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ORIGINAL ARTICLE
Vascular medicine

Assessment of the systolic rise time by photoplethysmography in peripheral arterial diseases: a comparative study with ultrasound Doppler

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Aims Peripheral arterial disease (PAD) is a major public health burden requiring more intensive population screening. Ankle brachial index (ABI) using arm and ankle cuffs is considered as the reference method for the detection of PAD. Although it requires a rigorous methodology by trained operators, it remains time-consuming and more technically difficult in patients with diabetes due to mediacalcosis. Techniques based on the study of hemodynamic, such as the systolic rise time (SRT), appear promising but need to be validated. We retrospectively compared the reliability and accuracy of SRT using a photoplethysmography (PPG) technique to the SRT measured by ultrasound doppler (UD) in PAD patients diagnosed with the ABI (137 patients, 200 lower limbs).

Methods and results There was a significant correlation between SRT measured with UD (SRTud) compared with that with PPG (SRTppg, $r = 0.25$; $P = 0.001$). Best correlation was found in patients without diabetes ($r = 0.40$; $P = 0.001$). Bland and Altman analysis showed a good agreement between the SRTud and SRTppg. In contrast, there was no significant correlation between UD and PPG in diabetes patients. Furthermore, patients with diabetes exhibited a significant increase of SRTppg ($P = 0.02$) compared with patients without diabates but not with the SRTud ($P = 0.18$). The SRTppg was significantly linked to the arterial velocity waveforms, the type of arterial lesion but not vascular surgery revascularization technique.

Conclusion This monocentric pilot study shows that SRT measured with the PPG signal reliably correlates with SRT recorded with UD. The PPG is an easy to use technique in the hand of non-expert with a potential interest for general screening of PAD, especially in diabetes patients, due to its ease to use.

Keywords Peripheral arterial disease • Photoplethysmography • Doppler • Diabetes

Introduction

Peripheral arterial disease (PAD) of the lower limbs represents a major public health burden which concerns more than 200 million patients worldwide, two-thirds of them are asymptomatic[1] and characterized by a long infra-clinical delay before diagnosis. In diabetes patients, it is highly recommended by health authorities in many countries to screen both symptomatic and asymptomatic patients at cardiovascular risk for PAD[2] especially in diabetes patients. The ankle brachial index (ABI) is currently the gold standard method

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to screen for PAD. Despite its simplicity, this technique requires a rigorous methodology and remains time-consuming[3] with several inter-individual limits affecting its reliability and repeatability.[4–6] In addition, in diabetes patients at high cardiovascular risk, mediacalcosis decreases the sensitivity of ABI. This may require the use of alternative techniques such as toe pressure measurement.[7]

Investigation of the arterial tree using ultrasound techniques is considered as an alternative method for the screening of PAD and the diagnosis of chronic leg ischaemia.[8] The systolic rise time (SRT) is the time between the foot and the peak of the pulse wave. It is derived from the velocity waveforms recorded using the ultrasound Doppler (UD) method. The SRTud showed its diagnostic value in the evaluation of leg perfusion in PAD.[9] Furthermore, a good correlation between ABI and SRTud has been reported when the ABI is lower than 0.9.[10]

However, the UD technique requires a trained operator to perform reliable measurements. In contrast, recording of the pulse wave distally using photoplethysmography (PPG) is an operator-independent technique that could be promising for the screening of PAD. Similarly, to the UD waveform, the SRT is a parameter that can be easily extracted from the PPG pulse signal.[11] A prospective study including 222 legs using PPG coupled with an electrocardiogram[12] showed that SRT had a sensitivity of 84% and a specificity of 82% to detect PAD when the ABI is lower than 0.90. However, to our knowledge, there has been no study comparing the diagnostic value of SRT recorded by UD to SRT determined by PPG.

Therefore, the main objective of our study was to compare SRT using PPG to the SRT measured by UD in patients with PAD defined by ABI. The secondary objective was to compare the two SRT methods according to the clinical characteristics of the patients, namely the presence of diabetes, and the characteristics of the arterial lesions.

Methods

Patients'data

Data from consecutive patients were extracted from the clinical register recorded between November 2020 and April 2021. Patients from the register were screened either for a clinically suspected PAD or during their follow-up of a diagnosed PAD medically or surgically treated. A patient's record was eligible for the analysis if all data were available and no specific criteria were applied.

Clinical characteristics of patients

Cardiovascular risk factors (i.e. age, gender, diabetes, tobacco intake, arterial hypertension) as well as the medical and surgical vascular medical history were collected.

The PAD stage was defined using the Leriche and Fontaine classification. The type of surgery (i.e. stent, bypass or mixed) and its main site were determined as follows: proximal site including the aorta up to the external iliac and distal site including the common femoral artery up to the popliteal arteries.

Ankle brachial index

Blood pressure measurements were carried out on both arms and both ankles by an automatic oscillometric blood pressure measuring device (CARESCAPE V100) or by continuous UD probe[13] recorded at the level of the anterior and posterior tibial arteries of each leg. The measurements were taken after a minimum of 10 min of supine rest period. Ankle brachial index was calculated from the ratio between the arterial systolic ankle pressure collected from the anterior and posterior tibial artery the highest systolic brachial arterial pressures. A PAD was defined for each leg by an ABI of <0.9.

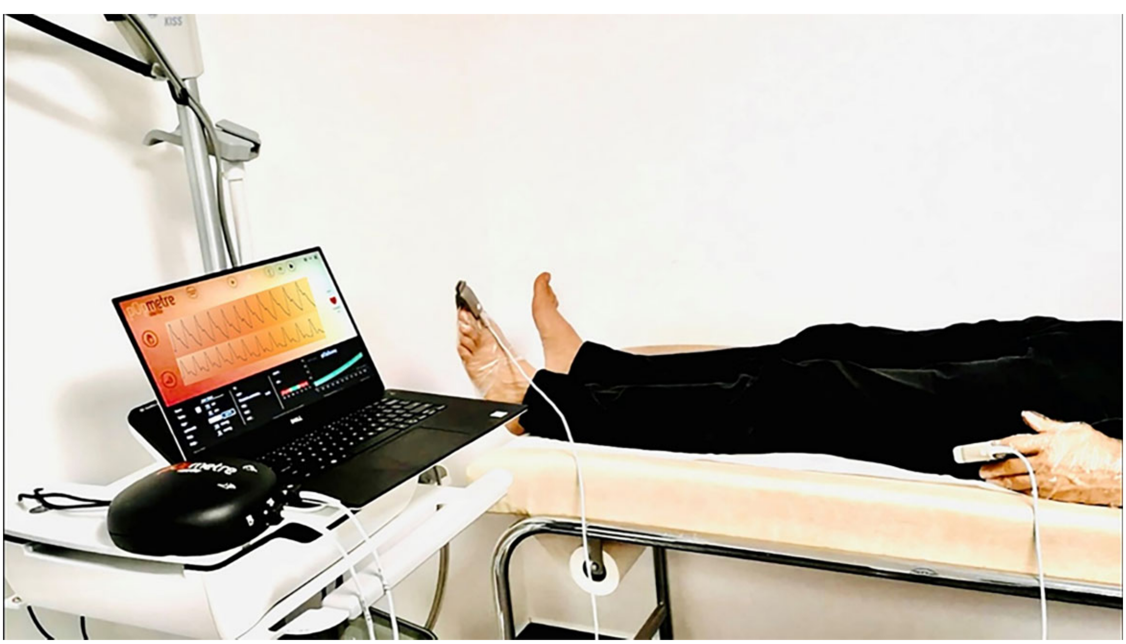

Figure 1 Systolic rise time measurement with pOpmètre® System

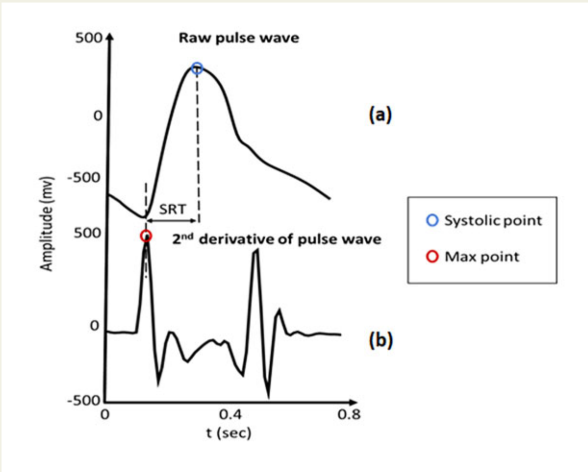

Figure 2 Calculation of systolic rise time by the pOpmètre® system, (a) raw photoplethysmography signal, (b) second derivative of the raw photoplethysmography signal. The max point of the second derivative is reported to the raw signal to detect the footwave of the pulse wave and calculate the systolic rise time.

Systolic rise time measurement by photoplethysmography

The PPG signal was collected using the pOpmètre® system (Axelife France, see *Figure 1*), at a sampling frequency of 1000 Hz providing a temporal resolution of 1 ms.[14] Briefly, the PPG signal corresponds to the variation of light absorption by the skin microvascular bed when the pressure wave passes over the pulp arteriole. The PPG signal is monitored by a photodetector placed nearby an emitting near-infrared LED. One PPG sensor was positioned on the right finger and the second sequentially on the right then on the left toe. The measurement was performed after at least 10 min of supine rest and local warming of the feet with disposable plastic socks. For each patient and each foot, 10 pulsed waves were recorded and stored. The SRT from the toe and the finger was calculated from the second derivative of the signal, allowing for the accurate detection of the ascending phase of the PPG signal (*Figure 2*). The SRT ratio was calculated by dividing the finger SRT by toe SRT for each foot.

Ultrasound Doppler measurement

Each patient underwent an ultrasound examination of the lower limb arteries using a S2000 (Siemens, Germany) using a high-frequency (5–7 MHz) Duplex ultrasound Doppler probe. All major arterial branches from the aorta to the ankle of both lower limbs were screened. B-mode imaging and Doppler velocity waveforms were recorded starting from the aorta down to the external iliac, femoral (common and superficial), popliteal and tibial arteries. The ultrasound SRT was determined manually by the operator on the Doppler velocity waveform collected from the posterior and anterior tibial artery. The distal flows were characterized according to the Saint-Bonnet classification of UD waveforms.[15,16] According to the velocimetric criteria, a moderate stenosis was defined by an increase in velocity amplitude ranging from 50% to 70% while severe stenosis was considered if >70%. Arterial occlusion was defined by the absence of detectable flow in the arterial segment.

Ethical consideration

This retrospective monocentric study was performed on data issued from a clinical register housed at the Vascular Medicine Department of the University Hospital of Nice – France. The register has been approved by the Data Protection Committee at the University hospital of Nice (cohort register referenced BS-004) and therefore compliant with the ethical use of patient's clinical data, including an oral consent from the patient.

Table 1 Description of the study population [Median (IQR) for quantitative data and effective (percentages) for qualitative data]

	All legs (n = 200)	ABI < 0.9 (n = 108)	ABI > 0.9 (n = 92)
Age (years)	73 (65–78)	74 (67–78)	71 (62–78)
SRTppg (ms)[a]	202 (172–239)	225 (195–249)	180 (160–202)
SRTud (ms)[a]	80 (63–101)	85 (68–121)	75 (62–90)
Type of vascular surgery			
Stent	31 (15.5%)	13 (12%)	18 (19.6%)
Bypass	27 (13.5%)	19 (17.6%)	8 (8.7%)
Both	9 (4.5%)	6 (5.6%)	3 (3.3%)
Type of lesions severe stenosis/occlusion	29 (14.5%)	24 (22.2%)	5 (5.4%)
non-severe stenosis	29 (14.5%)	23 (21.3%)	6 (6.5%)
Saint-Bonnet's waveform classification[16]			
A	97 (48.5%)	40 (37%)	57 (62%)
B	25 (12.5%)	21 (19.4%)	4 (4.3%)
CD	52 (26%)	41 (38%)	11 (12%)
N	26 (13%)	6 (5.6%)	20 (21.7%)
			All patients (n = 100)
Gender			69 men (69%)
PAD Leriche-Fontaine stage			
0			37 (37%)
1			22 (22%)
2			26 (26%)
3			7 (7%)
4			7 (7%)
TD2[b]			30 (30%)
Site of vascular surgery			
Proximal			27 (27%)
Distal			24 (24%)

[a]Systolic rise time.
[b]Type 2 diabetes.

Statistical analysis

All values are presented as median (interquartile range) for quantitative data and as percentages for qualitative data. Comparisons between the PAD groups were made using the Kruskal–Wallis tests. A Welch *t*-test was used to test the hypothesis of equality of means with several samples of unequal variance. Correlations between SRT measured by PPG and UD were determined by Pearson's test. Receiver operating characteristic curve was used to find out the best specificity/sensitivity. For all statistics,

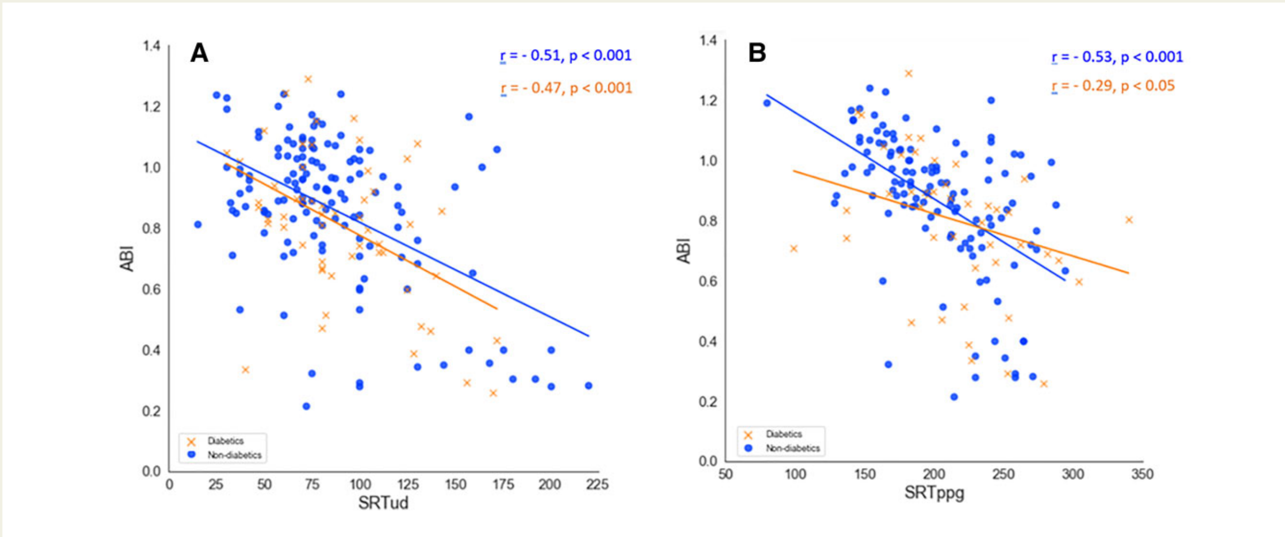

Figure 3 Relationship between ankle brachial index and systolic rise time. (A) ABI = 1.13–0.003*SRTud; $P < 0.001$ for non-diabetes and ABI = 1.11–0.003*SRTud; $P < 0.001$ for diabetes. (B) ABI = 1.45–0.003*SRTppg; $P < 0.001$ for non-diabetes and ABI = 1.1–0.001*SRTppg; $P < 0.05$ for diabetes.

the confidence interval was set at 95% and a *P*-value <0.05 was considered significant, without adjustment for multiple comparisons.

Results

Studied population:

All clinical and UD characteristics are detailed in *Table 1*. Among the 137 patients included in the register during the study period, data from 100 patients could be analyzed according to the inclusion criteria. Eighteen were excluded due to limb amputation and nineteen were incomplete. The patients were aged 71 ± 7 years, with 69% men. Sixty percent had PAD according to the ABI criteria, 30% were treated for Type 2 diabetes (T2D), of which two-third had an ABI < 0.9.

Relationships between photoplethysmography and ultrasound Doppler

The relationship between ABI and SRT measured by PPG (SRTppg) and by UD (SRTud) is presented in *Figure 3*. This graph shows a negative correlation between ABI vs. SRTppg and SRTud, in both the diabetes and non-diabetes groups ($r = -0.46$; $P < 0.001$ and $r = 0.46$; $P = 0.001$, respectively).

To evaluate the effectiveness of the ABI lower than 0.9 detection by SRT, an ROC curve for various thresholds of SRT is presented in *Figure 4*. The area under the curve (AUC) value of 0.73 indicates that identification of ABI by SRTppg is more accurate than SRTud (AUC = 0.57). An ROC curve analysis showed that SRTppg cut-off value of 200 ms identifies PAD with a sensitivity of 70% and a specificity of 71% for ABI <0.9. In contrast, about SRTud a cuttoff of 80 ms showed 58% sensitivity and specificity.

The agreement beetween SRTppg and SRTud is described with a Bland and Altman plot (*Figure 5*). The average of the difference between the two methods was 120 ms, meaning that, on the average, the SRTppg is greater by 120 ms compared with the SRTud. Ninety-five percent of the data lie within the range of agreement (23–218.6). To interpret this result, the normal distribution of the differences was verified by the Shapiro–Wilk test that indicates a *P*-value of 0.03 confirming the normality of the distribution with a 1% threshold.

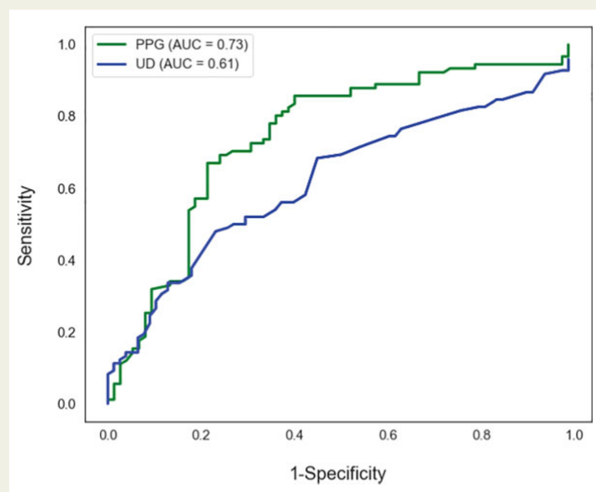

Figure 4 Receiver operating characteristic (ROC) curves of SRTppg and SRTud identification of ankle brachial index lower than 0.9

A weak positive, but significant, correlation was found between SRT measurements with PPG vs. UD ($r = 0.25$; $P = 0.001$). In the T2DM subgroup, the correlation coefficient was not significant ($r = 0.08$; $P = 0.6$) compared with the non-TD2M subgroup ($r = 0.40$; $P < 0.001$). Furthermore, compared with non-diabetes patients, diabetes patients exhibited a significant increase of SRTppg ($P = 0.02$) but not of the SRTud ($P = 0.18$)

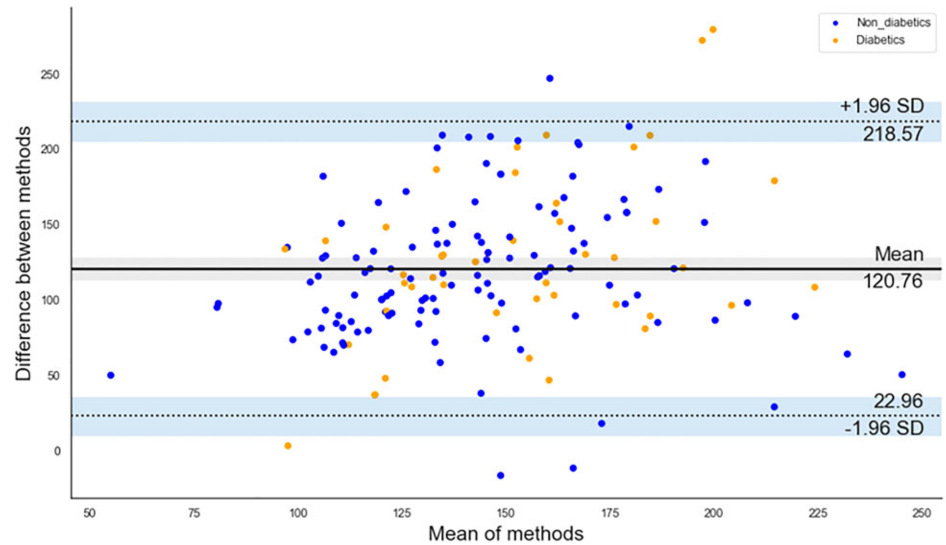

Figure 5 Bland Altman plot for SRTppg and SRTud.

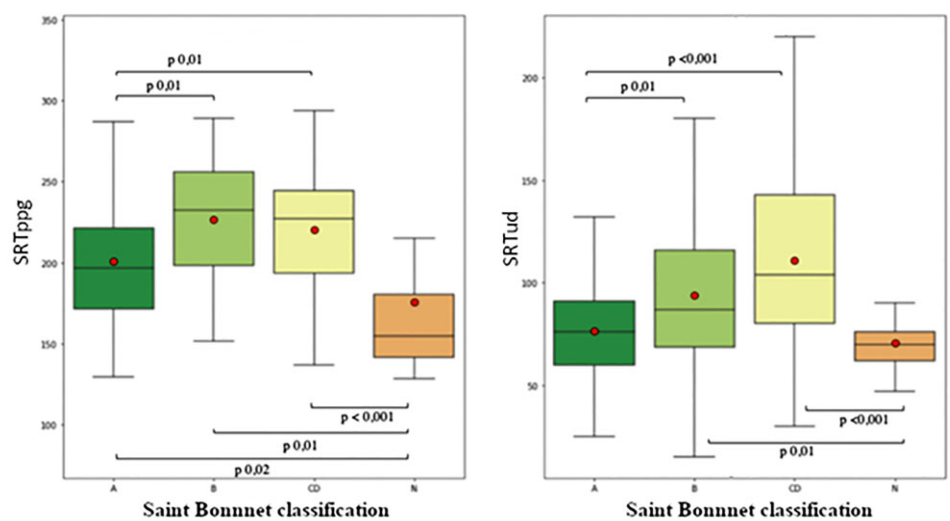

Figure 6 SRTud and SRTppg according to the Saint-Bonnet waveform type classification of ultrasound Doppler velocity waveforms.

Links between ultrasound Doppler waveforms and systolic rise time

A significant difference between the SRTppg values was found for all types of Saint-Bonnet waveforms (*Figure 6*), excepted between the B and CD waveform types. For SRTud, similar differences were found, excepted between the A and N, and B and CD waveform types. Receiver operating characteristic curves were built to assess the performance of SRTppg and SRTud to predict Saint-Bonnet waveforms. Receiver operating characteristic curves analysis shows that SRTppg and SRTud are more discriminant for doppler waveform of type N (SRTppg: AUC = 0.75, SRTud: AUC = 0.69) and A (SRTppg: AUC = 0.58, SRTud: AUC = 0.64) (*Figure 7*). Area under the curve for the other type was <0.43 (SRTppg: AUC = 0.75, SRTud: AUC = 0.69) and for type A (SRTppg: AUC = 0.58, SRTud: AUC = 0.64) (*Figure 7*).

Moreover, the analysis showed that SRTppg and SRTud had comparable sensitivity and specificity respectively of 80% and 56% vs. 82% and 56% to detect N waveform type. For type A waveforms, sensitivity and specificity of SRTppg were 55% and 58% while SRTud was 56% and 57%, respectively.

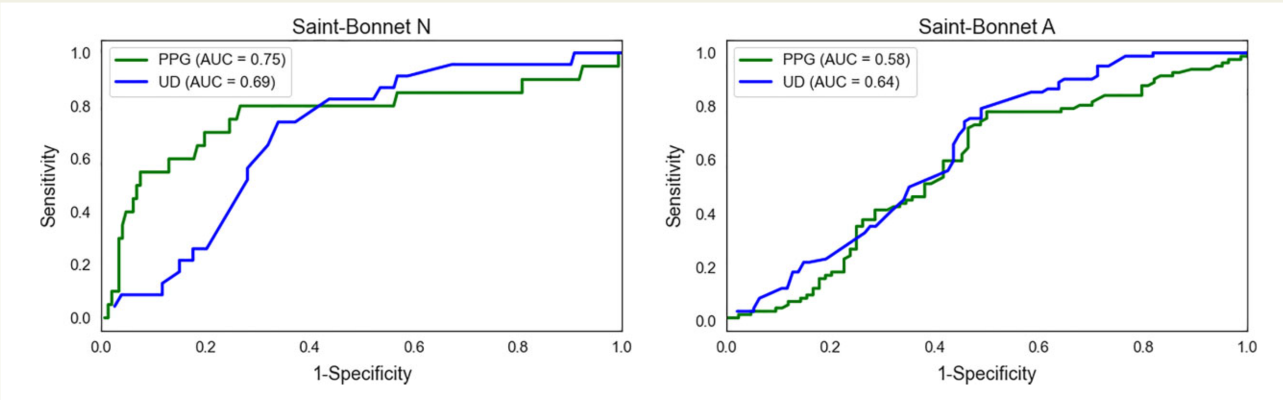

Figure 7 Receiver operating characteristic (ROC) curves of SRTppg and SRTud identification of Saint-Bonnet waveform classification.

Effect of arterial lesions on systolic rise time

The SRTppg and SRTud were significantly altered by the type of arterial lesion ($P < 0.001$). Compared with the normal patency, SRTud was significantly increased in other type of lesions (non-severe stenosis: $P = 0.04$, severe stenosis or occlusion: $P < 0.001$). There was also a significant difference between the SRTud measured in non-severe stenosis vs. severe stenosis ($P = 0.02$). For the SRTppg, there was no significant difference between the absence of stenosis and the presence of a non-severe stenosis ($P = 0.49$) but a significant difference of SRTppg was found between the absence of stenosis and the presence of a severe stenosis and/or occlusion ($P < 0.001$).

The SRTppg was not significantly affected by the site of the arterial lesions (i.e. proximal vs. distal: $P = 0.15$) while significant differences between proximal and distal site of lesions were observed with SRTud ($P < 0.001$). Finally, both SRTppg and SRTud were not significantly affected by the type of vascular revascularization surgery ($P = 0.99$ and $P = 0.50$ respectively)

Discussion

Ankle brachial index is a standardized method recommended for the screening of PAD.[6] However, the reproducibility of this method varies according to some studies[4] and does not give valuable information about the vasculature state at a microvascular level. Furthermore, the diagnostic value of ABI is unreliable in the case of increased arterial wall stiffness, such as mediacalcosis in patients with diabetes.[15,16] Therefore, the measurement of SRT with UD represents a reliable alternative that can help to study the peripheral haemodynamic changes induced by arterial lesions[17] with a good predictive value[18] and correlate well with ABI.[10] However, the use of UD remains a more technically demanding technique requiring an experienced operator and therefore not suitable for large population screening in the hands of non-vascular specialists.

Photoplethysmography is a potentially interesting alternative technique for the screening of PAD, its greatest advantages its operator independency with a learning curve <30 min. The simplicity, rapidity, feasibility, patient acceptability, and correct agreement with the reference technique[19,20] make it suitable for large-scale screening. Previous studies using PPG have also reported a significant correlation with ABI.[21–24] In the present study, we observed a significant correlation between SRTppg and SRTud in patients with or without PAD although the difference between these techniques remains significant.

In our study, the SRTppg and SRTud were significantly influenced by the presence of T2D. Compared with subjects without diabetes, we found a significant difference between the SRTppg but not with SRTud. This finding can be explained by the fact that, contrary to the UD probe that records arterial flow from the main limb arteries, the pulpar arterial blood flow recorded with the PPG sensor likely reflects the microvascular beds which is primarily affected in patients with diabetes.

Our study also showed that the SRTppg and SRTud are both significantly linked to the characteristics of the arterial velocity waveforms as determined by the Saint-Bonnet classification, as well as the severity of the arterial lesions. The Saint-Bonnet classification is a method that determines the level of severity according to the velocity waveforms.[25] Interestingly, the SRTppg was highly discriminative for each severity stages of the classification which could provide additional hemodynamic information although none of the SRT could discriminate between the monophasic and the release time of the velocity waveform. This could be explained by the fact that both SRT mainly reflect the upstroke part of the arterial velocity waveform. Although the SRTppg signal was altered by the presence of stenotic lesions, this was not significantly related to the site of the arterial lesions. This result is in agreement with a previous study suggesting that the SRT is not significantly different between proximal lesions (i.e. aorto-iliac level) and more distal lesions (e.g. femoral level).[26] Interestingly, neither SRTud nor SRTppg were influenced by the presence of arterial ectasia, indicating that these methods are not suitable for the detection of these lesions in the general population. Furthermore, both the SRTppg and SRTud were not significantly influenced by the type of revascularization methods (i.e. bypasses or stenting) suggesting that the bypass material has no significant influence on the arterial hemodynamic and can restore the 'normal' velocity waveforms profiles.

Finally, the difference between SRTppg and SRTud can be related to the difference in technology (ultrasound vs. infrared light), the difference between velocity and PPG waveforms where the peak systolic is blunted in the velocity waveform than the PPG one,[27] the signal processing methods and the fact that UD detects the blood flow and PPG detects the arteriole dilation with the pressure wave arriving in the pulpar artery.

Study limitations

Although PPG shows several advantages over UD to determine SRT for the screening of PAD, it also has several limitations: The quality of the recorded PPG signal depends on the physiological and environmental conditions (e.g. skin temperature, ambient light or patient movements) which influence the haemodynamic states of the distal arteriolar flow independently from PAD.[11] The degree of peripheral vasoconstriction might hamper the measurement of finger/toe pulses as reported with others PPG device or oxymeters. Severe vasoconstriction as in Raynaud disease or hemodynamic shock are excluded for the use of PPG. Sufficient time is needed to warm up the hands and feet so that less than 2% of patients cannot be measured with PPG sensor.[28] A low amplitude signal due to poor microvascular perfusion can be differentiated from a low signal due to cold-induced vasoconstriction if the signal remains low after local warming of the toe and/or fingers by wearing socks clear plastic disposable and glove. Another limitation in our study is the fact that the diagnostic value of SRTppg in patients with diabetes was not evaluated against the toe-brachial index, a recommended method in this population with mediacalcosis.[15] Finally, irregular beats due to extrasystoles or atrial fibrillation remains a general limit to the determination of the SRT whatever the recording technique is used.[20]

Conclusion

Our study shows a weak but significant correlation of the SRT measured using the PPG signal recorded in the extremities with respect to the SRT measured with the UD, especially in non-diabetic patients. Although these two methods have a potential interest for the screening of PAD compared with ABI. Photoplethysmography has the advantage of ease to use in a short time (<5 min) and at a lower cost than the UD techniques because of much more costly devices. Although further studies are needed to confirm our findings, SRTppg could be an interesting method for PAD screening in the diabetic patients, especially in the hand of non-specialized medical staff.

Lead author biography

Professor Georges Leftheriotis (63 yrs), MD, PhD, is currently professor of physiology at medical school of University Cote d'Azur and head of the vascular department at University hospital of Nice. Within the last 15 years, his research focused on vascular calcifications and cardiovascular risk in metabolic syndrome. He published more that 200 per-reviewed articles and led or participated in more than 50 scientific research programmes in these domains. He is the former president of the French physiological society, a founding member of the 2015–2021 Cost action 'EuroSoftcalc.net', a past member of the scientific board of the French vascular medicine society and founding member of the executive board of the newly created international scientific society for ectopic calcification (ISSEC).

Data availability

Due to its proprietary nature and ethical concerns, supporting data cannot be made openly available. For further information about the data you can refer to Professor Georges Leftheriotis.

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