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Screening Peripheral Artery Disease Using the Systolic Rise Time Measured with Photoplethysmography

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ABSTRACT

Screening for Peripheral Artery Occlusive Disease (PAOD) remains a challenge in the prevention and care of patients with arteriosclerosis. The Ankle Brachial Index (ABI) is currently the gold standard. However, ABI is time consuming and requires some expertise to perform which is a limiting factor for global screening. The measurement of the Systolic Rise Time (SRT) of the pulse wave of the lower limb may provide an easier alternative to detect PAOD. In a retrospective pilot study, we analyzed the possibility of detecting PAOD using the SRT of the toe waveform using the Photo-PlethysmoGraphic signal (PPG).

Methods: We measured 79 subjects (41 patients diagnosed with different stages of PAOD and 38 healthy volunteers without known PAOD). In each subject, at least one lower limb was assessed with classical ABI (minimum of 2 tibial arteries using a Doppler probe). All subjects underwent a PPG assessment on the finger and the toe simultaneously using pOpmètre® (Axelife – France). In-house software (JAVA) was used to calculate the SRT of all recorded signals.

Results: from the 154 lower limbs recorded, 8 were excluded for technical reasons: problematic cuff measurement of the ABI (in very severe PAOD, medial calcification & amputation) or bad quality of the PPG signal with very low amplitude. Finally, 146 lower limbs were analyzed including 72 healthy and 74 subjects with PAOD. The mean age of the population was 69±12 years with 75% men, 6% diabetics, 47% hypertensive, 49% without clinical PAOD defined as stage 0 in this study; 16% in stage 1; 32% in stage 2; 2% in stage 3 and 1% in stage 4 according to the Leriche classification. The SRT cut-off value of 160 ms identifies PAOD with a sensitivity of 78% vs 73% for ABI < 0.9 and a specificity of 86% vs 87%; a positive predictive value (PPV) of 85% vs 86% and a negative predictive value (NPV) of 79% vs 75%. In addition, the ratio between toe-SRT and finger-SRT cut-off value of 1 identifies PAOD with a sensitivity of 76% and a specificity of 74%.

Conclusion: SRT measured using a PPG pulse signal of the toe is promising as a simple non-invasive method to diagnose PAOD (duration <14 seconds) and determine if is there any PAOD with similar specificity and sensitivity to the reference method. These results need to be confirmed through a prospective study.

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Introduction

Peripheral Artery Occlusive Disease (PAOD) of the lower extremities is a major global public health problem. Nearly 120 million people are affected in all over the world and two-thirds of them have an asymptomatic form [1,2]. The prevalence increased by 25% from 2000 to 2010 and is currently estimated at between 30 and 40% of the population aged over 55 years [1]. PAOD is therefore a frequent pathology that can remain silent for years and whose prognosis is marked by cardiac and cerebro-vascular complications that can severely alter a patient's functional and essential prognosis.

PAOD is characterized by a long period of subclinical and silent lesions only accessible to clinical screening [3]. In order to reduce its complications, the World Health Authority recommends early individual screening of asymptomatic people at high risk for cardiovascular events [4].

Currently, the ankle-brachial pressure index (ABI) is the first-line screening reference method for the diagnosis of PAOD. However, this method is time consuming and has significant

inter-individual variability limiting its reliability and repeatability [5]. Furthermore, in diabetics, medial calcification decreases the sensitivity of ABI which can be misinterpreted in this high-risk population and needs to be replaced by toe-Brachial index that is much more difficult to measure [5].

A number of alternative methods have been developed, some of which are deemed easier to use, are less operator-dependent and are more acceptable to patients while still providing meaningful information. Reflection photoplethysmography (PPG) is a non-invasive method for studying peripheral blood volume pulsations by detection and temporal analysis of skin back-scattered optical radiation which can be monitored at different body locations such as fingertips, earlobes, forearms, forehead [1]. Various parameters extracted from the shape of the pulse wave recorded by photoplethysmographic sensors (PPG) have showed a good agreement to detect PAOD compared to ABI [2-4]. Among these indices, the Systolic Rising Time (SRT) corresponds to the time between the foot and the peak of the pulse wave. SRT reflects the arterial hemodynamic state particularly downstream to an arterial stenosis or obstruction and increases in the case of untreated PAOD [6].

Several studies have addressed the method of bilateral photoplethysmography (Allen and Murray 2000) which compares two PPG signal sequences recorded at anatomically symmetric sites of the human body (e.g. both earlobes or both index fingers), trying to extract physiologically important information from the observed differences. One study addressed the study of pulse wave analysis of a coupled recording of PPG and ECG signal. The study showed a sensitivity of the SRT to detect a PAOD of 84.2% and a specificity of 82.1 % when the ABI < 0.9 (i.e. the validated threshold for PAOD). However, the validity of this study was limited by the fact that the comparisons were done between the two legs in the same patient, which in case of bilateral PAOD could be of limited value.

Whatever the method, measurement of parameters reflecting the systolic acceleration such as SRT appears a suitable substitute to ABIs, especially in patients with non-compressible arteries such as diabetics. However, the previous studies were comparative between the 2 sides excluding the possibility that atherosclerosis could be affect both limbs and also didn't make a correlation with the clinical stages. Since the arterial bed from the upper limb is rarely affected by arteriosclerosis, we propose a new method to improve the detection and screening of PAOD based on the dual PPG simultaneous recordings of the pulse wave from the toe and the thumb.

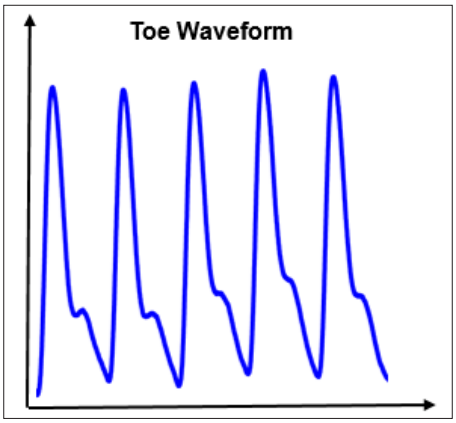

Figure 1: Toe Pulse wave recorded by the pOpmètre®.

Figure 2: measurement process

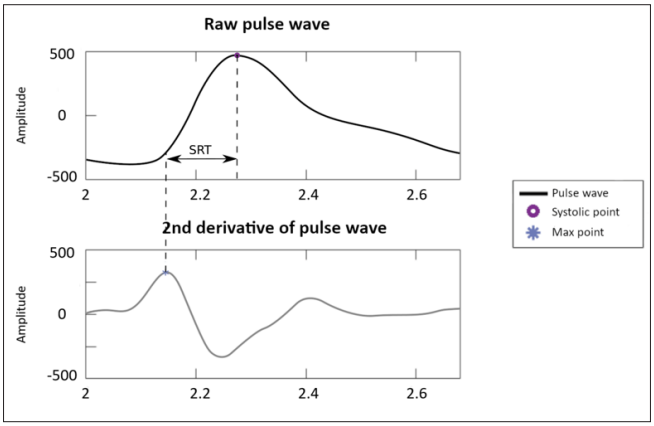

Figure 3: Calculation of SRT

Ankle-Brachial Index (ABI) measurement

For each patient, ankle and brachial pressures were measured using ultrasound Doppler at the anterior and posterior tibial artery of the right and left legs at least after 10 min supine rest. The right and the left ABI were computed as the ratio of the highest ankle systolic pressures measured in the right and left anterior and posterior tibial arteries and the highest systolic brachial arterial pressure [6]. An ABI value < 0.90 was considered for detection of PAOD.

Data analysis and statistics

According to their distribution, values are presented as mean ± standard deviation. Statistical comparison between groups were performed using a Kruskal & Wallis test. A binary classifier was used which classifies patients as sick or non-sick according to the SRT threshold. For each threshold, we therefore have a response vector of presence/absence of PAOD that we compare to our "real" vector of sick (ABI <0.9) and non-sick (ABI> 0.9) to calculate sensibility, specificity, negative and positive predictive values. The ROC curve allows us to measure the performance of the classifier and to visualize the anti-specificity according to the sensitivity for each chosen threshold of the SRT [7]. The association between ABI values and SRT were determined by a linear regression and the statistical significance of the correlation coefficients were determined using Pearson test. We used the linear regression equation to calculate ABIc. We studied the concordance between ABIc and ABI using Bland-Altman analyses. For all statistics, a P value < 0.05 was considered significant unless specified.

Results

Patients

Among the 154 recorded legs, SRT could not be measured in 8 patients due to poor or absent PPG signal recordings (toe amputation and very severe PAOD with merely no flow recordable at the toe). A total of 146 lower limbs could be analyzed of which 74 had an ABI > 0.90. Patients were divided into 2 groups with (PAOD+) or without PAOD (PAOD-). PAOD+ patients were aged 73 ± 10 vs 64 ± 13 years for those without PAOD. The mean ABI value was 0.71 ± 0.2 in PAOD+ and 1.09± 0.16 in PAOD- patients. The toe SRT was 187 ± 0.03 ms in patients with PAOD versus 133 ± 0.02 ms in patients without PAOD. There was no significant difference between the PAOD+ and PAOD- patients for the thumb SRT (164 vs 154 ms; p=0.14). The toe/thumb SRT ratio was significantly higher in the PAOD+ compared to the PAOD- (1.17 vs 0.89; p<10-4). We found an inverse linear relationship between SRT and ABI (r^2= 0.48; p<10-4, see figure 5).

Accuracy of Dual PPG to detect PAODThe ROC curve allowed for the best identification of PAOD with a SRT >160 ms for detecting PAOD (Figure 4) [7]. Using this threshold value of SRT, the sensitivity of 78% and a specificity of 86%, a positive predictive value (PPV) of 85% and a 79% negative predictive value (NPV) of SRT to detect a PAOD. The sensitivity and specificity of the ABI was 73% and 87% respectively for the assessment of PAOD according to Leriche & Fontaine grades. The correlation between SRT and ABI was statistically significant with R= -0.69 (p<0.001, ABI = -4.86SRT + 1.67, Figure 5). The box plot in figure 7 shows the differences between PAOD+ and PAOD- according to SRT or ABI. In both cases, the difference was significant (p< 10-4) between the PAOD+ and PAOD-. Furthermore, we have used Bland and Altman analysis to compare real ABI and estimated ABIc. The results showed good agreement between these measurement methods since there is no significant systematic difference between these two measurements (the estimated bias is 0).

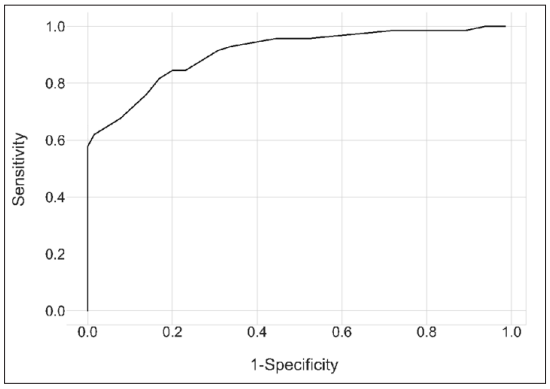

Figure 4: ROC Curve of SRT

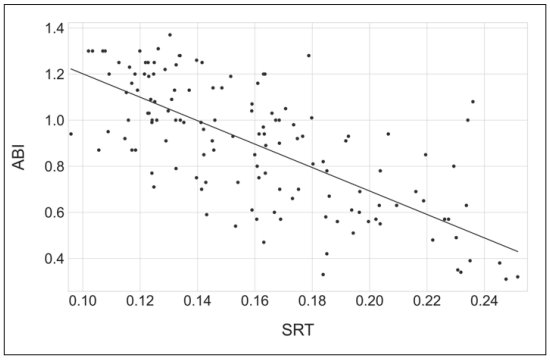

Figure 5: SRT value as function of ABI. N=146; R= -0.69; p-value < 0.01; ABI = – 4.86*SRT + 1.67

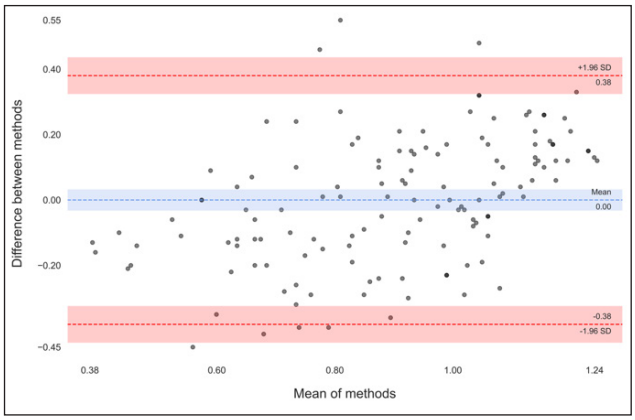

Figure 6: Bland-Altman plot for calculated ABI and measured ABI values

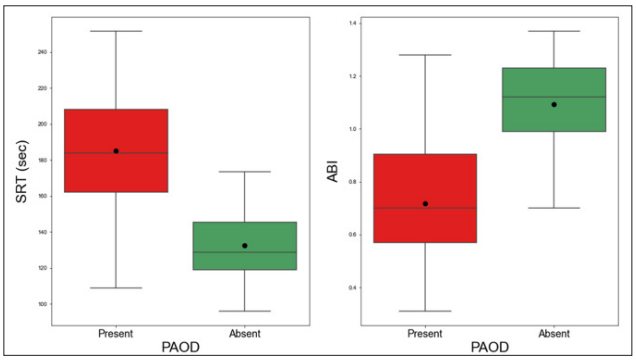

Figure 7: Boxplot of SRT and ABI in terms of different PAOD+ and PAOD.

Discussion

Our study showed comparable results between ABI and SRT to detect PAOD in term of sensibility and specificity to clinically detect a PAOD. We also found a significant inverse relationship between ABI and SRT indicating that SRT is a reliable surrogate for ABI.

Accuracy of dual PPG to detect PAOD

Our dual PPG method using the thumb as a reference for a normal SRT value showed that both toe SRT increases with PAOD due to increased resistance induced by the stenosis or obstruction upstream to the recording site [2]. Using PPG, Green et al showed that a SRT threshold of 200 ms had a sensitivity of 97%, a specificity of 93% and a diagnostic accuracy of 94% for the screening of PAOD using the toe PPG pulse wave [8]. Later, Bagi et al showed that SRT in the affected leg was highly correlated to the ABI for the diagnosis of PAOD [9]. In our study, although the sensitivity/specificity where much lower, we found a lower SRT at the toe (> 160 ms) which predicted PAOD defined on the basis of ABI with a sensitivity and specificity of 73% and 86% respectively and a Leriche and Fontaine stage 1 and above was discriminated with an excellent specificity and sensitivity (87 & 86 % respectively) in comparison to the ABI values in the same population (73 & 87 %).

Although the sensitivity was lower than previous study, our results for the sensitivity and specificity remained within the range of previous publication using PPG. This difference could be explained by the different methodologies employed in the other studies. In the study of Allen, the SRT was compared between the "healthy" and "diseased" legs in the same PAOD patients, while in our study we compared 2 different group of patients at different

stages of PAOD. Difference in the SRT value and threshold are likely due to the fact that we used different hardware devices with different response time and in the signal processing methods to calculate the SRT. Therefore, it is likely that for each method, it is necessary to determine a specific SRT depending on the technology.

Table 1: Shows the variables for the main population of the study

	All subjects (n=146 legs)	Study with PAOD (n=74 legs)	Study without PAOD (n=72 legs)	Diabetics (n=7 legs)
Age (years)	69 (±12)	73 (±10)	64 (±13)	73 (±6)
Height (cm)	169 (±8)	168 (±9)	170 (±8)	173 (±0.7)
ABI	0.9 (±0.27)	0.7 (±0.2)	1.09 (±0.16)	0.67 (±0.21)
Toe SRT (ms)	0.160 (±0.04)	0.187 (±0.03)	0.133 (±0.02)	0.207 (±0.02)
Index SRT (ms)	0.158(±0.04)	0.164 (±0.04)	0.154 (±0.03)	0.176 (±0.03)
SRT Toe / SRT Index	1.03(±0.25)	1.17 (±0.25)	0.89 (±0.16)	1.20 (±0.17)

Accuracy of Dual PPG and toe-thumb SRT ratio to detect PAOD In order to reduce the intra and inter-individual variability in the SRT, we tested the accuracy to detect PAOD using the Toe/Thumb SRT ratio. Since the upper limb is less likely to develop atherosclerosis, we expected that the thumb SRT could be taken as the reference SRT for a given patient and improve the determination of a threshold to detect PAOD. The toe-thumb SRT ratio showed a significant difference between PAOD + and PAOD - but failed to improve the accuracy to detect a PAOD than the toe SRT alone suggesting that the SRT is likely a constant of the vascular tree for a given subject.

Advantages and limitation of detecting PAOD with SRT

Contrary to ABI, the PPG signal allows for the screening of PAOD in less than 5 minutes 12, requires no specific training and is operator independent. Another advantages are that PPG doesn't require the use of occluding cuffs which is a major limitation of ABI in case of a skin ulcer or pain and subject to false value in case of incompressible arteries due to mediacalcosis in diabetics and chronic renal insufficiency. Furthermore, PPG could represent an advantage in diabetic patients with medial calcification where ABI is not biased.

And easier to perform than Toe-ABI. Another advantage is represented by the fact that it can simultaneously record several site at the same time, limiting the risk of measurement fluctuation, such as the case for ABI with the hand-held Doppler method. However, the determination of SRT requires a minimum of 10 recorded cardiac cycles, without arythmia and cannot be analyzed in case of a very low amplitude signal such as in cold extremities or severe PAOD. Furthermore, standardized values for SRT measured with PPG are still lacking and may be dependent from several factors including the PPG technology and algorithm as well as the sites, the number of affected vascular axis and the severity of the arterial lesions.

Conclusion

The present study confirms that SRT assessed from PPG signal in the toe can detect early stages of PAOD with a comparable accuracy than ABI. However, the use of a SRT reference value recorded in the upper limb didn't improved the accuracy and the reasons for inter-individual differences in the threshold SRT values remains to be investigated [10-14].

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