

ORIGINAL ARTICLE

Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness

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Arterial tonometry is a method to assess arterial stiffness and has become a valuable tool in the stratification of cardiovascular risk. The arterial tonometry-derived augmentation index (AIx) is a marker of arterial stiffness and an independent predictor of mortality. As the AIx is relatively cumbersome to obtain, simpler methods such as analysis of pulse waves obtained by digital photoplethysmography have been proposed to estimate arterial stiffness. The objective of this study is to compare the usefulness of the stiffness index (SI) derived from digital photoplethysmography and the AIx derived from radial tonometry for stratification of cardiovascular risk. We studied 83 subjects with a heterogeneous cardiovascular risk profile and determined the ability of the two devices to differentiate subjects with low from subjects with high cardiovascular risk estimated by the Europe (EU)-heart score. Failure rate in both devices was similar (3.6%). AIx and SI were modestly correlated ($r=0.48$, $P<0.001$) and both indexes correlated with the EU-score ($r=0.54$, $P<0.001$) and ($r=0.56$, $P<0.001$), respectively. Both devices discriminated accurately between subjects with high cardiovascular risk (upper tertile of the EU-score) and low cardiovascular risk (lower tertile). However, only the SI differentiated significantly between subjects with intermediate risk (middle tertile) and high risk (upper tertile). Compared with the AIx, assessment of the SI derived by digital photoplethysmography is simple and possibly yields an advantage in risk stratification of subjects with intermediate and high cardiovascular risk. Therefore, digital pulse wave analysis may be a valuable tool to estimate arterial stiffness in large clinical studies.

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INTRODUCTION

Cardiovascular diseases are the foremost cause of death globally, and there are numerous risk factors such as diabetes, hypertension, dyslipidemia, smoking and obesity associated with their development and progression.^{1,2} The presence of these risk factors is known to alter vessel wall properties and increase arterial stiffness leading to accelerated atherosclerosis. In the absence of clinically apparent vascular disease the detection of subclinical atherosclerosis may enable early control of cardiovascular risk factors and thus prevent the development of overt vascular disease.^{3–6} Various non-invasive techniques measuring arterial stiffness are currently available.^{7,8} Most devices derive their measures of arterial stiffness from peripherally acquired waveforms using arterial tonometry. Arterial tonometry-derived augmentation index (AIx) has been shown to be an independent predictor of mortality and cardiovascular events in patients with hypertensive, cardiovascular and renal disease.^{7,9} However, measurements are often time consuming and a training to operate these devices is necessary. For risk assessment in large clinical trials and population-based studies it would be desirable to rely on a non-invasive technique that is user independent, rapidly performed and inexpensive.

Digital photoplethysmographic assessment of the peripheral arterial pulse waveform allows pulse wave contour analysis and estimation of arterial stiffness by the stiffness index (SI).¹⁰ However, data from large cohorts and a description of the feasibility of the technique compared with radial applanation tonometry in a heterogeneous population are lacking. Furthermore, it has not been thoroughly established, whether the SI accurately discriminates subjects with increased cardiovascular risk from subjects with no risk factors.

Therefore, the purposes of this study were to evaluate (i) the feasibility and failure rate of the digital volume pulse (DVP) analysis in subjects with different degrees of cardiovascular risk (ii) the correlation between the more established AIx and the SI derived by DPV analysis and (iii) the usefulness of the SI and AIx in discriminating subjects with high cardiovascular risk from subjects with low risk in a heterogeneous population of patients and healthy subjects.

METHODS

Subjects

A total of 62 patients with either chronic obstructive pulmonary disease ($n=35$) or obstructive sleep apnea ($n=27$) were recruited from the pulmonary out-patient clinic, and 21 healthy subjects were recruited as healthy controls.

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Subjects of both sexes aged between 18 and 75 years were included. We excluded subjects with mental or physical disability precluding informed consent or compliance with the protocol. To determine cardiovascular risk-by-risk factors all subjects were assessed with a full medical history and physical examination.

The study has been carried out in accordance with the Declaration of Helsinki of the World Medical Association. The local Ethical Committee approved the study and all subjects gave written informed consent to participate.

Blood pressure and assessment of cardiovascular risk

Blood pressure measurements were performed in triplicate in supine position. Risk factors were defined as a body mass index above 25 kg m^{-2} (WHO (World Health Organization) definition of overweight), arterial hypertension with a blood pressure $> 140/90 \text{ mm Hg}$,¹¹ a cholesterol level $> 5 \text{ mmol l}^{-1}$,¹² a fasting blood glucose level $> 7 \text{ mmol l}^{-1}$,¹³ and active smoking. The 10-year risk of fatal cardiovascular disease was assessed with the Systematic Coronary Risk Evaluation for the lower risk populations of Europe (EU-score).¹⁴ To analyze the usefulness of the arterial stiffness measurements for cardiovascular risk stratification subjects were grouped according to the number of risk factors and allocated to risk groups based on the EU-score.

Study protocol

The studies were undertaken in a temperature-controlled room with the study subject in supine position for at least 10 min before beginning with the measurements. Measurements were performed on the right arm and DPV analysis was performed immediately before arterial tonometry.

DPV analysis and the SI

The DVP is obtained by measuring the amount of transmitted red light through a finger pulp. The photoplethysmographic transducer uses a signal conditioning circuit to obtain an accurate and noise-free signal at a sampling frequency of 100 Hz. The amount of light transmitted is indirectly proportional to the blood volume in the finger pulp and its changes due to pulse waves. The critical points of the waveform used for further analysis are systolic peak, systolic inflection point and diastolic inflection point. The second peak of the DVP is modulated by reflection of the smaller sized distal arteries. The time delay between the systolic and diastolic peaks (or, in the absence of a second peak, the point of inflection) is related to the transit time of pressure waves from the root of the subclavian artery to the apparent site of reflection and back to the subclavian artery.¹⁵ The device collects six representative pulse waveforms with a pulse interval close to the average pulse interval. In case of irregular heartbeat the device prolongs the time of data capture. The arterial SI is defined as height divided by the time from the systolic to diastolic inflection point (Figure 1a).

Two measurements were performed in each subject to assess repeatability and the average of the two measurements was used for final analysis.

Radial arterial tonometry and AIx

Radial artery pulse waveforms were recorded at a sampling rate of 128 Hz with a pressure tonometer and designated software (SphygmoCor, At-Cor Medical, Sydney, Australia). Briefly, mean values of ~ 10 radial pressure waves are used to generate a mean radial pressure waveform. The peripheral (radial) AIx is the ratio of second to the first peak of the radial pressure wave expressed in percentage. The software uses a mathematical transfer function to determine the aortic pressure waveform and to estimate central arterial stiffness.¹⁶ The central (aortic) AIx quantifies augmentation of central aortic pressure because of the reflected component of the pulse pressure waveform as illustrated (Figure 1b). The aortic AIx typically increases with age as the arteries become stiffer (or less compliant).^{17,18} Following the recommendations of the manufacturer a measurement was only accepted when the operator index (with a range from 0 to 100 with increasing quality) was above 80.

Data analysis and statistics

Results are shown as mean values and standard deviation (s.d.) unless otherwise stated. Pearson's correlation was used to investigate relationships between SI,

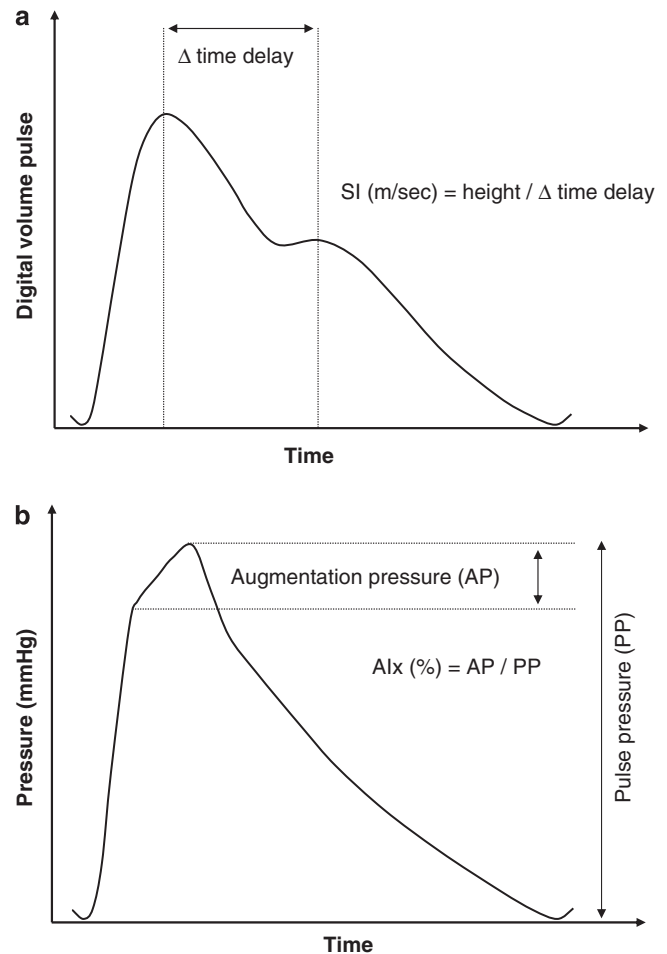


Figure 1 (a) The stiffness index (SI) is obtained from a photoplethysmograph measuring the digital volume pulse. The SI is calculated as the subject's height divided by the time delay between the first systolic peak and the early diastolic peak of the waveform. (b) The aortic pressure waveform is estimated from the radial arterial pressure wave using a validated mathematical transfer function. The aortic augmentation index is defined as the difference between the second and first systolic peak (augmentation pressure) divided by the pulse pressure (AIx, expressed as percentage of the pulse pressure).

AIx and the EU-score. Differences between groups were evaluated by using analysis of variance followed by *post hoc* analysis (Newman-Keuls test). Receiver operating characteristic curve analysis was undertaken to determine the optimal cutoff value of arterial stiffness indices for predicting the presence of cardiovascular risk factors. Multivariate analysis was performed to assess the associations between indices of vascular stiffness and cardiovascular risk factors including arterial hypertension, hypercholesterolemia, overweight, diabetes and smoking. A probability of $P < 0.05$ was assumed as significant.

RESULTS

Study population

Table 1 shows the characteristics and the cardiovascular risk profile of the 83 subjects (14 females) entering the study. In Table 2 subjects are grouped according to the number of cardiovascular risk factors.

Feasibility of measurements

The SI could not be obtained by photoplethysmographic DVP in three study subjects (3.6%). In all three cases the SI could not be calculated

Table 1 Subject characteristics

	Study subjects
No. of subjects	83
Male/female	69/14
Age (years)	53.2 (17.3)
Height (cm)	174.3 (9.3)
Weight (kg)	84.8 (22.1)
BMI (kg m ⁻²)	27.9 (6.8)
Mean systolic BP (mm Hg)	127.5 (13.6)
Mean diastolic BP (mm Hg)	80.3 (11.4)
Mean arterial BP (mm Hg)	91.1 (9.5)
Mean heart rate (min ⁻¹)	71.8 (13.7)
Hypertension (%)	49
Cholesterol (mmol l ⁻¹)	5.0 (1.1)
Hypercholesterolemia (%)	49
Active smoking (%)	8
Diabetes (%)	11
Statin therapy (%)	23
Antihypertensive medication (%)	47
EU-score (%)	2.1 (1.8)

Abbreviations: BMI, body mass index; BP, blood pressure; EU, Europe.

Hypertension was defined as a blood pressure >140/90 mm Hg; hypercholesterolemia defined as a total cholesterol >5 mmol l⁻¹; EU-score: the European Society of Cardiology based heart score estimating the 10-year risk (%) of fatal cardiovascular disease in low-risk populations of Europe.

Table 2 Cardiovascular risk stratified by the number of cardiovascular risk factors

	No cvrf	One cvrf	Two or more cvrf	P-value ^a
No. of subjects	22	16	41	
Male/female	22/0	16/3	41/7	
Age (years)	32.6 (17.1)	55.2(14.8)	61.8 (6.7)	<0.001
Height (cm)	178.0 (7.0)	171.5 (11.0)	174.1 (8.3)	0.067
Weight (kg)	70.3 (8.7)	73.4 (18.2)	97.1 (22.3)	<0.001
BMI (kg m ⁻²)	22.2 (2.4)	24.8 (4.8)	31.9 (6.6)	<0.001
Mean systolic BP (mm Hg)	124.1 (7.4)	126.4 (14.2)	130.4 (15.5)	0.191
Mean diastolic BP (mm Hg)	72.8 (7.0)	82.7 (11.1)	84.1 (11.5)	<0.001
Mean arterial BP (mm Hg)	89.8 (5.9)	94.0 (11.5)	90.7 (10.2)	0.378
Mean heart rate (min ⁻¹)	70.1 (5.9)	72.1 (9.3)	70.8 (14.4)	0.900

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; cvrf, cardiovascular risk factor; EU, Europe.

^aP-value comparing the three groups (ANOVA).

from the contour of the DPV curve because the systolic peak of the volume pulse could not be differentiated from the diastolic peak, thus no inflection point could be found.

In three subjects (3.6%) radial artery tonometry failed to determine AIx. Atrial fibrillation lead to an unacceptable amount of variation among the pulse waves in two cases and in one case the amount of pulse height variation was too high for an acceptable measurement.

Within subject repeatability of the SI

To assess within subject repeatability of the SI subjects were measured two times. The mean difference (s.d.) of the SI between the two measurements was -0.08 (0.98) m/s, corresponding to 3.5 (4.6)%.

Correlation of AIx and SI

Peripheral and central (aortic) AIx derived by applanation tonometry were modestly correlated with the SI ($r=0.48$, $P<0.001$ and $r=0.51$,

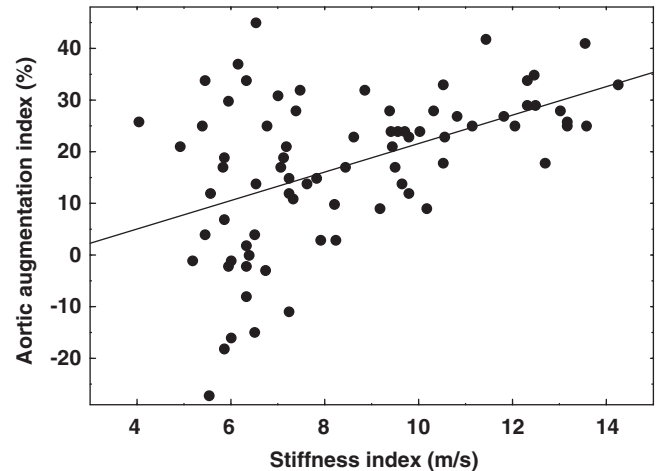


Figure 2 Scatterplot showing the relationship between the stiffness index derived by digital pulse volume analysis and the aortic augmentation index derived by radial applanation tonometry ($r=0.48$, $P<0.001$).

$P<0.001$), respectively (Figure 2). If only subjects with low cardiovascular risk (lower tertile of the EU-score) were included in the analysis no correlation between SI and AIx was observed ($r=0.20$, $P=0.34$). In subjects with increased cardiovascular risk (middle and upper tertile of the EU-score) there was a modest correlation between SI and AIx ($r=0.30$, $P=0.03$).

Cardiovascular risk stratification by SI

Of all subjects, 22 (26.5%) had no cardiovascular risk factor, 16 subjects (19.3%) had one risk factor and 41 subjects (49%) had 2 or more risk factors. As shown in Figure 3a, mean SI was significantly lower in subjects with no risk factors 6.4 (1.2) m/s, compared with subjects with one risk factor 8.5 (2.3) m/s, and subjects with two or more risk factors 9.4 (2.6) m/s ($P<0.001$). Comparing the groups by EU-score tertiles (Figure 3b) demonstrated significant differences in SI ($P<0.001$) between groups and SI correlated with the EU-score ($r=0.56$, $P<0.001$).

Receiver operating characteristic curve analysis revealed that the best sensitivity and specificity to predict elevated cardiovascular risk occurred at a SI value of 7.14 m/s (area under curve 0.83 ± 0.05 , $P<0.001$, Figure 4a).

Multivariate analysis including all conventional cardiovascular risk factors indicated that active smoking (β -coefficient: 0.23, $P=0.03$) and a BMI >25 kg m⁻² (β -coefficient: 0.33, $P=0.01$) were independently associated with the SI.

Cardiovascular risk stratification by AIx

The peripheral AIx and the central (aortic) AIx derived by radial pulse wave analysis were significantly higher in subjects with one or more cardiovascular risk factors compared with subjects without any cardiovascular risk factor ($P<0.001$, Figures 5a and 6a). Grouped according to tertiles of the EU-score the peripheral and aortic AIx were significantly higher in the upper tertile compared with the lower tertile ($P<0.001$, Figures 5b and 6b) and the EU-score correlated with aortic AIx ($r=0.54$, $P<0.001$) and peripheral AIx ($r=0.60$, $P<0.001$). In contrast to the SI aortic and peripheral AIx were not statistically different between the middle and upper tertile of the EU-score.

Receiver operating characteristic curve analysis revealed that the best sensitivity and specificity to predict elevated cardiovascular risk

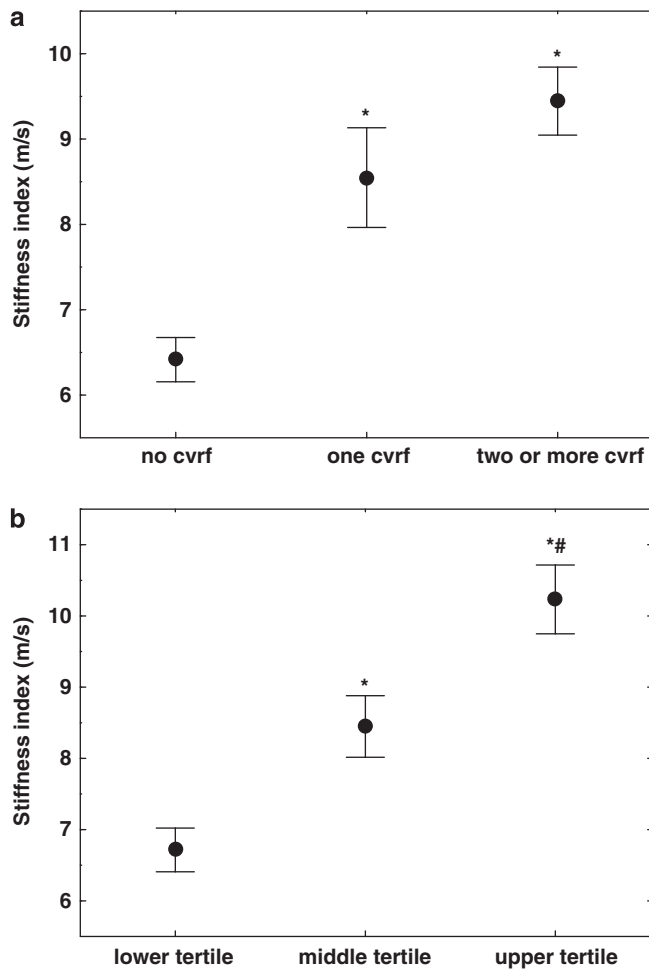


Figure 3 (a, b) In panel **a** the stiffness index (s.e.) of all subjects is grouped according to the number of cardiovascular risk factors (* $P < 0.001$ vs. no cardiovascular risk factor). In panel **b** the stiffness index (s.e.) of all subjects is grouped according to lower, middle and upper tertile of the EU-score (* $P < 0.01$ vs. lower tertile of the EU-score). † $P < 0.01$ between upper and middle tertile of the EU-score.

occurred at an aortic AIx value of 5.5% (area under curve 0.85 ± 0.05 , $P < 0.001$, Figure 4b).

Multivariate analysis including conventional cardiovascular risk factors indicated that arterial hypertension (β -coefficient: 0.32, $P = 0.01$) and cholesterol (β -coefficient: 0.30, $P = 0.01$) were independently associated with the aortic AIx.

DISCUSSION

This study demonstrated (i) that assessment of arterial stiffness derived by photoplethysmographic DPV analysis was easy to perform with a high success rate similar to radial arterial tonometry-derived AIx, (ii) that the SI correlates with the AIx and (iii) that the SI allows stratification of cardiovascular risk in a heterogeneous population including both healthy subjects and patients with increased cardiovascular risk.

We performed this study in order to provide reliable information on the usefulness of the Pulse Trace device (Pulse Trace, Care Fusion, San Diego, CA, USA) in subjects with various cardiovascular risk profiles as there is limited experience regarding its failure rate and ability to discriminate subjects according to their cardiovascular risk.

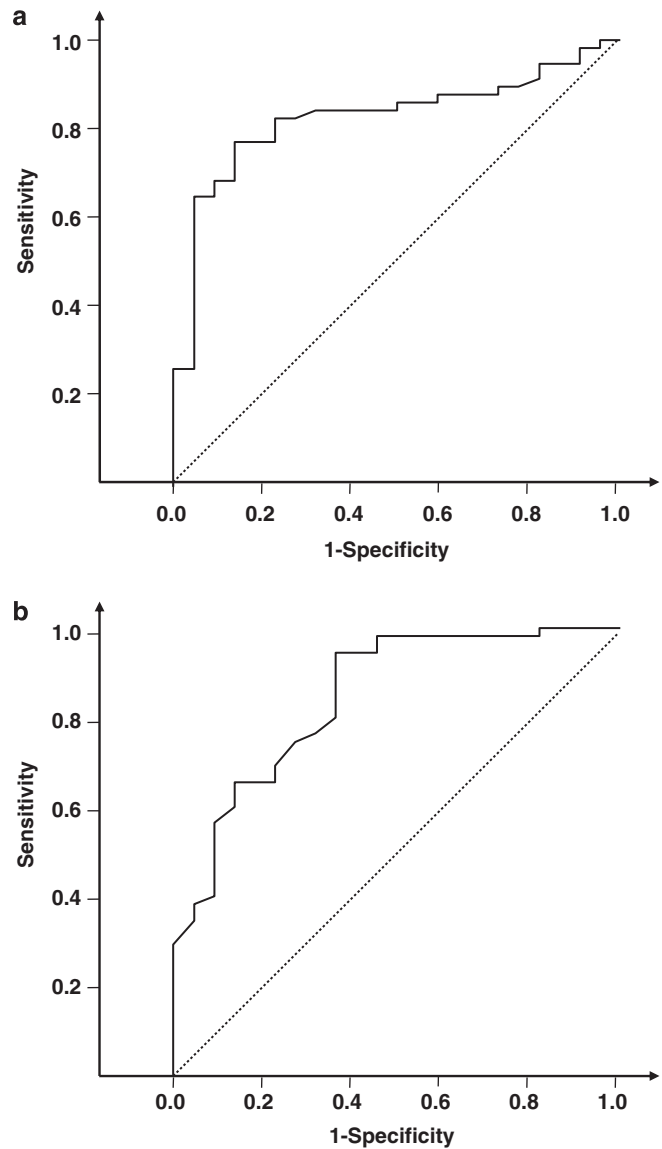


Figure 4 (a, b) The performance of the stiffness index (**a**) and the aortic augmentation index (**b**) in identifying patients with one or more cardiovascular risk factors was evaluated by plotting a ROC curve. The area under the curve for the stiffness index (**a**) was 0.83 ± 0.05 , $P < 0.001$, and for the aortic augmentation index (**b**) 0.85 ± 0.05 , $P < 0.001$.

Compared with radial applanation tonometry the measurement of the SI by DPV curve analysis is relatively simple, operator independent and less time consuming.¹⁹ This is because digital pulse analysis is performed hands-off after correct placement of the finger clip whereas arterial tonometry depends on the correct placement and manually applied stable pressure on the radial artery, which often takes considerable time, experience and patience. This is important when a large number of patients need to be assessed in short time or when measurements need to be standardized, for example, in multicentre trials.

The failure rate was low in both devices investigated (3.6%). In a study from Sollinger *et al.*,¹⁰ analysis of DPV showed a considerable higher failure rate and the SI could not be determined in 15 out of 97 patients (15.5%).¹⁰ However, patients investigated in the latter were

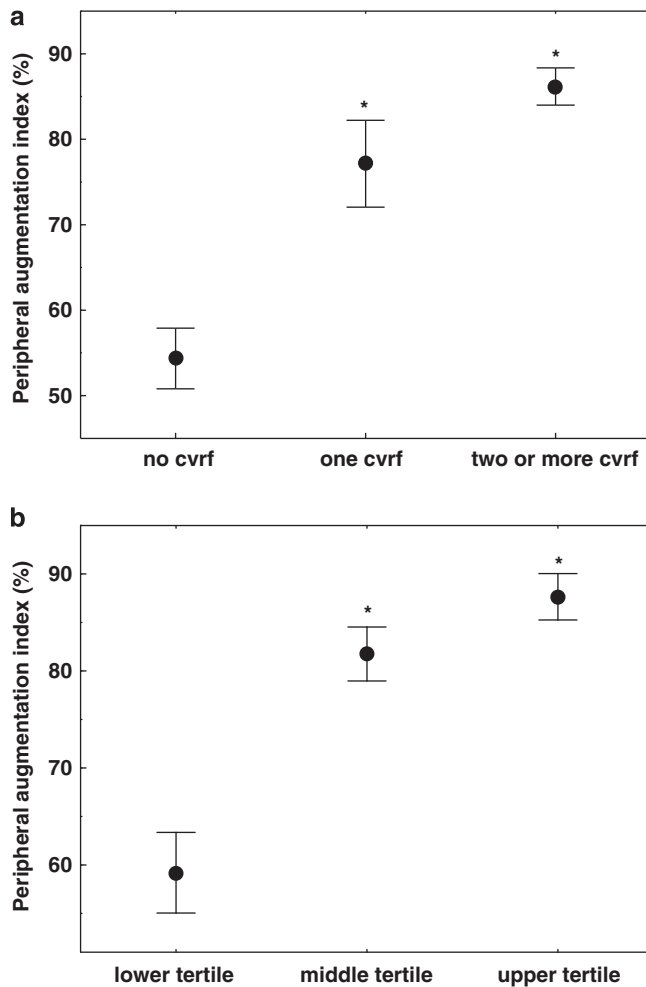


Figure 5 (a, b) The peripheral augmentation index (s.e.) of all subjects is grouped according to increasing cardiovascular risk factors (a; $*P < 0.001$ vs. no cardiovascular risk factor). The peripheral augmentation index (s.e.) of all subjects is grouped according to lower, middle and upper tertile of the EU-score (b; $*P < 0.001$ vs. lower tertile).

a homogeneous group with a high comorbid status of either patients on hemodialysis or renal transplant recipients, thus arterial stiffness may have progressed so far that the DPV analysis reached its technical limitation. Therefore, the high failure rate observed by Sollinger *et al.* may not be representative for studies of heterogeneous cohorts.

Within subject variability of the SI using the Pulse Trace device was 3.5% in this study and comparable to the findings reported by Gunarathne *et al.*²⁰ (5.4%). As measurement of the SI with the Pulse Trace device is operator-independent, inter-observer variability of the SI was neither assessed in the current nor in the study by Gunarathne *et al.*²⁰ Comparable within subject variability of the AIx assessed by the Sphygmocor device has been reported by Wilkinson *et al.*²¹ (5.3%) and Siebenhofer *et al.*²² (6.4%). Using the operator index of the Sphygmocor device to assure consistency of waveforms the inter-observer variability was found to be 7.5% in a recent study by Wassertheurer *et al.*²³

We found a modest correlation between the digital SI and the peripheral and central AIx derived by arterial applanation tonometry. The results are in concordance with a study comparing different methods of arterial stiffness assessment.¹⁹ In this study, the SI derived

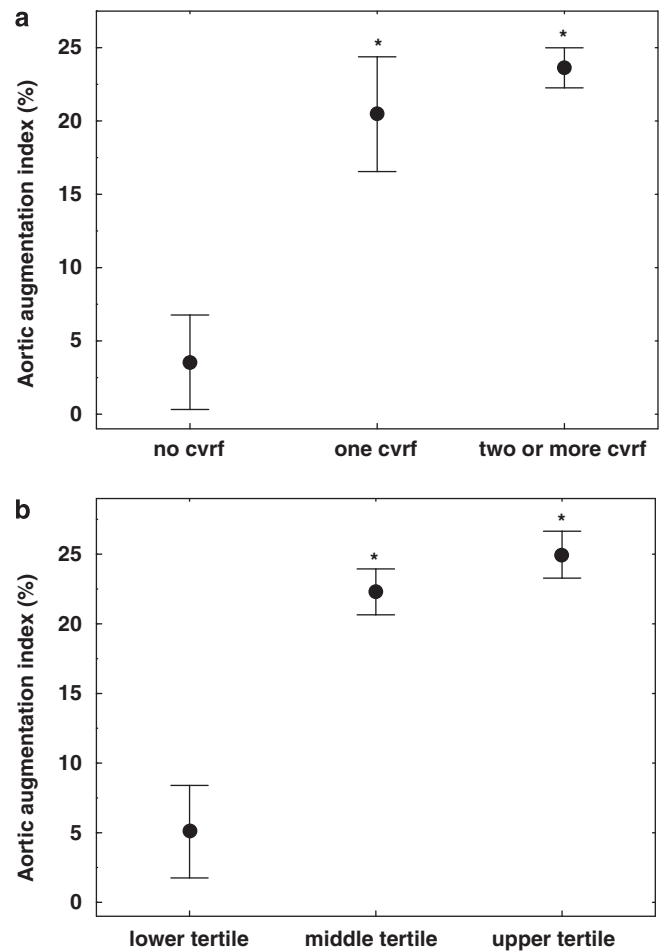


Figure 6 (a, b) The central (aortic) augmentation index (s.e.) of all subjects is grouped according to increasing cardiovascular risk factors (a; $*P < 0.001$ vs. no cardiovascular risk factor). The central (aortic) augmentation index (s.e.) of all subjects is grouped according to lower, middle and upper tertile of the EU-score (b; $*P < 0.001$ vs. lower tertile).

from the PulseTrace correlated with arterial stiffness measured by simultaneous acquisition of pressure waves using two tonometers ($r=0.55$).¹⁹ A likely explanation for the only modest correlation between SI and AIx may be that AIx and SI do not reflect the same properties or characteristics of the vasculature. This difference is more pronounced at lower degrees of arterial stiffness (Figure 2). It has been stated that the DVP obtained by photoplethysmography and pressure pulse waveforms assessed by tonometry have a complex relation that is not fully understood.²⁴ In this study, active smoking and BMI were factors independently associated with the SI, whereas arterial hypertension and cholesterol level were the independent determinants of the aortic AIx.

Peripheral and central AIx are both measures of arterial stiffness. However, central AIx is more accurately reflecting aortic stiffness and is influenced by left ventricular function, whereas the peripheral AIx is a measure of wave reflexion in the conduit arteries.²⁵ Essentially no difference between the two in terms of correlation with SI and cardiovascular risk stratification was shown.

Estimation of cardiovascular risk using risk scores is widely accepted and requires combination of established cardiovascular risk factors to

be measured. We used tertiles of the EU-score for low-risk countries in Europe, which includes age, gender, systolic blood pressure, cholesterol and glycemic status to stratify for cardiovascular risk. The EU-score is relatively simple to obtain and allows individual estimation of fatal cardiovascular risk in a format suitable for clinical practice.¹⁴ SI increased progressively and statistically significantly with higher cardiovascular risk as estimated by the EU-score, whereas both peripheral and aortic AIx were not statistically different between the upper tertile and the middle tertile of the EU-score. This finding implies that the SI may discriminate more accurately between groups of elevated cardiovascular risk and might be of advantage in a clinical setting, where numerous subjects emerge with a higher cardiovascular risk profile. However, data from prospective cohort studies on cardiovascular events and mortality are needed to define the relative accuracy of SI and AIx as predictors of cardiovascular risk.

Our findings have important implications for clinical practice, because the assessment of cardiovascular risk and atherosclerotic disease is widely used in diverse patient populations and in clinical trials. We found (i) that the photoplethysmographic DPV is easy to measure with a low failure rate and high reproducibility and (ii) that SI as a surrogate of arterial stiffness correlated with the more established AIx and (iii) that SI seemed to be a better discriminator of cardiovascular risk when compared with the AIx in subjects with increased cardiovascular risk as assessed by the EU-score. An increased SI may thus be of clinical and prognostic importance in stratification of cardiovascular risk. Adequately powered studies assessing both cardiovascular risks by established risk factors and arterial stiffness will be required to evaluate whether cardiovascular outcomes can be reliably estimated with photoplethysmographic digital pulse wave analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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