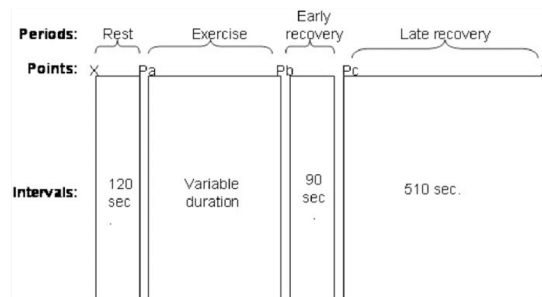
**2.1.1. Population.** We retrospectively analysed all consecutive 485 different patients referred for exercise-induced vascular-type claudication and those who had undergone a standard treadmill walking test with tcpO<sub>2</sub> recording including a chest probe over a 3 years period, starting April 2006. Vascular-type claudication is defined as a pain in the lower limb that is absent at rest, is induced by exercise and disappears within 10 min when exercise is stopped. Results from non-invasive vascular investigations (ankle to brachial systolic blood pressure index: ABI), medical history, treatments were retrieved from patient's files, but were not made known at the time of exercise test analyses.

**2.1.2. Exercise test.** The treadmill tests started with a 120 s resting period in the standing position. Then, tests were performed using a 10% slope and a constant 3.2 km h<sup>-1</sup> speed (reached within 1 min to facilitate the patient's adaptation). Patients were encouraged to perform the test for the longest time possible. Exercise was discontinued at the patient's request (limiting symptoms), or in the absence of limiting symptoms, after a total walking duration of 20 min. A 10 min recovery period was observed in the standing position after the end of the exercise test.

**2.1.3. Transcutaneous recording.** After a 20 min resting period, patients were installed in a room with a temperature of  $21 \pm 2$  °C. Measurements were performed using the TINA TCM400 tcpO<sub>2</sub> devices (Radiometer, DK). A one-point calibration to air was performed three times before each experiment. The temperature of the probe was set to 44.5 °C to allow maximal local vasodilatation, thereby decreasing the arterial to skin surface oxygen pressure gradient. Afterwards, the tcpO<sub>2</sub> measurements were automatically temperature-corrected to 37 °C by the TINA device. The electrode was placed over the right scapula on the back, except in patients that have had a right thoracotomy. In this case, the probe was placed on the left side.

A pre-test heating period of 15 to 20 min with the patient standing on the treadmill was required to allow stable tcpO<sub>2</sub> resting values to be reached and local heating of the skin. The data were recorded every 2 s throughout the test and transferred to a spreadsheet on personal computers for analysis. From the spreadsheet of each patient, we noted the exact duration of exercise as well as the average absolute tcpO<sub>2</sub> value over the resting period (REST). Then the REST value was subtracted from all data points and results expressed as the difference from baseline ( tcpO<sub>2</sub>: mmHg).

**2.1.4. Construction of the models.** From previous experiments, we noted that most changes in tcpO<sub>2</sub> lied within -10 and +15 mmHg from the REST value and that end-recording values were on the average 10 mmHg higher than the REST values. Then, for each patient, nine different models were automatically generated using a home-made program that constructed models according to the presence or absence and to different positions of the maximal (+15) and minimal (-10) values in the model. The models all started with a 2 min zero value from the point X and ended at Z = +10; see figure 1. The first point of interest Pa was fixed at



**Figure 1.** Diagram of the different intervals defined for the models to mimic the periods of treadmill tests. See the text for further details.

2 min and Pb at 10 min before Z. The Pa–Pb interval adapted to the exercise duration of each patient. The Pb-to-Z interval was arbitrarily divided into a first 90 s Pb–Pc interval followed by a 510 s Pc–Z interval since we previously noted that when tcpO<sub>2</sub> increased during exercise, the highest test value was generally observed approximately one and a half minute after the end of exercise.

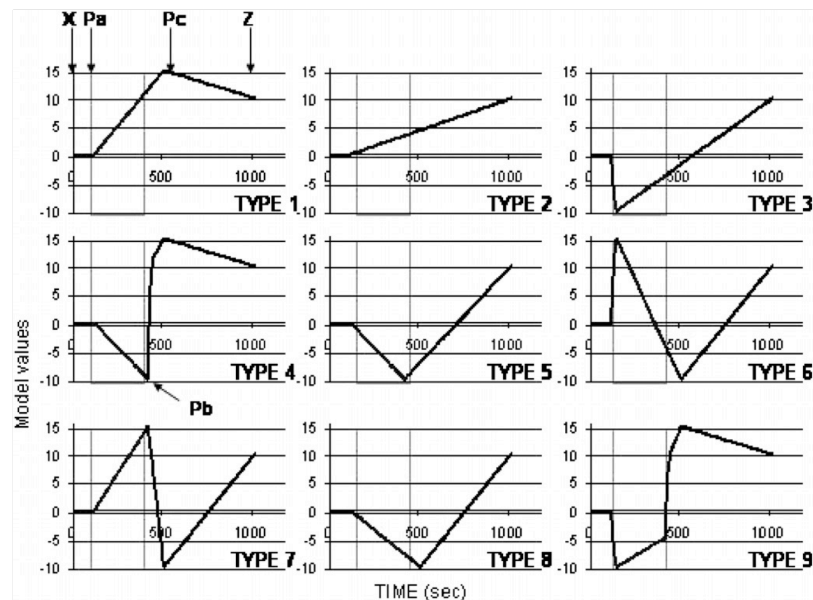
The program automatically generated models according to various positions of the maximal and minimal values at Pa, Pb or Pc. An example of the nine models generated for exercise durations of 6.33 min is presented in figure 2. For each patient, the program produced a nine-column spreadsheet, one for each model, with one point every 2 min to fit with the recording sample rate for tcpO<sub>2</sub>. A special function was included in the program to smooth the generated curves with a log function to account for the half-time response of the tcpO<sub>2</sub> probes to abrupt changes in PO<sub>2</sub> (Grouiller *et al* 2006).

**2.1.5. Analysis of the data.** For each patient, a comparison of each subject's tcpO<sub>2</sub> changes to each of the different models was performed with the cross correlation technique using an Excel sheet with cross correlation over  $\pm 15$  data points. In the cross correlation analysis, the highest 'r' correlation coefficient ( $r_{\max}$ ) is equal to Pearson's coefficient. All patient curves were compared to models 1 and 2 but a minimal decrease at rest of 2 mmHg was required to compare the patient profile to models 3 to 9. This was performed to account for eventual small short-lived physiological or technical changes in recorded transcutaneous values or for a progressive downward drift of tcpO<sub>2</sub>, in order to avoid misclassification. Thereafter, patients were classified by groups according to the number of the models to which their tcpO<sub>2</sub> profile showed the highest  $r_{\max}$  value (best- $r_{\max}$ ). A best- $r_{\max}$  value > 0.650 was arbitrarily fixed to define a good fitting.

## 2.2. Experiment 2

What we aimed here was to estimate whether the group distribution of the different tcpO<sub>2</sub> profile types observed in experiment 1 was found comparable in another group.

**2.2.1. Population.** A prospective analysis was carried out on all consecutive different patients referred for exercise-induced vascular-type lower limb pain and those who had undergone a



**Figure 2.** Example of nine automatically generated models with an exercise duration of 304 s. Gray squares are exercise periods. And examples of the points of interests X, Z, Pa, Pb and Pc.

standard treadmill walking test with tcpO<sub>2</sub> recording at the chest level. As in experiment 1, results from non-invasive vascular investigations (ankle to brachial systolic blood pressure index: ABI), medical history, treatments were retrieved from the patient's files, but were not made known at the time of exercise test analyses.

**2.2.2. Exercise test and transcutaneous recording.** The treadmill tests and tcpO<sub>2</sub> recordings were performed as in experiment 1. We prospectively included all new patients referred to the laboratory in the period: April 2009 to February 2010.

**2.2.3. Analysis of the data.** Fitting of the values was performed by comparing recorded values to the same nine different automatically generated models as in experiment 1. As in experiment 1, a  $\text{best-}r_{\text{max}} > 0.650$  was used to define a good fitting and the classification repeated for patients with a  $\text{best-}r_{\text{max}} > 0.650$ . Pearson's chi-square test was used to compare the distribution of profiles among the four most-represented groups of the present population with the distribution observed in experiment 1.

**2.2.4. Sample size estimation.** We aimed to have at least ten patients in each of the four most represented groups even in patients with  $\text{best-}r_{\text{max}} > 0.650$  to allow for the chi-square comparison with our previous results. According to the profile-type distribution, confidence

intervals and proportion of patients with prevalence  $\text{best-}r_{\max} > 0.650$  previously observed, the minimal number of subjects to be analysed in experiment 2 was 250.

### 2.3. Experiment 3

**2.3.1. Population.** This experiment was carried out with the hypothesis that the absolute starting value might differ from one probe position to another, but that the profiles at the level of the two probes will be comparable. We aimed to confirm that  $\text{tcpO}_2$  changes are independent of starting  $\text{pO}_2$  absolute value and thus of the exact probe position.

**2.3.2. Exercise test and transcutaneous recording.** Exercise testing and transcutaneous  $\text{pO}_2$  recording were performed as in experiments 1 and 2 but a second probe was positioned on the chest, at least 5 cm from the first probe.

**2.3.3. Analysis of the data.** The cross correlation was performed over  $\pm 15$  data points. In this experiment, values for  $r_{\max} > 0.8$ ,  $r_{\max}$  between 0.5 and 0.8, and  $r_{\max} \leq 0.5$  were used to define excellent, satisfactory and unsatisfactory profile reproducibility, respectively.

**2.3.4. Sample size estimation.** We estimated the mean Pearson coefficient of correlation to be 0.85 or more with a type 1 error of 5% and a power of 90% (two-sided hypothesis). The minimal number of subjects to be analysed was 10 (Machin *et al* 1997).

### 2.4. Experiment 4

**2.4.1. Population.** The reproducibility of the chest  $\text{tcpO}_2$  profile during walking was studied through test–retest recordings separated by a minimum of 1 month. In this test–retest prospective study a signed informed consent was obtained from each patient.

**2.4.2. Exercise test and transcutaneous recording.** Exercise testing and transcutaneous  $\text{pO}_2$  recording were performed as in the other experiments. It should be noted that the exact position of the probe to be used for the second test was not recorded during the first test.

**2.4.3. Analysis of the data.** The data analysis and classification of the quality of the results were performed as for experiment 3 (see section 2.3.3).

**2.4.4. Sample size estimation.** We estimated the mean  $r_{\max}$  to be 0.75 or more with a type 1 error of 5% and a power of 90% (two-sided hypothesis). The minimal number of subjects to be analysed was 15 (Machin *et al* 1997).

### 2.5. Ethical considerations

The protocols were approved by the ethic's committee and conform to Helsinki Declaration. As observational studies, no informed consent was required from patients in experiments 1 and 2. The prospective studies presented in experiments 3 and 4 were performed as specific analyses of the 'Evaluation Objective des Ischémies Proximales' (EOIP) study; NIH database: NCT00152737, and a signed informed consent was obtained from each patient.

### 2.6. Statistical analysis

Data management and cross correlation were performed with an Excel spreadsheet. Statistical analysis for *t*-tests and chi-square tests were carried out with SPSS V15.0. Results are expressed in mean  $\pm$  SD. For all statistical tests, a two-tailed probability level of  $P < 0.05$  was used to indicate statistical significance. Non-significant results are reported N.S.

## 3. Results

### 3.1. Experiment 1

The patients studied were 420 males/65 females, aged  $61.4 \pm 11.1$  years, height  $169 \pm 8$  cm, weight  $77 \pm 14$  kg. The lowest (right or left) measurable ankle to brachial index was  $0.80 \pm 0.24$ . Co-morbid conditions included history of vascular surgery ( $n = 146$ ), diabetes mellitus ( $n = 80$ ), coronary disease or cardiac surgery ( $n = 85$ ), history of minor stroke or carotid surgery ( $n = 47$ ), and chronic pulmonary disease ( $n = 30$ ). Treatments included anti-platelet or anti-coagulant drugs ( $n = 387$ ), cholesterol-lowering agents ( $n = 266$ ), converting enzyme inhibitors or sartans ( $n = 182$ ), beta blockers ( $n = 88$ ), anti-diabetic agents ( $n = 80$ ), anti-hypertensive drugs ( $n = 64$ ), and broncho-dilators ( $n = 20$ ). On the average, the maximal walking distance on treadmill over the whole group was  $364 \pm 326$  m. All patients walked at least 1.5 min. On treadmill, 395 patients could not complete the 20 min of the test and showed exercise limitation. Among the 90 patients who completed the 20 min of the test, 46 were completely asymptomatic and 44 had non-limiting claudication.

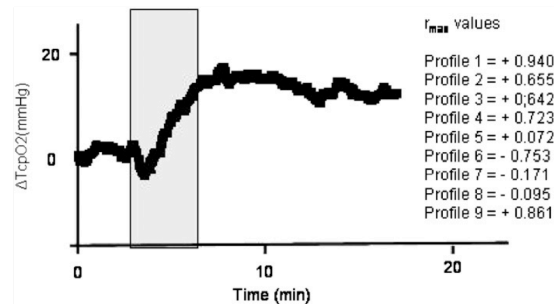
The chest tcpO<sub>2</sub> REST value was  $66.8 \pm 12.4$  mmHg. Figures 3 and 4 show examples of different profiles and of cross-correlation coefficients obtained. Figure 5 shows the distribution of best- $r_{\max}$  values in the population. The median best- $r_{\max}$  among the 485 patients was 0.870. Most of the low best- $r_{\max}$  values resulted from patients showing almost flat tcpO<sub>2</sub> profiles, some others from patients who showed ample, apparently random, oscillations of tcpO<sub>2</sub>. As shown in table 1, four models (1, 2, 4 and 9) were observed in 94.8% of the 485 patients and the models rarely found were often those for which the best- $r_{\max}$  was low. Thereafter, in patients with best- $r_{\max} > 0.650$ , more than 97% of the patients were classified into only four groups. Among the four most represented groups, more than half (60.4%) of the 419 patients were kept in group 1.

### 3.2. Experiment 2

The studied patients were 238 males/54 females, aged  $63.6 \pm 11.51$  years, height  $169 \pm 8$  cm, weight  $76 \pm 15$  kg. The lowest (right or left) measurable ankle to brachial index was  $0.77 \pm 0.24$ . Co-morbid conditions included history of aortic or lower limb vascular surgery ( $n = 115$ ), diabetes mellitus ( $n = 67$ ), coronary disease or previous cardiac surgery ( $n = 29$ ), history of minor stroke or carotid surgery ( $n = 11$ ), arthritis ( $n = 15$ ), chronic pulmonary disease ( $n = 12$ ), sciatica or lumbar spine syndrome ( $n = 23$ ) or cancer ( $n = 32$ ). Treatments included anti-platelet or anti-coagulant drugs ( $n = 237$ ), cholesterol-lowering agents ( $n = 192$ ), converting enzyme inhibitors or sartans ( $n = 164$ ), beta blockers ( $n = 83$ ), anti-diabetic agents ( $n = 63$ ), anti-hypertensive drugs ( $n = 29$ ), and broncho-dilators ( $n = 18$ ).

On the average, the maximal walking distance on treadmill over the whole group was  $280 \pm 284$  m. All patients walked at least 1.5 min. On treadmill, 263 of the 292 patients could not complete the 20 min of the test and showed exercise limitation. Of these, although all patients were referred for claudication, 236 reported lower limb pain with ( $n = 35$ ) or without ( $n = 201$ ) non-vascular symptoms such as fatigue dyspnoea or dizziness; the other 27





**Figure 3.** Example of tcpO<sub>2</sub> changes from rest ( tcpO<sub>2</sub>) in a patient performing a 5 min and 4 s (304 s) test. The minimal tcpO<sub>2</sub> for this patient was minus 3 mmHg. The figure shows the different  $r_{\max}$  values obtained for this patient for each of the nine models shown in figure 2. The best- $r_{\max}$  for this patient was observed with profile type 1. Grey squares is the exercise period.

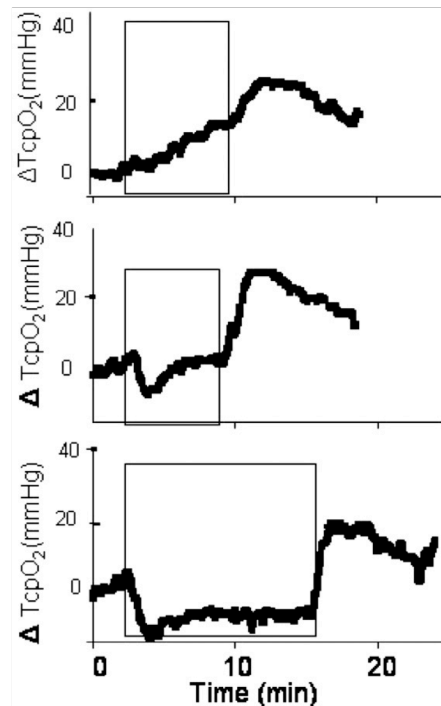
**Table 1.** Number of patients from experiment 1, classified in each of the nine model types with the mean  $\pm$  SD of best- $r_{\max}$  found in the patients within each type before and after exclusion of the 66 patients for which the best- $r_{\max}$  was lower than 0.650.

| Model type | <i>n</i> | All patients ( <i>n</i> = 485) |               | Patients with best- $r_{\max}$ > 0.650<br>( <i>n</i> = 419) |                  |               |
|------------|----------|--------------------------------|---------------|-------------------------------------------------------------|------------------|---------------|
|            |          | %                              | Mean $\pm$ SD | <i>n</i>                                                    | %                | Mean $\pm$ SD |
| 1          | 298      | 61.4 (57.0–65.8)               | 799 $\pm$ 185 | 253                                                         | 60.4 (55.5–65.1) | 864 $\pm$ 80  |
| 2          | 51       | 10.5 (7.3–13.6)                | 795 $\pm$ 146 | 45                                                          | 10.7 (7.9–14.1)  | 836 $\pm$ 75  |
| 3          | 7        | 1.4 (0.6–3.0)                  | 865 $\pm$ 80  | 7                                                           | 1.7 (0.7–3.4)    | 865 $\pm$ 80  |
| 4          | 33       | 6.8 (4.7–9.4)                  | 877 $\pm$ 125 | 32                                                          | 7.6 (5.3–10.6)   | 897 $\pm$ 52  |
| 5          | 4        | 0.8 (0.2–2.1)                  | 777 $\pm$ 110 | 3                                                           | 0.7 (0.2–2.1)    | 824 $\pm$ 68  |
| 6          | 4        | 0.8 (0.2–2.1)                  | 472 $\pm$ 195 | 0                                                           | 0.0 (0.0–0.0)    | –             |
| 7          | 8        | 1.6 (0.7–3.2)                  | 445 $\pm$ 199 | 1                                                           | 0.2 (0.0–1.3)    | 750           |
| 8          | 2        | 0.4 (0.1–1.5)                  | 734 $\pm$ 292 | 1                                                           | 0.2 (0.0–1.3)    | 940           |
| 9          | 78       | 16.1 (12.9–19.7)               | 897 $\pm$ 68  | 77                                                          | 18.4 (14.8–22.4) | 901 $\pm$ 60  |

reported no lower limb limiting symptoms among which 13 reported dyspnoea. Among the 29 patients who could complete the 20 min of the test, 16 were completely asymptomatic and 13 had non-limiting claudication. The chest tcpO<sub>2</sub> value at rest was  $68.3 \pm 12.0$  mmHg.

As shown in table 2, four models (types 1, 2, 4 and 9) were observed in 91.8% of the 292 patients. As in the first population studied, the models rarely found (3, 5, 6, 7 and 8) were mainly those for which the best- $r_{\max}$  was low, specifically for type 6 and 7 models. Thereafter, after exclusion of the 46 patients with low best- $r_{\max}$ , 94% of the patients were classified in one of the four groups corresponding to models types 1, 2, 4 and 9. Among these four most represented groups, 65.4% of the 231 patients were kept in group 1 (best correlation with type 1 profiles). Only 6% of the patients were classified into groups 3, 5, 7 or 8 and no patient was kept in group 6.

No difference was found in the distribution of the patients within the four most frequent groups (1, 2, 4 and 9) as compared to the distribution observed in experiment 1, either before



**Figure 4.** Typical examples of type 1 (upper graph) and type 9 (middle and lower graphs) tcpO<sub>2</sub> changes from rest ( $\Delta \text{tcpO}_2$ ). Grey squares are exercise periods.

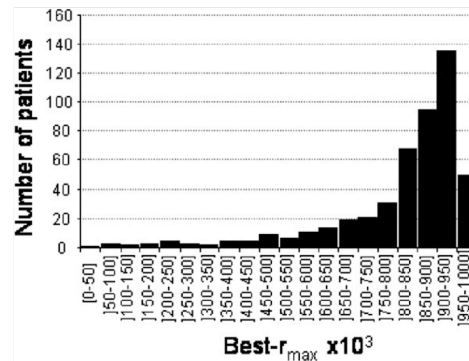
( $\chi^2 = 7.1$ ,  $p = 0.07$ ) and after ( $\chi^2 = 7.3$ ;  $p = 0.06$ ) exclusion of profiles with a best  $r_{\max}$  0.650.

### 3.3. Experiment 3

We tested 15 patients: 14 males and 1 female, aged  $63 \pm 11$  years, height  $167 \pm 8$  cm, weight  $73 \pm 12$  kg. The tcpO<sub>2</sub> value at rest was  $63.9 \pm 7.1$  mmHg on probe 1 and  $63.2 \pm 10.7$  on probe 2 (N.S). Although mean values were not different, on the average the absolute differences in tcpO<sub>2</sub> between the two probes were  $4.4 \pm 6.8$  mmHg. The mean  $r_{\max}$  value for the cross correlation analysis for the 15 analysed pairs of profiles was  $0.919 \pm 0.091$ . Then, a very high correlation exists between the profiles obtained from two different probes in the same patient, despite eventual differences in absolute starting values.

### 3.4. Experiment 4

We studied 31 patients (28 males and 3 females), aged  $63 \pm 11$  years, height  $168 \pm 6$  cm, weight  $73 \pm 13$  kg. All these patients had stable claudication and had no surgery or change

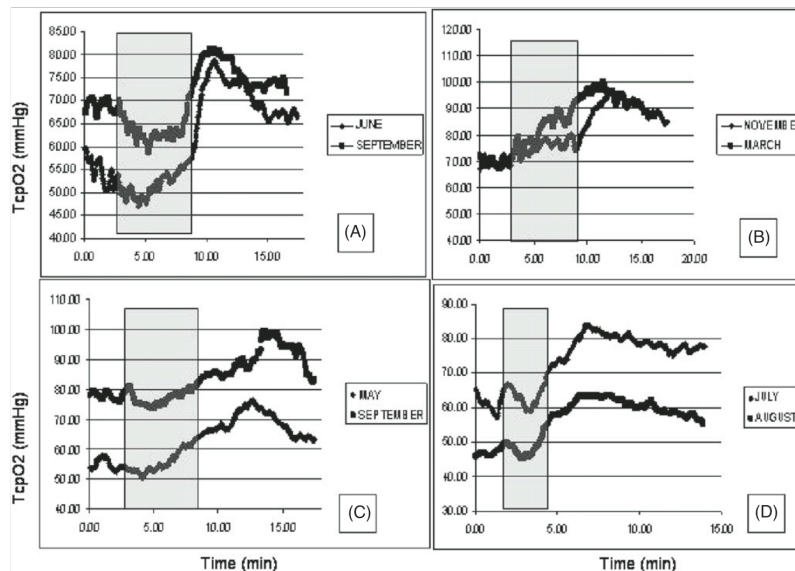


**Figure 5.** The distribution of best- $r_{\max}$  values obtained for the 485 patients.

**Table 2.** Number of patients from experiment 2, classified in each of the nine model types with the mean  $\pm$  SD of best- $r_{\max}$  found in the patients within each type before and after exclusion of the 46 patients for which the best- $r_{\max}$  was lower than 0.650.

| Model type | n   | All patients (n = 292) |               | Patients with best- $r_{\max} > 0.650$<br>(n = 246) |                  |               |
|------------|-----|------------------------|---------------|-----------------------------------------------------|------------------|---------------|
|            |     | %                      | Mean $\pm$ SD | n                                                   | %                | Mean $\pm$ SD |
| 1          | 180 | 61.6 (56.0–67.0)       | 794 $\pm$ 181 | 151                                                 | 61.4 (55.2–67.3) | 859 $\pm$ 80  |
| 2          | 42  | 14.4 (10.8–18.9)       | 797 $\pm$ 145 | 37                                                  | 15.0 (11.1–20.1) | 835 $\pm$ 76  |
| 3          | 5   | 1.7 (0.6–4.1)          | 767 $\pm$ 202 | 4                                                   | 1.6 (0.5–4.3)    | 854 $\pm$ 64  |
| 4          | 16  | 5.5 (3.3–8.8)          | 828 $\pm$ 117 | 14                                                  | 5.7 (3.3–9.4)    | 862 $\pm$ 78  |
| 5          | 4   | 1.4 (0.4–3.6)          | 818 $\pm$ 65  | 4                                                   | 1.6 (0.5–4.3)    | 818 $\pm$ 65  |
| 6          | 1   | 0.3 (0.0–2.1)          | 466           | 0                                                   | 0.0 (0.0–0.0)    | –             |
| 7          | 8   | 2.7 (1.3–5.4)          | 472 $\pm$ 185 | 1                                                   | 0.4 (0.0–2.5)    | 710           |
| 8          | 6   | 2.1 (0.8–4.5)          | 843 $\pm$ 44  | 6                                                   | 2.4 (1.0–5.3)    | 843 $\pm$ 44  |
| 9          | 30  | 10.3 (7.3–14.3)        | 883 $\pm$ 91  | 29                                                  | 11.8 (8.3–16.5)  | 892 $\pm$ 78  |

in their treatment between the two tests. The lowest ABI in this group was  $0.72 \pm 0.22$ . The median delay between the two tests was 5 months (1–9 months). The duration of the walking period was  $6.2 \pm 4.9$  min for test 1 and  $6.1 \pm 4.4$  for test 2 ( $< 320$  m). The  $\text{tcpO}_2$  value at rest was  $67.4 \pm 10.7$  mmHg on test 1 and  $69.3 \pm 11.8$  on test 2 (N.S). Although mean values were not different, on the average the absolute differences in  $\text{tcpO}_2$  between the two tests were  $9.5 \pm 7.1$  mmHg. The  $r_{\max}$  value for the cross correlation analysis for the 31 analysed pairs of profiles was  $0.800 \pm 0.129$ . Twenty patients showed an excellent reproducibility ( $r_{\max} > 0.8$ ), nine patients had a satisfactory reproducibility and two patients an unsatisfactory reproducibility. The low  $r_{\max}$  coefficient for these latter two patients was related to the fact that  $\text{tcpO}_2$  showed very little change during exercise except apparently random oscillations around baseline values. The examples of test–retest recordings are presented in figure 6.



**Figure 6.** Examples of test-retests recordings in four different patients. Grey squares show the walking periods of the first test. Patient 'A' shows type 9 profiles on the two tests separated by 3 months. Note that the walking lasted 1 min less at the second test. The other three patients have type 1 profiles with intervals between tests ranging 1 to 4 months. Walking duration was almost the same at the two tests.

#### 4. Discussion

Characterization of the chest tcpO<sub>2</sub> profile during treadmill walking tests can be easily done with the cross correlation technique through an Excel spreadsheet. This study suggests that most of the tcpO<sub>2</sub> changes observed can be classified into only four of nine pre-defined profile types, among which approximately 75% to 80% patients showed assumed normal changes. The distribution of profiles is reliable in a prospective study of a population different from the population of experiment 1. The tcpO<sub>2</sub> profiles are independent of the position of the probes. They are also reproducible in test-retest recordings and thus seem characteristic of each patient's response to treadmill walking.

The physiological effects of exercise include an increase in the total ventilation, an increase in the tidal volume and an improvement of the ventilation to perfusion ratio. These mechanisms are expected to result in an increase in arterial pO<sub>2</sub> at least for mild to moderate exercise in both normal and diseased subjects (Rubin *et al* 1982). Then changes in tcpO<sub>2</sub> fitting the type 1 and 2 models follow the expected changes in arterial pO<sub>2</sub>. Thus, it is likely that these two tcpO<sub>2</sub> profiles (types 1 and 2) can be considered normal profiles. The second most frequently observed profile in experiment 1 and the largely represented profile in experiment 2 was of type 9 and consisted of an abrupt decrease at exercise start followed by a slow upward drift during walking, a recovery overshoot (values higher than starting values) and finally a slow decrease during the late recovery period, referred to here as walking-induced transcutaneous

hack (WITH). Post-exercise overshoots have been reported in the literature. The presence of post-exercise ejection fraction overshoot was reported in normal subjects and cardiac-diseased patients (Kano *et al* 1997, Kubota and Zoladz 2005). Other possible explanations for the tcpO<sub>2</sub> overshoot are the presence of post-exercise metabolic hyperactivity in type 1 fibres following sub-maximal exercise (Sahlin *et al* 1997, Korzeniewski and Zoladz 2005) or abrupt changes in venous oxygen content (Sumimoto *et al* 1993). The overshoots we found strongly resemble the overshoots observed by Hugues (Hughes *et al* 1984) with both transcutaneous and iterative intra-arterial samplings in patients with pulmonary emphysema. These WITH profiles are somewhat different from those that we expected to find in exercise-induced arterial hypoxemia (EIAH). Indeed, in EIAH, arterial pO<sub>2</sub> (and then tcpO<sub>2</sub>) is expected to decrease progressively throughout exercise, to reach a minimum at the end of exercise and to normalize progressively after the exercise as in type 5 and 8 models. It should be noted here that EIAH was described mainly for progressive or constant but heavy-load exercises and that little is known about pO<sub>2</sub> changes occurring during moderate constant-load exercise. Whether the transient initial decrease and recovery overshoot of tcpO<sub>2</sub> observed for constant-load moderate exercise (WITH profile: type 9) would change to a progressive decrease throughout exercise and progressive recovery for incremental or heavy-load constant exercise (consistent with EIAH) is an interesting assumption that requires future experiments. The type 4 model appears to be a combination of the models expected to occur as a result of EIAH (types 5 and 8) with a progressive exercise-induced decrease and of the recovery overshoot observed in type 9 model (WITH profile). It is very likely that it represents an abnormal response during exercise, with a rapid post-exercise normalization.

It could be proposed that the WITH profiles, observed on tcpO<sub>2</sub> values, result from cutaneous vasoconstriction during the sole exercise period. Although the potential competition between muscle and skin blood flow is known for years (Bevegard and Shepherd 1967) and occurs specifically at the outset of exercise, it is dependent on the level of exercise. Further, during sub-maximal exercise muscle metaboreflex stimulation is capable of modulating cutaneous vascular conductance in glabrous, but not in the nonglabrous chest skin (Kondo *et al* 2003). Specifically cutaneous vascular conductance increased (and not decreased) during handgrip exercise at the chest level (Kondo *et al* 2003). Since the work load performed on treadmill in our study is independent of the estimated cardiac or pulmonary capacity of the patients, it cannot be excluded that the workload performed may represent a high percentage of the maximal capacity in some patients. Whether, the WITH profiles occur specifically in patients with altered cardio-respiratory function as a reflex cutaneous vasoconstrictor response to a high level of exercise, relative to their maximal exercise capacity, is an interesting assumption. The presence of a WITH profile would then be an indirect index of impaired cardiovascular function. In such a case arterial pO<sub>2</sub> and saturation would remain stable while transcutaneous pO<sub>2</sub> decreases due to cutaneous vasoconstriction. Future studies are needed to compare tcpO<sub>2</sub> results to saturation or direct arterial sampling in the detection of abnormal exercise arterial oxygen transport responses in our population. Whatever, assuming that WITH profiles reflect a transient fall in arterial oxygen pressure that slowly increases when exercise is continued, it is likely that only a transient decrease of SaO<sub>2</sub> will occur at exercise onset in such patients in starting arterial pO<sub>2</sub>. Such a transient decrease will hardly be differentiated from a technical problem in saturation recording. Lastly, it is of particular interest to note that if a direct arterial blood sampling was performed in these patients in the last seconds of exercise (as done in most cases when searching for exercise induced hypoxemia), the arterial pO<sub>2</sub> might not be (or only slightly be) decreased as compared to resting values. At worse, if the blood sampling is done a few seconds after the end of exercise for technical reasons (difficult puncture, delayed sampling, abrupt stop), arterial pO<sub>2</sub> shall be higher than the resting

value leading to the exclusion of an abnormal (or at least unusual and suspect) pO<sub>2</sub> response to exercise. A study (the 'initial VHS study') is currently ongoing to perform a direct comparison of tcpO<sub>2</sub> changes to arterial pO<sub>2</sub> changes through multiple iterative sampling throughout the rest, exercise and recovery periods. Preliminary results seem to confirm that arterial pO<sub>2</sub> changes do follow tcpO<sub>2</sub> changes with an initial transient pO<sub>2</sub> decrease at outset of walking and that a recovery overshoot similar to the ones observed by Hughes (Hughes *et al* 1984) is found.

When classification was performed prospectively in a second group, the first three most frequently observed tcpO<sub>2</sub> profiles were of types 1, 2 and type 9. The results observed in table 2 of the present study are strongly concordant to those found in experiment 1. Last, reproducibility of the tcpO<sub>2</sub> profile in intra-test and test-retest recordings was good. Although our environmental conditions are standardized in the laboratory, we think that the average 5 months delay between the two tests in experiment 4 precludes that the changes observed are independent of the patient's physiological adaptation to exercise.

## 5. Conclusion and perspectives

A prospective study has to be carried out including both haematological and respiratory tests and the comparison of the results observed between the different tcpO<sub>2</sub> categories has to be made. The underlying mechanisms and eventually associated diseases that could be found in patients showing WITH remain to be studied. Among these, exercise-induced right-to-left shunts are potential candidates.

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## **Physiopathologie et évaluation de la capacité de marche au cours de l'artériopathie oblitérante des membres inférieurs**

Résumé =

Lorsqu'une ischémie a lieu dans un territoire tissulaire des membres inférieurs, elle peut être à l'origine de douleurs survenant à la marche, limitant ainsi la capacité de marche des patients. Cette évaluation de la capacité de marche est difficile en raison de la difficulté qu'ont les patients à évaluer leurs limitations à la marche. Différents outils de mesure ont été développés comme des questionnaires, des tests de laboratoire notamment sur tapis et des tests ambulatoires comme le GPS. Les travaux menés ont permis de montrer les limites d'un questionnaire préalablement validé (Walking Impairment Questionnaire) et de développer un nouveau questionnaire d'évaluation de la capacité de marche plus court et tout aussi fiable. De plus, le concept de variabilité de la capacité de marche à court terme a été mis en évidence par GPS. Cette variabilité à court terme pourrait être l'une des explications à cette difficulté d'évaluation de la capacité de marche. Les durées optimales du test sur tapis à charge constante ont aussi été précisées. Enfin, différentes localisations ischémiques ont été présentées au niveau des membres inférieurs et nous avons montré que certains patients avec une limitation de la capacité de marche ont une hypoxémie d'effort à la marche. Celle-ci pourrait être la cause de leur limitation de leur capacité de marche. Ces travaux permettront de mieux évaluer la capacité de marche de l'artériopathe à la fois pour le diagnostic mais aussi pour la prise en charge thérapeutique.

## **Physiopathology and walking capacity assessment in peripheral artery disease**

Résumé =

When exercise induced-ischemia occurs in the lower limbs, a pain called intermittent claudication may occur with walking, then limiting the walking capacity of the patients. This assessment of this walking capacity is challenging because patients have difficulties to assess their walking limitations. Different measurement tools have been developed to evaluate different ischemic localizations appearing in walking and the influence of exercise induced-hypoxemia. The work has demonstrated the limits of a previously validated questionnaire (Walking Impairment Questionnaire) and we have developed a new questionnaire for assessing the walking capacity. Using GPS, the concept of short-term variability of the walking capacity has also been highlighted. This short-term variability may be one of the explanations of patient difficulties to assess their walking capacity. Moreover, the optimal duration of a constant load treadmill test has been clarified. Finally, different ischemic localizations in lower limbs were presented and we showed that some patients with walking capacity limitations present an exercise-induced hypoxemia, which might be a cause of the walking capacity limitations. In conclusion, this work may help to better assess the walking capacity for the diagnosis but also for the therapeutic management of patients with lower extremity peripheral artery disease.