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### ► **To cite this version:**

Pierre-Yves de Müllenheim, S. Chaudru, G Mahé, Jacques Prioux, Alexis Le Faucheur. Clinical Interest of Ambulatory Assessment of Physical Activity and Walking Capacity in Peripheral Artery Disease. *Scandinavian Journal of Medicine and Science in Sports*, 2016, 26 (7), pp.716-730. <10.1111/sms.12512>. <hal-01237089>

**HAL Id: hal-01237089**

**<https://univ-rennes.hal.science/hal-01237089v1>**

Submitted on 10 Mar 2026

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**Clinical interest of ambulatory assessment of physical activity and walking capacity in peripheral artery disease**

**Running head**                      Physical activity and walking capacity in PAD

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## **ABSTRACT**

The purpose of the present review was to provide, for the first time, a comprehensive analysis and synthesis of the available studies that highlighted the clinical interest of the ambulatory assessment of either physical activity (PA) or walking capacity in patients with lower extremity peripheral artery disease (PAD). We identified 96 related articles published up to March 2015 through a computer-assisted search of the MEDLINE, EMBASE, and Web of Science databases. Ambulatory-measured PA or related energy expenditure (EE) in PAD patients was performed in 87 of the 96 included studies. The main clinical interests of these measurements were: i) the assessment of PA/EE pattern; ii) the characterization of walking pattern; iii) the control of training load during home-based walking programs. Ambulatory-measured walking capacity was performed in the remaining studies, using either global positioning system receivers or the Peripheral Arterial Disease Holter Control device. Highlighted clinical interests were: i) the assessment of community-based walking capacity; ii) the use of new outcomes to characterize walking capacity, besides the conventional absolute claudication distance; iii) the association with the patient's self-perception of walking capacity. This review also provides for the clinicians step-by-step recommendations to specifically assess PA or walking capacity in PAD patients.

**KEY WORDS:** Peripheral Artery Disease; Activity Monitors; Functional Impairment; Walking Pattern; Rehabilitation

## INTRODUCTION

Peripheral artery disease (PAD) of the lower extremities is a chronic and highly prevalent disease, with 202 million people living with PAD in 2010 worldwide (Fowkes et al., 2013). PAD adversely impacts the individual's quality of life (Hirsch et al., 2006) and causes a roughly three-fold increase in mortality risk compared with people without PAD (Criqui et al., 1992). Despite the 5-year cardiovascular mortality that ranges between 15 to 30% in PAD patients (Hirsch et al., 2006), PAD most likely remains the most underdiagnosed atherosclerosis disease (Hirsch et al., 2001; Mohler, 2003).

Patients with PAD have both greater functional impairment of the lower extremities (McDermott et al., 2001; McDermott et al., 2002) and lower physical activity (PA) levels than non-PAD subjects (Sieminski & Gardner, 1997; McDermott et al., 2000). Epidemiological studies have shown that both low functional performances (McDermott et al., 2007; McDermott et al., 2008; McDermott et al., 2011) and low PA levels (Garg et al., 2006; Garg et al., 2009) were significantly and independently associated with a higher risk of mortality in PAD patients than in non-PAD subjects. Thus, measuring both functional impairment and PA is of importance in the management of PAD patients for diagnosis, follow-up, and treatment purposes (McDermott, 2013).

Functional assessment has been traditionally performed using procedures confined to laboratory or medical settings and has some inherent limitations (Hiatt et al., 2014; McDermott et al., 2014). The two most common functional tests used in PAD are the treadmill walking test and the 6-minute walk test (Hiatt et al., 2014; McDermott et al., 2014). Despite being keystones in PAD management, controversies remain as to whether the treadmill walking test or the 6-minute walk test is the better functional test (Hiatt et al., 2014; McDermott et al., 2014; Le Faucheur et al., 2015). However, consensus supports that an optimal functional test should directly correlate with the patient's physical limitations in their "real-life" setting (Hiatt et al., 2014; McDermott et al., 2014). Interestingly, during the last ten years, ambulatory devices that offer the opportunity for measuring original parameters related to functional impairment in the community have been made available. The assessment of daily PA has also become increasingly common in clinical practice, and this trend also occurred with PAD, particularly since the mid-1990s (Sieminski et al., 1997; Gardner & Poehlman, 1998).

In the past 20 years, several studies using ambulatory devices in PAD patients have been published, with important results that may directly impact the management of these patients. To date, no specific review has provided a comprehensive analysis and synthesis of the available studies that highlight the clinical interest of the

ambulatory assessment of PA in PAD patients. Although some recent reviews proposed an overview of the different ambulatory devices to be used in clinical practice, they specifically focused on the measurement of PA, not functional impairment, and they did not address the specific use of such ambulatory devices in PAD patients (Strath et al., 2013; Trost & O'Neil, 2014). In contrast, in the present review, we also highlighted the clinical interest of the ambulatory assessment of functional impairment (walking capacity) in PAD patients. An additional originality of the present review was to provide, for the clinicians, step-by-step recommendations to specifically assess ambulatory PA or functional impairment in PAD patients.

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## **METHODS**

### **Terminology: functional impairment (walking capacity) and PA in PAD**

Lower extremity function, physical functioning, disability, functional impairment or functional limitations are myriad terms that have been used interchangeably to describe the impairment in lower extremity function that affects PAD patients. The use of numerous terminologies has prevented the identification of a precise definition. Readers should refer to the International Classification of Functioning for the precise definition of related terms, such as functioning, disability or impairment (World Health Organization, 2013). In the context of PAD, the so-called functional impairment has been traditionally measured through the assessment of walking capacity during a treadmill walking test (Hiatt et al., 1995; Hirsch et al., 2006; Hiatt et al., 2014). The two most studied parameters have been the initial and absolute claudication distances (or time) during a treadmill walking test. The initial claudication distance is defined as the walking distance at which the patient first experiences lower-limb pain (Hiatt et al., 1995; Hirsch et al., 2006; Hiatt et al., 2014). The absolute claudication distance is defined as the maximal walking distance that can be performed by the patient before stopping because of maximal lower-limb pain (Hiatt et al., 1995; Hirsch et al., 2006; Hiatt et al., 2014). Walking capacity is an objective qualifier of activity limitations in a PAD patient, specifically for walking, and is thus a criterion that clearly reflects impairment and disability. Throughout the present paper, we will use the term “walking capacity” as the benchmark of “functional impairment”.

PA is a distinct concept from walking capacity. PA is defined as any body movement that results in an increase in the energy expenditure (EE) above the resting level (Caspersen et al., 1985). PA is a complex construct that relates to the subject's behavior and that is defined by several domains and dimensions, as well as contextual aspects (dimensions of time and place, position or posture) (Butte et al., 2012).

Thus, whereas PA is related to what a person does on a daily basis in their actual environment, walking capacity describes what a person is able to do (walk), at the maximum of their capacity, in a situation in which the context is controlled (such as in a standardized evaluation setting). Thus, measuring walking capacity does not imply that we are measuring a surrogate of (daily) PA, and *vice-versa*.

### **Literature search strategy and features extraction**

A literature search was conducted to identify articles published up to March 2015. The rationale for the literature search strategy is presented on Figure 1. Two authors (P.Y.d.M. and A.L.F.) performed a computer-assisted search of the MEDLINE, EMBASE, and Web of Science databases. The search was configured to

obtain all citations corresponding to the combinations of several terms related to PAD, ambulatory devices, and PA or functional impairment (Figure 1). This combination aimed to narrow the focus to articles dealing with ambulatory measurements of PA and/or walking capacity/functional impairment in PAD patients. Two additional filters were used to focus on only English-language articles and studies dealing with humans (this last filter was not available for the Web of Science database search). After duplicates removal, the two authors (P.Y.d.M. and A.L.F.) read the titles and abstracts related to the citations yielded from the computer-assisted search to select articles for full-text reading. An article was considered suitable for full text reading if the abstract seemed to imply a participation of PAD patients with a focus on ambulatory measurements of walking impairment or PA. Finally, from the included articles, we focused on various features of the studies to provide a classification regarding the clinical interest of ambulatory measurement of PA and walking capacity. These features of interest were the following: specific aims of the ambulatory measurements performed in the included studies, devices used and outcome measures studied. All identified studies are presented on Table 1. In order to facilitate the readability of the “Results” section, only selected studies are cited to illustrate the clinical interest of ambulatory measurement of PA and walking capacity.

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## RESULTS

The number of selected articles at each step of the search strategy is presented on Figure 1. Overall, 96 articles were included in the present review. Three articles were excluded because they focused on only the methodological framework of a future study (Murphy et al., 2008; Cunningham et al., 2010; McDermott et al., 2012). Ambulatory-measured PA in PAD patients was performed in 87 of the 96 included studies. Ambulatory-measured walking capacity was performed in only 9 of the 96 studies. Table 1 shows an overview of the resulting classification of the 96 included articles with the different clinical interests of ambulatory measurement of PA and walking capacity. Models and technical features of the devices used are presented in both Table 1 and Appendix 1. Readers should be aware of the technical features and the differences between simple pedometers, newer enhanced pedometers, and the various accelerometers models (Appendix 1). The type of device used inevitably determines the type of outcome measure(s) available and used for clinical interpretation.

### RESULTS FOR AMBULATORY ASSESSMENT OF PHYSICAL ACTIVITY

#### Assessment of PA and EE pattern

Most (69/87) of the studies that used ambulatory devices in PAD patients focused on the assessment of daily PA and/or EE levels (*e.g.*, Sieminski et al., 1997; Garg et al., 2006; Garg et al., 2009; Murphy et al., 2012; McDermott et al., 2013; Lauret et al., 2014; and see Table 1 for complete listing). Accelerometers and simple pedometers worn at the waist were the two types of ambulatory devices mainly used for this assessment (Figure 2). The Caltrac™ accelerometer was the main model employed (50/87).

*Devices validity and reliability.* Although different models of devices were used (n=12; Table 1) for the assessment of ambulatory PA and EE pattern in PAD patients, only three studies were conducted for validation purpose (Sieminski et al., 1997; Gardner & Poehlman, 1998; Fokkenrood et al., 2014). Validity of the Caltrac™ accelerometer and the Omron® pedometer was firstly established by correlating 2-day EE (kilocalories/d) estimates (Caltrac™) and steps/day measurements (Omron®) with PA questionnaires scores (Sieminski et al., 1997). Low but significant correlations ( $r=0.33-0.51$ ,  $P<0.01$ ) were found between these devices outcomes and the questionnaires scores. Gardner and Poehlman (1998) found moderate-to-strong correlations between the measured outcomes from these devices and the PA-related EE measured by doubly labelled water (Omron®:  $r=0.614$ ,  $P=0.002$ ; Caltrac™:  $r=0.834$ ,  $P<0.001$ ). Reliability of the Caltrac™ ( $r=0.84$ ,  $P=0.610$ ) and the Omron® ( $r=0.86$ ,  $P=0.746$ ) was also established over a 2-day monitoring (Sieminski et al., 1997). The DynaPort MoveMonitor is a newer model of accelerometer sensor that allows acceleration to be measured along three axis

(Fokkenrood et al., 2014). This device has been shown to be accurate for steps counting, and for detecting diverse sets of postures and daily activities in PAD patients (*e.g.*, locomotion, lying, and sitting). However, accuracy remained poor for shuffling and “sitting to standing” transfers detection (Fokkenrood et al., 2014).

*Applications studies in PAD.* Because of the features of the ambulatory devices used, only a measure of PA or EE volume was generally conducted, and a few data regarding the intensity of PA were collected (Table 1). Ambulatory devices have been shown to be more precise than questionnaires for the assessment of daily PA and EE levels (Gardner & Poehlman, 1998; McDermott et al., 2000). Multiple associations between PA/EE levels and a number of outcomes related to health and disease have been highlighted in PAD patients (Table 1). PAD-specific features, such as PAD severity, leg symptoms or natural history, have also been linked to PA/EE levels in PAD patients. For instance, as compared to non-PAD patients, it has been shown that PAD patients had a 42% lower daily accelerometer-measured EE and a 45% lower daily pedometer-measured steps number ( $P < 0.001$ ) (Sieminski & Gardner, 1997). Greater PA levels have also been shown to be significantly associated with higher ankle-brachial index values (Sieminski & Gardner, 1997; McDermott et al., 2002), greater distance achieved in the 6-minute walk test (McDermott et al., 2008), reduced mortality (Garg et al., 2006), reduced functional decline (Garg et al., 2009), lower level of circulating inflammatory biomarkers (McDermott et al., 2004; Craft et al., 2008), and a lower cognitive dysfunction (Zimmermann et al., 2011). Most of these studies were cross-sectional studies, thus causal relationships could not be determined and only associations could be drawn. Interestingly, recent studies, using newer accelerometers (Table 1), provided first information about daily PA intensity levels (Lauret et al., 2014; Loprinzi & Abbott, 2014; Fokkenrood et al., 2015), activity types performed (Lauret et al., 2014; Fokkenrood et al., 2015), and time spent in inactivity (Vaz Fragoso et al., 2014). Lauret et al. (2014) found that PAD patients with intermittent claudication spent significantly less time in vigorous-intensity PA ( $4 \pm 8$  min/day) than control subjects ( $11 \pm 10$  min/day) and that more than 50% of intermittent claudication patients did not meet PA guidelines (Lauret et al., 2014). Among diabetic people, Loprinzi et al. (2014) showed that patients with an abnormal ankle-brachial index engaged in 23% less time in moderate-to vigorous PA than patients with a normal ankle-brachial index. A longitudinal study showed that a 3-month supervised exercise program leads to more PAD patients with intermittent claudication meeting PA recommendations (Fokkenrood et al., 2015). Barbosa et al. (2015) investigated personal and environmental barriers to PA in PAD patients. The level of PA, measured via a simple pedometer, was found to be inversely

associated with age and lack of green areas, and positively associated with the absolute claudication distance (Barbosa et al., 2015).

### ***Characterization of ambulatory walking pattern***

With the development of newer generation of ambulatory devices, new parameters have been made available, allowing clinicians to specifically assess ambulatory walking pattern (Table 1). Besides the assessment of additional dimensions of PA by measuring the intensity or the duration of ambulation, the study of ambulatory walking pattern is of particular interest in PAD patients since it can be modified due to claudication (McDermott et al., 2001; Gardner et al., 2010). The StepWatch 3™ (Gardner et al., 2007; Gardner et al., 2008; Gardner et al., 2010; Gardner et al., 2010; Gardner et al., 2011; Ritti-Dias et al., 2011; Gardner et al., 2012; Gardner et al., 2013; Gardner et al., 2014) and the activPAL™ (Clarke et al., 2013; Stansfield et al., 2015) are the two ambulatory devices currently used in PAD patients for such purpose (Table 1 & Figure 2). Although these devices have been extensively used and validated across different populations, validity studies conducted specifically in PAD patients are lacking. Only Gardner et al. (2007) reported unpublished data for the StepWatch 3™. Authors indicated an excellent accuracy of the StepWatch 3™ for step counting (accuracy of  $99\pm 1\%$ ) during a 6-minute walk test in 15 PAD patients. A high test-retest intraclass reliability coefficient for the measurement of total daily strides ( $r=0.87$ ) and total daily minutes of activity ( $r=0.85$ ) for a 7-day period was also claimed (Gardner et al., 2007). No validity and reliability data in PAD patients are available for the activPAL™. Further, when interpreting the outcome measures given by these devices, confusions have been made between true cadence and step accumulation within an epoch of time (Stansfield et al., 2015). This can lead to misinterpretation (Stansfield et al., 2015), thus clinicians should be aware of the definition of the outcome measures used (see “discussion” section).

Using the StepWatch 3™, Gardner et al. (2007) showed that compared to non-PAD patients, PAD patients with intermittent claudication had lower total daily ambulatory activity, due to both less time ambulating and fewer strides accumulated within 1-min epochs. Using the activPAL™, Stansfield et al. (2015) showed that, although PAD patients with intermittent claudication had the same daily activity time and almost the same mean walking cadence as non-PAD controls, they had a lower total daily strides volume due to a lower daily stride accumulation within 1-min epochs. Gardner et al. (2008) showed that daily ambulatory stride accumulation was more closely correlated with PAD patients' walking capacity as compared to daily ambulatory strides or

ambulatory duration. Clarke et al. (2013) discriminated upright events from walking events in a PAD population from a 7-day recording. Their hypothesis was that PAD patients with intermittent claudication would have, on average, more walking events per upright events than controls as they would need to stop and start more frequently due to ischemic pain. The authors computed the ratio of walking events to upright events to provide an Event-Based Claudication Index and reported that this index was greater in PAD patients with intermittent claudication than in controls. **Others** studies reported associations in PAD patients between walking pattern and clinical, physiological or biological features (Gardner et al., 2010; Gardner et al., 2010; Gardner et al., 2011; Ritti-Dias et al., 2011; Gardner et al., 2012; Gardner et al., 2013; Gardner et al., 2014).

### ***Control of training load during home-based walking programs***

An interesting clinical use of ambulatory devices concerns the control and the quantification of the training load during home-based walking programs in PAD patients. Indeed, the lack of structuring of interventional components is one of the limitations claimed regarding home-based walking programs, and it is recognized that prescribed exercise should be methodologically similar to supervised exercise programs (Mays et al., 2013). The training load can be defined by the following components over an entire exercise program: exercise duration and exercise intensity achieved over each session, number of sessions per day and session frequency per week. Only four studies used an ambulatory device (the StepWatch 3™) for a clear quantification of the training load (Gardner et al., 2011; Hiatt et al., 2011; Gardner et al., 2014; Gardner et al., 2014). In the study conducted by Gardner et al. (2011), the duration and stride accumulation in minute epochs, recorded at each walking session by the StepWatch 3™, were used to compute the training load in metabolic equivalents per minute (MET-min). Hiatt et al. (2011) computed the training load somewhat differently. Authors calculated the total duration of walking sessions provided a stride accumulation  $\geq 10$  strides/min was attained over at least a 10-min period. In both the studies by Gardner et al. and Hiatt et al., the ambulatory device used did not allow the patients to obtain on-line or post-session results (Gardner et al., 2011; Hiatt et al., 2011; Gardner et al., 2014; Gardner et al., 2014). Feedback to patients and regulation of the training load was performed using logbooks, in which the patients recorded their walking sessions. Then, by returning both the ambulatory devices and the logbooks to the research staff on a regular basis, the patients received feedback from an exercise physiologist. Interestingly, using these procedures, some studies reported that a home-based exercise program had high adherence and was efficient in improving walking capacity similar to a standard supervised exercise program (Gardner et al., 2011;

Gardner et al., 2014). Other available studies that used ambulatory devices for PAD rehabilitation reported insufficient results to make interpretations (Larsen & Lassen, 1966; Nicolai et al., 2010; Collins et al., 2011).

## **RESULTS FOR AMBULATORY ASSESSMENT OF WALKING CAPACITY**

### ***Assessment of community-based walking capacity***

Ambulatory-measured walking capacity was performed using either Global Positioning System (GPS) receivers (Le Faucheur et al., 2008; Le Faucheur et al., 2010; Tew et al., 2013; Gernigon et al., 2014; Nordanstig et al., 2014; Nordanstig et al., 2014) or the Peripheral Arterial Disease Holter Control device (Boissier et al., 1997; Coughlin et al., 2001; Coughlin et al., 2006). Although the latter allows clinicians to perform ambulatory measures, it was used only under laboratory conditions, most likely because the device is too cumbersome for the patients (Figure 2). The outcome measures available from these devices were mainly the initial claudication distance (not for GPS), the absolute claudication distance or the outdoor total walked distance over 40 minutes (GPS). More parameters related to walking capacity have been analyzed from GPS measurement (Table 1).

The available studies have shown that low-cost GPS devices are valid for assessing community-based walking capacity and without patient supervision in most cases (Le Faucheur et al., 2008; Le Faucheur et al., 2010; Tew et al., 2013; Gernigon et al., 2014). Using a validated signal processing methodology of GPS walking speed, it has been previously shown that walking and stopping bouts occurring at random during a prolonged walk could be detected accurately (Le Faucheur et al., 2007). In a small sample of PAD patients (n=24), in which this methodology was applied with specific recommendations for walking, the same group of authors reported a significant correlation ( $r=0.81$ ,  $P<0.001$ ) between the absolute claudication distance measured by GPS and the one measured during the treadmill walking test (Le Faucheur et al., 2008). In addition, it was found that absolute claudication distance measured by GPS was, on average, 3 to 5 times higher than the treadmill-measured absolute claudication distance (Le Faucheur et al., 2008). Another team of researchers recently reported significant correlations between the GPS total walking distance during a 40-min outdoor walk and both the total walking distance in the 6-minute walk test and the reported quality of life in PAD patients (Nordanstig et al., 2014; Nordanstig et al., 2014).

Most of the available studies that used GPS receivers in PAD were conducted on a relatively small sample of patients (n<50) in a pre-defined place and with the patients equipped by an investigator. Recently, Gernigon et al. (2014) addressed the issue of the clinical applicability of the GPS technique. Authors determined whether GPS could be used as a routine unsupervised tool in a large sample of PAD patients, from multiple centers, and

in various geographic areas. From a total of 218 patients who performed an outdoor walk, it was found that 93% of the GPS recordings were technically satisfactory. In addition, authors provided data obtained from a large cohort of PAD patients (n=203) to characterize their community-based walking capacity. The median highest measured distance between two stops during community walking was 678 m (25<sup>th</sup>–75<sup>th</sup> percentiles: 381–1333 m), whereas the median self-reported maximal walking distance was 250 m (25<sup>th</sup>–75<sup>th</sup> percentiles: 150–400 m; **P < 0.001**). Mean walking speed was 3.6 km/h (25<sup>th</sup>–75<sup>th</sup> percentiles: 3.1–3.9 km/h), with few variations during the walk. Among the patients who had to stop during the walk, the mean stop durations were <10 minutes in all but one individual (Gernigon et al., 2014).

#### ***Exploration of new parameters to characterize walking capacity***

Using the GPS procedure, a new concept, the short-term variability of walking capacity, was highlighted. During a 45- to 60-min walk, it was found that the walking distances between two stops induced by lower-limb pain were highly variable (Le Faucheur et al., 2010). Authors stated that this variability may contribute to the difficulties experienced by patients in estimating their absolute claudication distance at a usual pace, thereby contributing, at least partly, to the low concordance between estimated and measured absolute claudication distances in PAD patients (Watson et al., 1997). It was also found that in most PAD patients, the walking distances between two stops induced by lower-limb pain were inversely related to the duration of the stop that preceded each walking bout (Le Faucheur et al., 2010). This suggests that the early restart of walking, after pain relief, leads to shortened walking distance, most likely due to incomplete ischemic recovery from the preceding walk.

#### ***Association with patient's self-perception of walking capacity***

There is a well-known and wide discrepancy between the walking capacity perceived by the patient and the walking capacity measured during treadmill walking test or a corridor walk (Watson et al., 1997). Tew et al. showed that self-reported measures of walking limitation tended to correlate better with a GPS community-based assessment of absolute claudication distance than with the treadmill walking test and the 6-minute walk test (Tew et al., 2013). Interestingly, most of these correlations were improved when PAD patients completed new self-reports 7 to 10 days after the first completion, a period within which the patients performed the GPS community-based assessment. The authors stated that the improved correlations were mainly due to the GPS measure, which increased the patients' awareness of their walking capacity (Tew et al., 2013).

## **DISCUSSION**

The American Heart Association recently published, for the first time, a statement regarding the assessment of PA and EE for clinical and research applications (Strath et al., 2013). Although this paper did not specifically focus on PAD, readers should refer to this document because it provides an interesting methodological framework regarding the use of ambulatory devices for measuring PA and EE in clinical populations. On the basis of the present review, Table 2 provides for the clinicians step-by-step recommendations to specifically assess PA or walking capacity in PAD patients. To complement Table 2, methodological considerations (step 1 to step 5 of Table 2) and specifications regarding clinical interpretation (step 6 of Table 2) are also provided below. In addition, Appendix 1 and Figure 2 provide further information for most of the ambulatory devices that have been used in PAD.

## **PRACTICAL CONSIDERATIONS FOR AMBULATORY ASSESSMENT OF PHYSICAL ACTIVITY**

### **Methodological considerations**

*Simple pedometers.* The use of simple pedometer to assess PA and EE pattern in PAD patients is questionable. Simple pedometers accumulate steps over the entire period of recording, and the main outcome measure provided is the total number of steps. PAD patients exhibit lower walking speed and gait disorders due to intermittent claudication (Gardner et al., 2010), two conditions that clearly limit the use of simple pedometers for steps counting in this clinical population (Cyarto et al., 2004; Storti et al., 2008). According to the models of pedometer used, both the total distance and the total volume of EE can also be estimated from input parameters, such as step length and body mass of the assessed subject. However, the accuracy in the estimation of walking distance or EE is lower than for step counting (Crouter et al., 2003). Thus, except for motivating behavior change, the use of simple pedometers in PAD patients appears to be of limited interest and most likely less reliable (Crouter et al., 2005; Bergman et al., 2008) than the use of newer enhanced pedometers and accelerometers.

*Newer enhanced pedometers.* Newer enhanced pedometers contain piezoelectric sensors and have a built-in time clock and memory function, enabling them to store the number of steps per minute. In fact, these pedometers have a built-in accelerometer sensor, which may confound their classification. The term “pedometer”, however, is used because the outcome measures provided remain step- or stride-related parameters (Strath et al., 2013). The ankle-worn StepWatch 3™ dual-axis accelerometer pedometer is the latest pedometer to be frequently used

in PAD patients in order to describe their walking pattern (Table 1 & Figure 2). This device seems also well suited to assess PA pattern. As specified on Table 2, a manual configuration of the StepWatch 3™ by the user is required from the StepWatch™ software, with two settings that need to be configured. The “sensitivity” setting determines the minimal acceleration threshold of the ankle from which the sensor is able to detect a stride. The “cadence” setting determines the frequency at which the sensor is able to count strides. The rationale for the configuration of these filters has been previously addressed (Coleman et al., 1999). Although the effectiveness of the settings configuration can be checked by the visual inspection of a light when the subject is walking, no specification and no recommendation have been given in studies that used the StepWatch 3™ in PAD patients (Gardner et al., 2007; Gardner et al., 2008; Gardner et al., 2009; Gardner et al., 2010; Gardner et al., 2010; Gardner et al., 2011; Gardner et al., 2011; Hiatt et al., 2011; Ritti-Dias et al., 2011; Gardner et al., 2012; Gardner et al., 2013; Gardner et al., 2014). It is unknown whether different configurations can produce different results and limit the comparison of studies. Importantly, caution is required by the clinicians when choosing the sampling epoch of the StepWatch 3™. According to the whole duration of the measurement that is expected, a sampling epoch as short as possible should be used (see Table 2, and below “clinical interpretation”).

*Accelerometers.* Accelerometers are of particular interest for the measurement of PA/EE pattern or the description of walking pattern in PAD patients. The outcome of accelerometry-based devices has been generically termed “activity counts”. An activity count is an arbitrary unit of PA derived from the digitized raw signal. The precise meaning and the calculation of accelerometers activity counts have been addressed elsewhere (Chen & Bassett, 2005). Importantly, count values across accelerometer models cannot be directly compared (Welk et al., 2012). As previously underlined, the uniaxial Caltrac™ accelerometer was the main model used in PAD, with the specific aim of measuring total PA volume since the device did not allow data to be stored on a minute-by-minute (or less) basis, as simple pedometers (Welk, 2002). Although the Caltrac™ accelerometer was expected to be more precise than simple pedometers in estimating total EE in PAD (Gardner & Poehlman, 1998), it remains of limited interest compared to the newer generation accelerometer devices and is now discontinued. Newer accelerometer sensors (*e.g.*, activPAL™, PAL Technologies; GT3X, ActiGraph; DynaPort MoveMonitor, McRoberts; see Table 1 and Appendix 1) allow acceleration to be measured in 1, 2 or 3 axis and have the advantage of capturing intensity, frequency and duration of PA in a time-stamped manner (Strath et al., 2013). Such devices offer higher capabilities to describe more accurately both PA and EE pattern in PAD patients. Beyond the sole measurement of activity counts, the newer generation of accelerometers

enable the user to extract the raw accelerometer signal for PA recognition using machine-learning algorithms (Strath et al., 2013; Fokkenrood et al., 2014). By discriminating sitting, standing, and walking events, these devices are of interest to assess sedentary behaviours in PAD patients (Fokkenrood et al., 2014; Lauret et al., 2014; Fokkenrood et al., 2015).

### **Clinical interpretation**

*Assess PA and EE pattern.* Correct interpretation of PA outcomes is challenging because it implies to be aware of the consequences of device processing (*i.e.*, how the device records and stores the data) and data handling (*i.e.*, how the researcher or the clinician performs both quality and quantity data control, and transforms raw data into PA outcomes). For a best understanding of the data processing used by the ambulatory devices for PA assessment purposes, readers should refer to related articles (Chen & Bassett, 2005; Yang & Hsu, 2010; Chen et al., 2012). The approach for handling procedure is clarified below.

Before interpreting collected data, clinicians should ensure that there are no spurious data within the subjects' data files (*e.g.*, counts values  $\geq 16,000$  within 1-min epoch, or counts values that are both superior to 0 and constant for 10 minutes or more). Spurious data should be considered as missing data (Masse et al., 2005). Then, clinicians should apply a methodology to control wear time of the ambulatory device used. Ideally, from collected data, clinicians should: i) apply an algorithm (decision rules) to define wear time and nonwear time periods over a day; ii) define a minimum number of hours of wear time/day to consider a day as "valid"; iii) define a minimum number of "valid" days over the entire period of data collection to ensure that the measurement is representative of the patient's PA pattern. Data regarding the appropriate methodology to be used in PAD patients in order to control wear time are lacking (Lauret et al., 2014; Loprinzi & Abbott, 2014; Vaz Fragoso et al., 2014; Fokkenrood et al., 2015), which precludes clear recommendations to be given for the clinicians. Using the DynaPort MoveMonitor, some authors considered that a day was "valid" if a minimum number of 20 steps was detected by the device and if the device was worn  $\geq 9$  or 10 hours (Lauret et al., 2014; Fokkenrood et al., 2015). However, the algorithm used to define wear time and nonwear time periods was not clarified. Available studies in PAD patients reported a minimum of 4 to 5 valid days to be reached to ensure of the representativeness of collected data (Lauret et al., 2014; Loprinzi & Abbott, 2014; Fokkenrood et al., 2015). To reach this minimum number of valid days, data are usually collected over a 7-day period.

Although future studies are needed in PAD, clinicians can refer to wear time validation procedures implemented from PA measurements performed on healthy population (Matthews et al., 2002; Catellier et al., 2005; Eslinger et

al., 2005; Paul et al., 2008; Choi et al., 2011; Hart et al., 2011; Choi et al., 2012; Tudor-Locke et al., 2012; Herrmann et al., 2013).

As previously explained, activity counts are the main outcome of accelerometry-based devices. Clinicians can interpret the data collected by simply analyzing the total number of counts over a day or a week. However, as shown on Tables 1 and 2, much more outcomes of interest can be computed by transforming activity counts data into indicators of PA volume (*e.g.*, kilocalories, MET-min, activity time) or PA intensity (*e.g.*, minutes spent in different intensity levels). Beyond activity counts, by using raw data given by newer generation accelerometers, PA recognition can be performed using machine-learning algorithms (Fokkenrood et al., 2014; Lauret et al., 2014; Loprinzi & Abbott, 2014; Fokkenrood et al., 2015). Loprinzi and Abbott (Loprinzi & Abbott, 2014) estimated the time spent in moderate-to-vigorous PA in PAD patients by using a threshold of 2020 activity counts per minute. In order to transform activity counts data into physiologically meaningful units, such as kilocalories or METs-min, clinicians need to use prediction algorithms to carry out such a conversion. However, all these procedures for activity counts translation are specific to a myriad of factors including: the brand of the device used, the wearing location of the device, the features of the studied subjects, and the types of physical activities used during the calibration studies (Heil et al., 2012). Data regarding specific procedures to be used in PAD are lacking (Fokkenrood et al., 2014). To face this problem, clinicians should apply procedures validated in populations with features as close as possible to those of PAD patients (Pruitt et al., 2008; Copeland & Eslinger, 2009; Hall et al., 2013; Santos-Lozano et al., 2013; Aguilar-Farias et al., 2014). Importantly, clinicians and researchers are encouraged to report accurately the methodology used for data processing and data handling.

*Characterize walking pattern.* When interpreting results to analyze the walking pattern of PAD patients, clinicians should not confuse “stride accumulation” and “cadence” to avoid clinical misinterpretation. These two concepts may reflect different aspects of walking limitation in PAD patients. Stride accumulation is the number of steps or strides typically accumulated within a given epoch (*e.g.*, 1-min epoch), while cadence is the stepping rate over a walking bout (Stansfield et al., 2015). For instance, the StepWatch 3™ software does not allow for cadence assessment but own algorithms can be used to derive cadence from steps or strides taken over a given walking bout (Stansfield et al., 2015). This raises the issue of the chosen sampling epoch, which determines the minimal duration of the detected walking bouts (*i.e.*, stepping periods). Knarr et al. (2013) showed that when increasing the sampling epoch, the total activity time recorded increased, and the total number of detected

walking bouts decreased. Thus, short sampling epochs (*e.g.*, 10 seconds or less) should be used to precisely study the walking pattern in PAD patients.

*Quantify training load.* Despite the high capabilities of ambulatory devices to quantify the training load of home-based walking programs, a few studies used ambulatory devices for such purpose, which makes difficult to give practical recommendations (see “Perspectives in PAD” subsection). Furthermore, most of the ambulatory devices used do not display on-line data on a digital screen, which means that patients cannot control themselves their training load. Recommendations given above when analyzing PA/EE pattern and walking pattern also apply here for the use of ambulatory devices to quantify training load. Gardner et al. (Gardner et al., 2011; Gardner et al., 2014) proposed an interesting methodology to compute the METs achieved over each training session from **steps** accumulation measured using the StepWatch 3™. However, caution should be taken when applying this methodology because the speed-step accumulation (over 1 minute) relationship has not been systematically studied in PAD patients. Moreover, this relationship is likely to be influenced by slope during home-based outdoor walking programs.

## **PRACTICAL CONSIDERATIONS FOR AMBULATORY ASSESSMENT OF WALKING CAPACITY**

### **Methodological considerations**

Because only GPS receivers have currently been used for an ambulatory assessment of walking capacity, Table 2 provides step-by step recommendations for only this device. It is of particular importance to use GPS devices that have previously been submitted to a validation procedure to ensure that the devices are sufficiently accurate in the detection of walking/resting bouts and the estimation of walking distances and speeds. One technical limitation of the GPS technique is the shorter battery life and lower data storage of GPS units than those of accelerometers. This limits the use of the technique in case of continuous or discontinuous prolonged recordings over multiple days. Other limitations are presented on Table 2.

### **Clinical interpretation**

The appropriate GPS outcome measure used to assess walking capacity should be considered by the clinicians. As specified in Table 1, when assessing GPS outdoor walking capacity in PAD patients, some authors have used the total walking distance measured during a 40-min outdoor walk (Nordanstig et al., 2014; Nordanstig et al., 2014), whereas others have used the highest measured distance between two stops (Le Faucheur et al., 2008; Le

Faucheur et al., 2010; Tew et al., 2013). The difference in the outcome measures computed seems to be a direct consequence of the GPS analysis methodology used. In the first case, the authors used a Smartphone GPS-based application to record walking distance (Nordanstig et al., 2014; Nordanstig et al., 2014). It appears that by using this device, the authors could not distinguish walking bouts from stopping bouts due to intermittent claudication. Thus, only the total walking distance over 40 minutes could be computed. In the other case, the highest measured distance between two stops computation relied on the use of a specific GPS processing methodology, as mentioned above (Le Faucheur et al., 2008; Le Faucheur et al., 2010; Tew et al., 2013). The use of the total walking distance measured during a 40-min outdoor walk remains debatable from a clinical interpretability point of view. Table 3 presents two (theoretical) different profiles of walking impairment in two PAD patients who walked during ~40 minutes. As shown, for an identical total walked distance of 1600 m over ~40 minutes, significantly different profiles of walking impairment could be observed. As a direct consequence, the clinical interpretation could be inadequate or incomplete when focusing on only the total walking distance over 40 minutes. The methodology used in view of GPS community-based assessment of outdoor walking capacity in PAD patients should be standardized.

Other limitations also apply to the clinical use of GPS systems. The occurrence and the inability to identify stops not related to lower-limb pain can lead to an underestimation of walking capacity. In some studies, to avoid this limitation, PAD patients reporting stops not related to lower-limb pain during the outdoor walk were excluded (Le Faucheur et al., 2008; Le Faucheur et al., 2010). The use of a watch with **marker events** embedded into a specifically designed GPS device should overcome this issue, but such a system is not available. Finally, ethical considerations should also be taken into account by the clinicians. Up to now, time-limited recordings have been conducted in PAD patients, but prolonged recordings raise the issue of respecting individual civil liberties.

## **CHALLENGES IN PAD**

### **Ambulatory assessment of PA**

*Methodological challenges.* As shown in the present review, an increasing number of studies in the past 20 years have used ambulatory devices to estimate PA/EE pattern in PAD patients. Most of these studies used the Caltrac™ accelerometer, which is now discontinued. That means that studies are required to validate newer accelerometers devices in PAD patients. The present review highlighted that among the currently available ambulatory devices, validity and reliability studies conducted specifically in PAD patients were lacking. Again,

we would remind that PAD patients exhibit lower walking speed and gait disorders due to intermittent claudication (Gardner et al., 2010). Thus, the accuracy of available ambulatory devices in steps/strides counting, and the precise **cadence/speed** relationship, influenced or not by slope, should be exhaustively studied.

Importantly, studies in PAD patients are also needed to determine counts thresholds to be used to discriminate PA intensity levels, as well as prediction algorithms to translate activity counts into physiologically meaningful units. Finally, although GPS has been used to assess PA and EE in other populations (Maddison & Ni Mhurchu, 2009), no study has been specifically conducted in PAD patients. Coupling multiple devices could be also an interesting research topic.

*Clinical challenges.* We reported here that multiple associations have been highlighted in PAD patients between PA/EE levels and a number of health/disease outcomes and PAD-specific features. A central feature of PAD patients' locomotion is the occurrence of lower-limb pain due to ischemia, thereby limiting their walking activity. The pattern of pain occurrence during daily life is likely to affect the pattern of PA and related EE in PAD patients. The objective measurement of pain occurrence during daily life has never been performed. Analyzing the pattern of PA, sedentary behavior and EE in the light of the pattern of pain occurrence in PAD patients is a fascinating issue. Finally, future studies should clarify the interest of ambulatory devices to track PA/EE during home-based walking programs. The quantification of training load is an important issue for the efficiency of home-based walking programs. Further, the relationship between walking capacity and PA changes following therapeutic interventions remains to be studied more deeply.

### **Ambulatory assessment of walking capacity**

*Methodological challenges.* The GPS technique presents some inherent technical limitations, among which the risk of signal loss and signal imprecision in cases of obstructed environments (Terrier & Schutz, 2005).

Coupling GPS with accelerometers or with newer generation pedometers (*e.g.*, the StepWatch 3<sup>TM</sup>) could be a promising solution to overcome this limitation. Although the precise computation of walking distances or speeds from accelerometers remains difficult, they are potentially valid for discriminating walking from non-walking bouts (Bonomi et al., 2009). This remains to be studied in the context of PAD patients.

*Clinical challenges.* Using GPS to assess community-based walking capacity in PAD patients, alone or in combination with other ambulatory devices, opens promising clinical perspectives. In addition to the sole assessment of the absolute claudication distance, GPS measurements enable clinicians to assess original walking parameters under community-based conditions, which are difficult to obtain through conventional laboratory

measurements, *e.g.*, free-living walking speed or stop durations induced by lower-limb pain. Measuring free-living walking speed is of interest because walking intensity has a direct consequence on the level of ischemia, and a small change in walking intensity results in a significant absolute claudication distance change (Gardner, 1993). Thus, an in-depth analysis of patient walking capacity should most likely take account of the absolute claudication distance and the walking speed.

At the diagnostic level, given the large reported difference in the assessment of walking capacity between GPS and treadmill walking test (Le Faucheur et al., 2008), GPS-measured ambulatory walking speeds and distances could provide better objective evidence of the magnitude of functional limitations of PAD patients. At the treatment level, absolute claudication distance during treadmill walking test is a major outcome measure for assessing the effect of treatment in PAD patients (Hiatt et al., 2014). However, focusing on the sole absolute claudication distance is most likely insufficient and does not enable clinicians to take into account various walking "strategies" that could be observed in treated patients (*e.g.*, no improvement in walking distance but increase in walking speed). Future studies should determine the effect of treatment procedure on GPS-derived parameters (*e.g.*, walking speeds and distances, stops duration between symptoms-limited walking bouts). In addition, GPS is a good candidate compared to accelerometers and could be used alone for controlling both walking speed and slope during community-based walking exercise programs. Finally, no objective data have been provided regarding the day-to-day variability of walking capacity. Performing multiple GPS recordings on multiple days over several weeks could provide interesting clinical information on walking impairment in PAD patients.

### **Perspectives**

Multiple studies have shown that ambulatory measured PA and walking capacity are of clinical interest at the diagnosis, treatment and epidemiological levels in PAD. PA and walking capacity are two different concepts. According to the objective of researchers and clinicians, this has important implications in both the choice of the ambulatory devices and the method in which they are used. Additional studies and technological enhancement should offer new opportunities for using and coupling multiple ambulatory devices in PAD patients.

### **Disclosure Statement**

None

## Funding

This study was supported by the University Hospital of Rennes (CORECT 2013 funding).

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## FIGURE LEGENDS

**Figure 1.** Flow of articles identified using the literature search.

Legend. \*entered as exploded MeSH Terms in MEDLINE and as exploded Emtree Terms in EMBASE; no specification in Web of Science.

**Figure 2.** Overview of ambulatory devices that can be worn by a patient to assess physical activity, walking pattern, and walking capacity.

Legend. Note that only some examples of ambulatory devices used in PAD are presented on the Figure. See text for details regarding the different models used. PADHOC: Peripheral Arterial Disease Holter Control device.

## SUPPLEMENTARY FILES FOR REVIEW

**Appendix 1.** Overview of the features of the ambulatory devices used for the measurement of physical activity or walking capacity in PAD.

ACCEPTED