Areas under peripheral pulse waves

Areas under peripheral pulse waves: a potential marker of atherosclerotic changes

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Abstract. *Objective:* In this study, we propose a method for finding atherosclerotic changes based on the ratios of areas under peripheral arterial pulse wave (PW) contours and analyze its performance. *Approach:* The PW signals were recorded with force sensors and photoplethysmographic sensors from ankle, wrist, cubital fossa, index finger and second toe from 30 atherosclerotic patients and 52 control subjects. In addition, day-to-day repeatability of the method was studied with 10 test subjects examined on 3 different days. The ratios of areas under the PWs were computed and the results were evaluated by means of receiver operating characteristic (ROC) analysis, intra-class correlation (ICC) coefficient and multiple linear regression analysis. *Main results:* Areas under ROC curves of 0.802-0.906 were found for different area ratios having statistically significant differences between the atheroslerotic group and control groups. ICCs over 0.80 were found widely for the beat-by-beat analyzed data and over 0.95 for the data based on the averages over different numbers of PWs. Multiple linear regression analysis showed linear dependence between the area ratios and age and the diagnosis of atherosclerosis. *Significance:* Our findings may facilitate development of novel diagnostic approaches and preventive strategies against cardiovascular disorders. However, further studies are needed to confirm the results. The presented study demonstrates the potential of arterial PW analysis in finding vascular abnormalities.

Keywords: Atherosclerosis, Electromechanical sensors, Photoplethysmography, Pulse wave measurements.

1. Introduction

Vascular system degenerates with age, but unhealthy lifestyle accelerates the process. From a clinical point of view, the degenerative changes of the arterial tree are seen as a continuum and indicators of increased risk factors for severe cardiovascular events, such as a stroke or myocardial infarction [1]. These changes include both the stiffening of the arteries due to aging, classically known as arteriosclerosis, and the thickening, stenosis or occlusion of the arteries due to the accumulation of cholesterol, i.e. atherosclerosis. A challenge in the detection of these conditions is that they can be asymptomatic for a relatively long time or be present concomitantly. Common methods for estimating atherosclerotic changes are to measure carotid-femoral pulse wave velocity or the intima-media thickness of the carotid artery by using an ultrasound transducer [1] imaging based angiograms, or high-fidelity tonometric sensors such as SphygmoCor or Complior devices [2, 3], but these require a skilled operator or expensive equipment and are not suitable e.g. for wide screening studies. Advanced atherosclerosis can be diagnosed by measuring ankle to brachial pressure index (ABI), but its performance varies widely [4] especially in patients with early-stage atherosclerotic changes in vasculature or excessively stiffened arteries in lower limbs due to diabetes and mediasclerosis [5]. At the present, to be able to detect especially subclinical atherosclerosis and to reduce morbidity and mortality, there is a growing need for alternative cost-effective, comfortable and rapid methods for monitoring the vasculature.

The peripheral pulse wave consists of a heart beat induced percussion wave and its reflections from the mechnical impedance discontinuities of the arterial tree. The propagation of these waves depends on arterial properties, including arterial wall properties, fluidic properties of the blood, blood pressure and vascular resistance [6, 7]. Based only on non-invasively recorded arterial pressure or volume pulse waves (PW), many measurement and analysis methods have been reported for characterizing the vascular status [3, 8, 9, 10, 11, 12, 13]. These include aging index (AGI) based on the second derivative of the index finger photoplethysmographic (PPG) blood volume PW [9], index finger PPG-derived reflection index as a ratio of diastolic and systolic peak amplitudes [10], stiffness index inversely proportional to the time difference between diastolic and systolic peaks [10], augmentation indices (AIx) for carotid and radial pressure PWs [11, 3], and comparison of the observed hallux PPG with a PW-curve considered as a reference value [12, 13]. The volume and pressure PWs have similar kind of features, but they are different because they are often recorded from different locations and because of their non-linear relationship [14].

In this study, we propose a straightforward and simple analysis method that uses multichannel PW measurements and evaluate its performance by means of discrimination capability, repeatability and multiple linear regression analysis. Our method is based on the ratios of the areas under amplitude-normalized PW curves recorded from different measurement points. We assume that the shape of the PW and thus areas under the amplitude-normalized PW curves are associated with the energy stored by the walls of the large arteries during the systole and released during the diastole as well as to the capability of the arterial tree to deliver blood to the periphery. In this proof-of-concept study, we hypothesize that the area ratios based on PWs recorded from different limbs reveal differences between atherosclerotic patients and the control subjects.

2. Materials and methods

2.1. Measurement hardware and sensor placement

The measurement data was collected by using electret sensors made of electromechanical film (EMFi) and PPG probes connected into a wireless body sensor network [8, 15]

(Fig. 1). EMFi sensors were placed to the wrist on the top of the radial artery, cubital fossa on the top of the brachial artery and ankle on top of the posterior tibial artery in order to record dynamic pressure signals. Transmission mode PPG probes (excitation wavelength of 905 nm) were placed on index finger and second toe to record blood volume PW signals. The EMFi sensors were located in close proximity of large superficial arteries that are easily accessed for a non-invasive measurement while index finger and second toe are suitable for transmissive PPG measurement. Measurement points in the lower limbs are attractive since the lower limbs are more prone to degenerative changes than upper limbs. Bipolar ECG was also recorded between the disposable Ag/AgCl electrodes placed under the clavicle and left lower abdomen. The duration of each measurement was 10–15 minutes.

The sampling frequency was 250 Hz for the EMFi- and ECG-signals and 500 Hz for the PPG. A more detailed description on the system is presented in [15].

2.2. Study subjects

The clinical patient measurements were conducted in two Finnish university hospitals (Tampere and Oulu). The study subjects were divided into different groups as shown in more detail in Table 1. Group A consists of diagnosed atherosclerotic patients older than 65 years having abnormal ABI (ABI$<$ 0.9 or ABI$>$ 1.3). Having the risk factors presented in Table 1 were not explicitly defined as an inclusion criterion for group A,

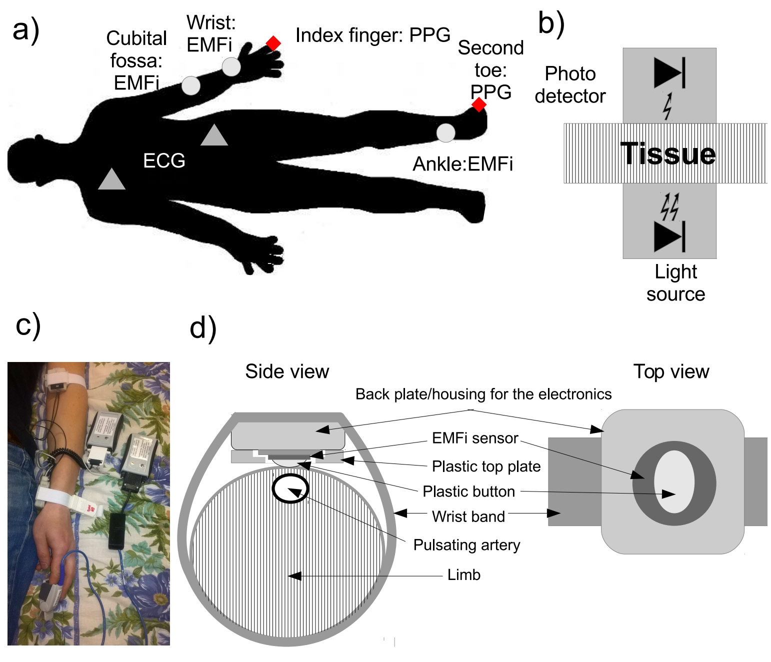

Figure 1. Sensor placement (a). Schematic presentation of the principle of transmissive PPG probe around a finger or toe (b). EMFi- and PPG-sensors placed on upper limb as well as radio units of the sensor nodes (c). d) Schematic presentation of the EMFi-sensor node (d).

but in practice, while being diagnosed as a vascular patient, all the subjects in group A had at least one cardiovascular risk factor or disorder. Group B consists of older than 65 years control subjects having normal ABI ($0.9 \leq$ABI≤ 1.3) and no history of the following conditions as inclusion criteria: cerebrovascular disease (amaurosis fugax, transient ischemic attack, ishcemic stroke), coronary artery disease (angina pectoris, myocardial infarction) or peripheral arterial disease (intermittent claudication, critical limb ischemia, acute limb ischemia).

As the elderly people with decreased arterial compliance have higher apriori probability for atherosclerotic changes and as they are a potential target group for screening studies, the main comparisons were done between groups A and B in order to see if the proposed method is able to separate excessive atherosclerotic changes from normal arterial aging. In order to see the age-dependency of the results, two groups of younger test subjects with no aforementioned cardiovascular symptoms or diagnosed disorders were included: groups C (inclusion criterion: age 40–64 years) and D (inclusion criterion: age < 40 years). Similar measurements as in the hospitals were conducted in Tampere University of Technology (Tampere, Finland) for the test subjects in groups C and D. These groups of younger subjects were included in the study without the ABI measurement since none of them was suffering from cardiovascular diseases. This is a minor limitation of the study, even though the prevalence of the atherosclerosis is higher in older population (roughly 65 years or older). Having a pacemaker was an exclusion criterion in all study groups for safety reasons.

The groups A–D contain altogether 82 subjects, but depending on the measurement point, there were 6–21 subjects per measurement point with no useful signal. The most common reasons for the missing signal were the low-amplitude PW signal (especially ankle PWs from atherosclerotic patients), cannula or catheter at the wrist or cubital fossa, plastered fracture and a miscellaneous random technical problem during the measurement.

The measurement setup was similar with 10 healthy test subjects in group E, but the measurements were repeated on three different days for each test subject in order to study the repeatability and day-to-day variations of the results. The median difference between the first and last measurement was 5 days, having first and third quartiles of 3 days and 9 days, respectively. Daily activities or the nutrition of the test subjects were not restricted. The time of day when the recordings were made varied between 8 am to 5 pm.

Table 1. Different study groups and the number and proportion of test subjects having different cardiovascular risk factors.

	A (Athero-sclerotic)	B (Old controls)	C (Middle-aged)	D (Young)	B+C+D (All controls)	A+B+C+D (All)	E (Day-to-day meas.)
Age*	74.8 ± 7.5	73.4 ± 6.3	55.7 ± 5.8	29.6 ± 4.6	60.2 ± 19.1	65.6 ± 17.3	26.9 ± 3.7
Subjects	30	31	9	12	52	82	10
Males	23 (76.7%)	9 (29.0%)	9 (100.0%)	12 (100.0%)	30 (57.7%)	53 (64.6%)	7 (70.0%)
Smoking	23 (76.7%)	7 (22.6%)	0 (0.0%)	0 (0.0%)	7 (13.5%)	30 (36.6%)	1 (10.0%)
Dyslipidemia	20 (66.7%)	5 (16.1%)	0 (0.0%)	0 (0.0%)	5 (9.6%)	25 (30.5%)	0 (0.0%)
Diabetes	15 (50.0%)	1 (3.2%)	1 (11.1%)	1 (8.3%)	3 (5.7%)	18 (19.5%)	1 (10.0%)
Rheum. arth.	1 (3.3%)	5 (16.1%)	0 (0.0%)	1 (8.3%)	6 (11.3%)	7 (8.5%)	1 (10.0%)
Hypertension	23 (76.7%)	7 (22.6%)	0 (0.0%)	0 (0.0%)	7 (13.5%)	30 (36.6%)	0 (0.0%)

*: mean±standard deviation. Rheum. arth.: Rheumatoid arthritis.

2.3. Ethics and patient safety

The study was approved by the local ethical review boards of the hospital districts (R14096 (Pirkanmaa Hospital District) and 245§ 69/2014 (Northern Ostrobothnia Hospital District)), the Finnish National Supervisory Authority of Health and Welfare (ID 272) and the technical departments of the hospitals. All volunteer test subjects were informed on the purpose of the study and informed consents were obtained. They had a chance interrupt their participation at any point.

2.4. Ratios of areas under PW curves

A leading hypothesis behind the proposed method is that the degenerated and stiffened arterial tree is less capable of storing the energy provided by the heartbeat during systole and releasing it gradually during the diastole [16]. In healthy and elastic arterial tree, the heart-beat induced percussion wave and its reflections are slightly overlapping but distinguishable from each other whereas in the stiffened arteries, the percussion wave and reflected wave are strongly overlapping or even joined together which affects areas under normalized PW-curves. This is seen especially as a missing dicrotic notch (an incisura point between the systolic and diastolic parts of the PW) in the lower limb PW resulting a monophasic PW. The lack of dicrotic notch results in often almost a triangular-shaped PW having larger area under the PW-curve after amplitude-normalization compared with a PW having a clear dicrotic notch. The arteries of lower limbs are also more prone to stenoses and occlusions which may cause the delayed peak value to the blood volume related PPG-signal [12, 13].

Examples on amplitude-normalized waveforms recorded from upper and lower limbs are shown in Fig. 2 for both atherosclerotic patients (A) and control subjects (C). A direct comparison between the areas under the PWs from different subjects is not sensible since the length of the cardiac cycle varies between subjects. In addition, beat-to-beat variations of the length of the PW affect especially the features seen in the diastolic part of the PW. For this reason, the area under the PW extracted from one measurement point is compared with the area under the normalized PW extracted from other measurement point.

Before determination of the areas under the amplitude-normalized PWs, the signals were low-pass filtered with a finite impulse response filter having a cutoff frequency of 10 Hz, transition band of 10–12 Hz, pass band ripple of 0.05 dB, and stop band attenuation of 100 dB [17]. After pre-processing, the classifying variables, i.e. the ratios R_i of the areas under the amplitude-normalized PW curves, are computed as

$$R_i = \frac{A_{N,i}}{A_{D,i}} \tag{1}$$

in which the numerator $A_{N,i}$ and denominator $A_{D,i}$ are the areas under the amplitude-normalized PWs from different measurement points. The tested combinations of (1) are presented in Table 2. The area under the PW was computed by using trapezoidal numerical integration of amplitude-normalized signal.

2.5. Evaluation of the method

In this study, the discrimination capability and the repeatability of the method were analyzed. Also multiple linear regression analysis was conducted in order to find if other factors than atherosclerotic changes act as confounders.

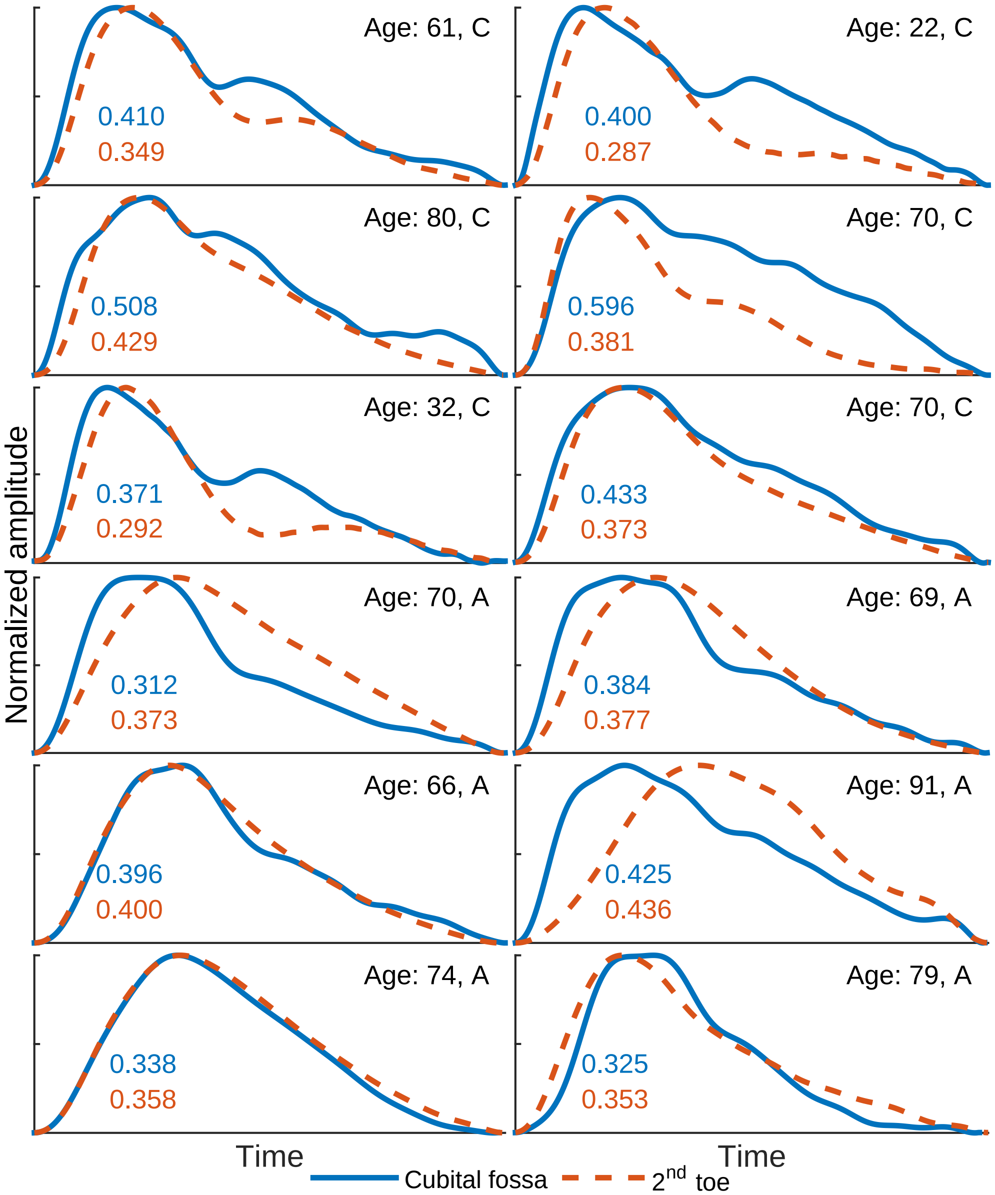

Figure 2. Examples on amplitude-normalized concomitant PWs recorded from the cubital fossa (EMFi sensor) (solid blue) and the second toe (PPG) (dashed red). Letters A and C in the right upper corner refer to atherosclerotic patient and control subject, respectively. Two numbers under the PW curves are the areas under the PW-curves in arbitrary units.

2.5.1. Discrimination capability The area ratios computed for the atherosclerotic patients (group A) are compared with each group of control subjects separately (groups B–D) by using two-tailed Mann-Whitney U-test. To avoid type I errors (false rejection of null hypothehis), Holm-Bonferroni correction is implemented for the p-values with total number of pairwise statistical tests of 30 [18]. The differences producing p-

Table 2. Different combinations of area ratios.

	Measurement point	
i	Area in numetor, $A_{N,i}$	Area in denominator, $A_{D,i}$
1	Wrist (EMFi)	Cubital fossa(EMFi)
2	Wrist (EMFi)	Ankle (EMFi)
3	Wrist (EMFi)	Finger (PPG)
4	Wrist (EMFi)	Toe (PPG)
5	Cubital fossa (EMFi)	Ankle (EMFi)
6	Cubital fossa (EMFi)	Finger (PPG)
7	Cubital fossa (EMFi)	Toe (PPG)
8	Ankle (EMFi)	Finger (PPG)
9	Ankle (EMFi)	Toe (PPG)
10	Finger (PPG)	Toe (PPG)

values less than 0.05 are considered statistically significant. For the area ratios having significantly different values (i.e. $p < 0.05$ also after Holm-Bonferroni correction) between group A and all other groups, receiver operating characteristic (ROC) curve is drawn and the following parameters are computed for different numbers of PWs as described in section 2.5.2:

- the area under the ROC curve (AUC),
- sensitivity $\mathrm{SE} = a/(a+c)$,
- specificity $\mathrm{SP} = d/(b+d)$,
- performance $\mathrm{PE} = (\mathrm{SE}+\mathrm{SP})/2$,
- accuracy $\mathrm{AC} = (a+d)/(a+b+c+d)$,
- positive predictive value $+\mathrm{PV} = a/(a+b)$, and
- negative predictive value $-\mathrm{PV} = d/(c+d)$

in which a is the number of true positive, b is the number of false positive, c is the number of false negative, and d is the number of true negative cases. The partition value for classifying the subject as atherosclerotic or healthy was found by weighting all partition value dependent indicators (SE, SP, PE, AC, +PV and -PV) equally.

2.5.2. Repeatability The repeatability of the results refers to the agreement of measurements of the measurand under same conditions, such as the same instrument, same observer and same location [19]. Intra-class correlation coefficient (ICC) is used to estimate the repeatability of the series of measurements and it is defined as a ratio of between-subject variance and the sum of between- and within-subject variances. One-way analysis of variance (ANOVA) based ICC [20] is estimated for the area ratios having statistically significant differences between the atherosclerotic patients (group A) and other groups B–D. ICC is calculated as

$$\mathrm{ICC} = (\mathrm{MS_{bs}} - \mathrm{MS_{ws}})/(\mathrm{MS_{bs}} + (k-1)\mathrm{MS_{ws}}) \quad (2)$$

in which $\mathrm{MS_{bs}}$ is between-subject mean squares, $\mathrm{MS_{ws}}$ is within-subject mean squares from ANOVA table and k is the number of observations per subject. The ICC as a repeatability indicator may be criticized because it assumes a normally distributed data with equal population variances which may be problematic especially with low number of datapoints per test subject [20]. Thus, we computed free-marginal multirater kappa (κ) [21] for the categorized data (i.e. the subjects were classified as healthy or atherosclerotic based on the same data as in ICC computation). The κ-analysis was implemented with the proportion of agreement expected by chance of $P_e = 1/(\text{number of categories}) = 1/2$ as

$$\kappa = (P_o - P_e)/(1 - P_e) \tag{3}$$

in which P_o is the proportion of overall observed agreement [21]. The free-marginal κ was selected instead of Fleiss' fixed-marginal κ because the value of the latter one depends strongly on the symmetry of the data [21]. In addition to κ and ICC, concordance correlation coefficient (CCC) [22] was computed for the dataset consisting of 2 results per test subject (2 averages based on 100 PWs).

Both ICC and κ were computed for beat-to-beat data of one period of 200 beats. In addition, both ICC and κ were computed for the certain numbers of averaged area ratios based on the certain number of beats as follows: 20 averages based on 10 beats, 10 averages based on 20 beats, 5 averages based on 40 beats, 4 averages based on 50 beats and 2 averages based on 100 beats. In order to study the day-to-day variations of the results, ICC and κ are computed for the study subjects in group E and based on the averages of each measurement.

2.5.3. Multiple linear regression In order to see if the risk factors or parameters presented in Table 1 act as confounders, multiple linear regression analysis was performed for the area ratios having statistically significant differences between the atherosclerotic patients (group A) and other groups B–D.

3. Results

3.1. Classification performance

The distributions of all the tested area ratios are presented in Fig. 3, grouped by each study group A–D. Statistically significant differences ($p < 0.05$) were found between the atherosclerotic patients (group A) and different groups of control subjects (groups B–D) in following 5 area ratios which were selected for the further analysis: wrist/ankle, wrist/toe, cubital fossa/ankle, cubital fossa/toe and finger/toe. As seen from the results, the area ratios that are based on the PWs recorded from the same limb do not show differences between the atherosclerotic patients and other study groups, but the area ratios of the PWs from upper and lower limbs reveal differences between control subjects and atherosclerotic patients.

Fig. 4 shows the ROC curves and AUC values based on the beat-to-beat data for the selected ratios having statistically significant differences between control subjects and atherosclerotic patients. In this study, we found AUCs of 0.802–0.906 (Figs. 4 and 5). In practice, depending on the partition value, one can e.g. read from Fig. 4 the values of SP≈0.7 and SE≈0.9 or SP≈0.9 and SE≈0.7 for the area ratio between cubital fossa and toe.

Fig. 5 shows the classification performance metrics based on different numbers of PWs per test subject. The partition value for categorizing the subjects healthy or atherosclerotic patients is selected by equally weighting all the performance indicators (SE, SP, AC, PE, +PV, -PV) based on our experimental data. However, the most optimal selection of the partition value depends on the possible real application of the

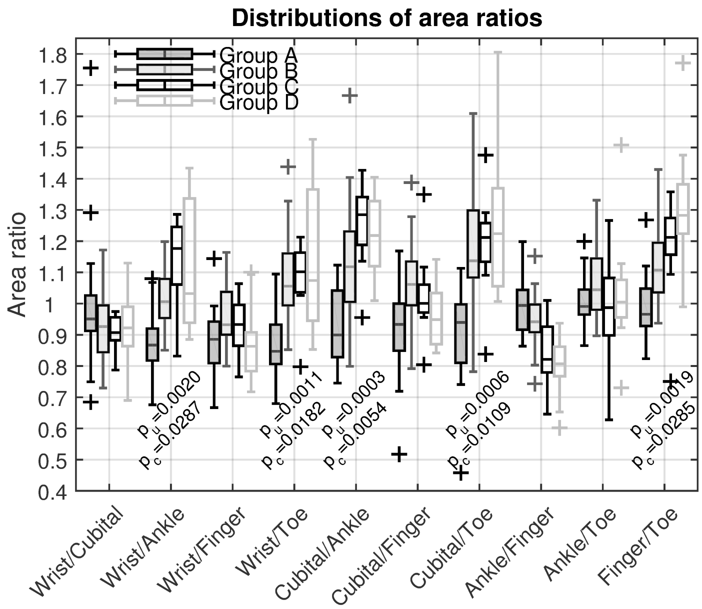

Figure 3. Distributions of different area ratios for different study groups. Statistically significant differences are marked with the highest p-value of pairwise comparisons group A vs. group B, group A vs. group C, and group A vs. group D. P-value p_u is un-corrected output of Mann-Whitney U-test, and p_c is the corresponding Holm-Bonferroni corrected value.

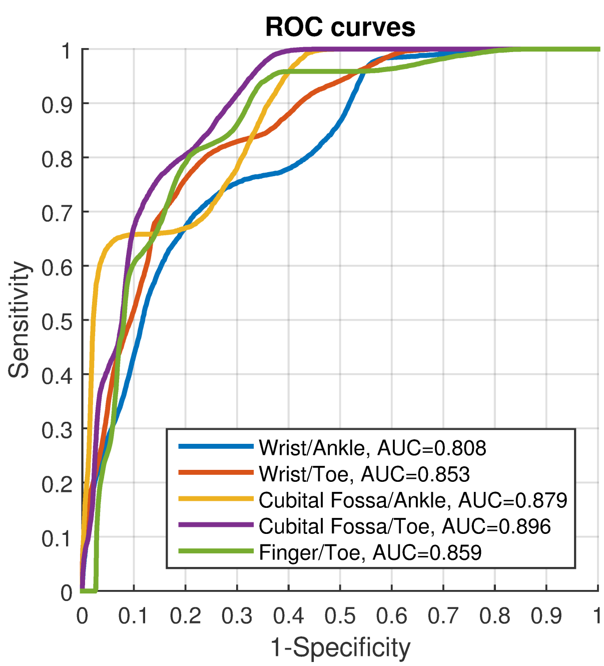

Figure 4. ROC-curves based on individual PWs.

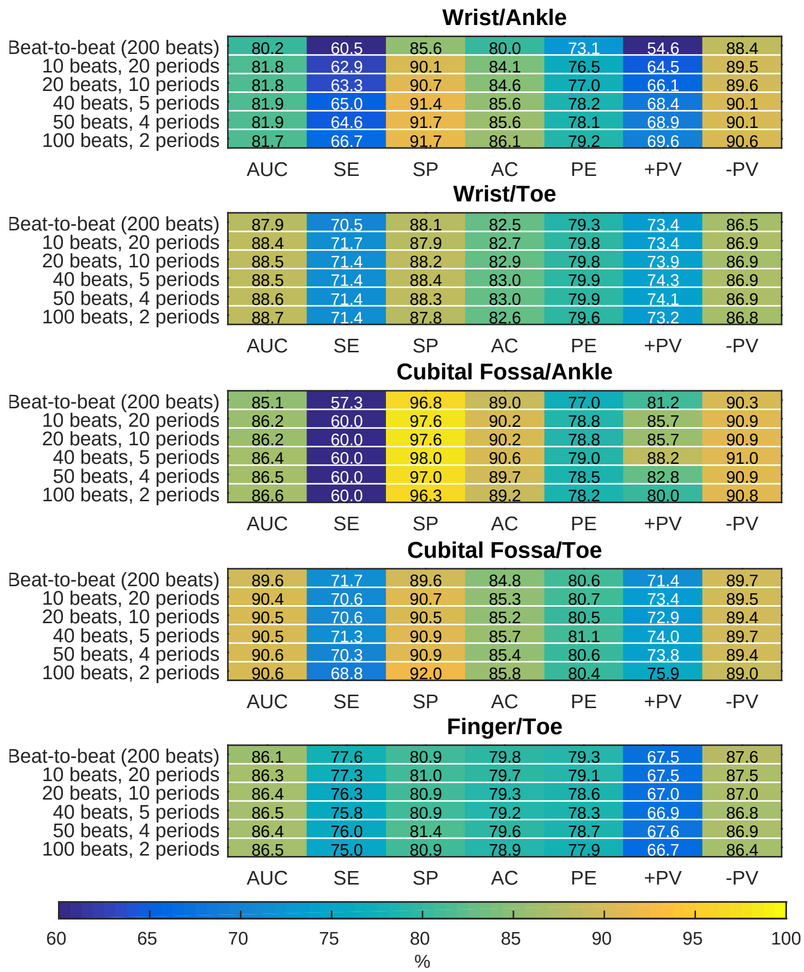

Figure 5. Classification performance metrics for different area ratios and numbers of PWs considered in calculating the area ratio.

proposed method, including the disease prevalence in the typical population under the examination.

3.2. Repeatability

ICCs with 95% confidence intervals are shown in Fig. 6 for the selected area ratios and grouped by different study groups A–D. These ICCs are based on individual PWs as well as averages of different numbers of PWs. As seen, the ICCs vary from 0.70 to 0.97 in beat-to-beat data, but as result of averaging, the ICCs are increased to the range of 0.92–0.99. Similarly, the values of free-marginal multirater κ (Fig. 7) vary 0.66–0.99 with beat-to-beat data and 0.75-1.00 with averaged data. The CCCs based on 2 results per subject (2 averages based on 100 PWs) are shown in Fig. 8 and are all higher than 0.95.

The results for day-to-day repeatability (group E) are shown in Fig. 9, both in terms of ICCs and κ. As seen, the ICC varies from insignificant 0.1 to moderate

0.55 which is possibly explained by the demographics of the study group: group E contained only young subjects having probably stronger vasoregulatory oscillations than the older subjects. Still, the values of 0.60–0.87 were found for the day-to-day measurements based κ-values, indicating that the numerical values of area ratios in group E vary mostly in the healthy range. The area ratio between cubital fossa and toe having the highest κ value differed only by one misclassification from the perfect day-to-day repeatability. With both ICC and κ, the 95% confidence intervals are wide because of the relatively low number of test subjects.

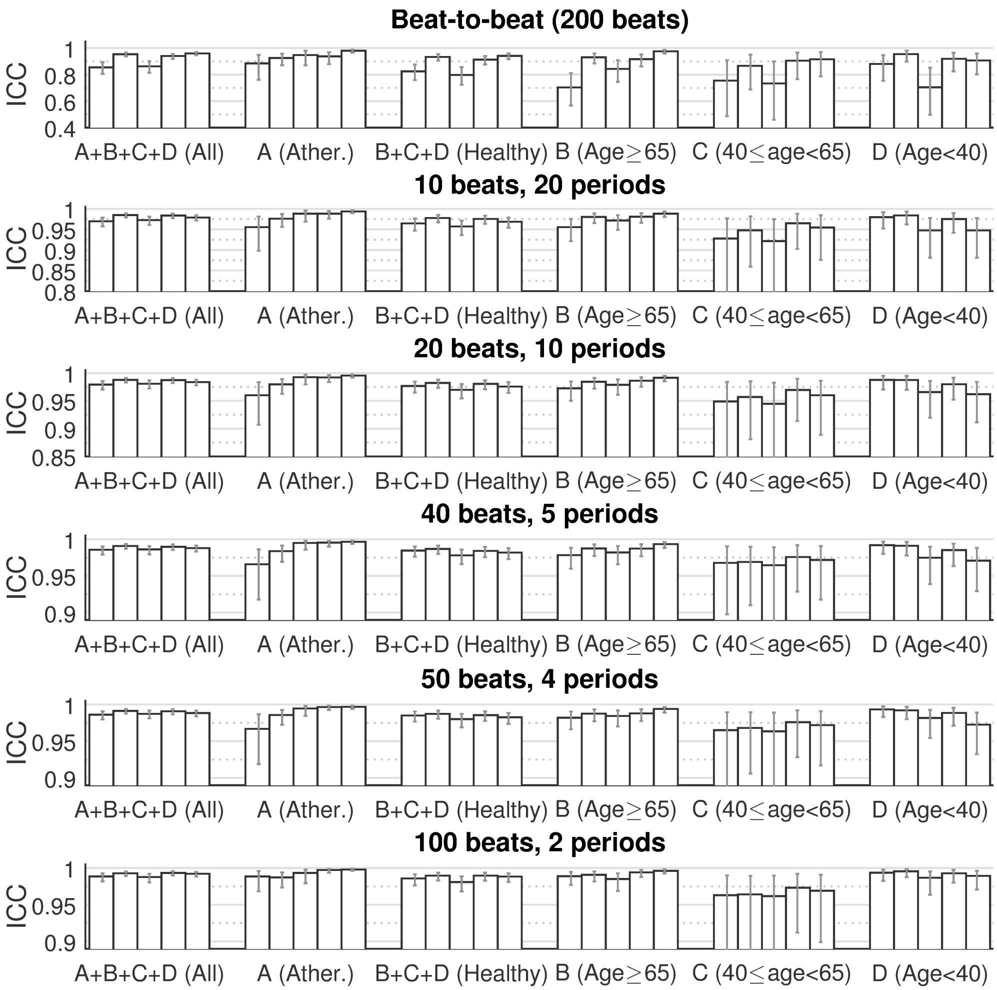

Figure 6. Intra-class correlation (ICC) with 95% confidence limits for the averages based on different numbers of PWs and for different study groups. The order of bars in each group of 5 bars: wrist/ankle, wrist/toe, cubital fossa/ankle, cubital fossa/toe, finger/toe.

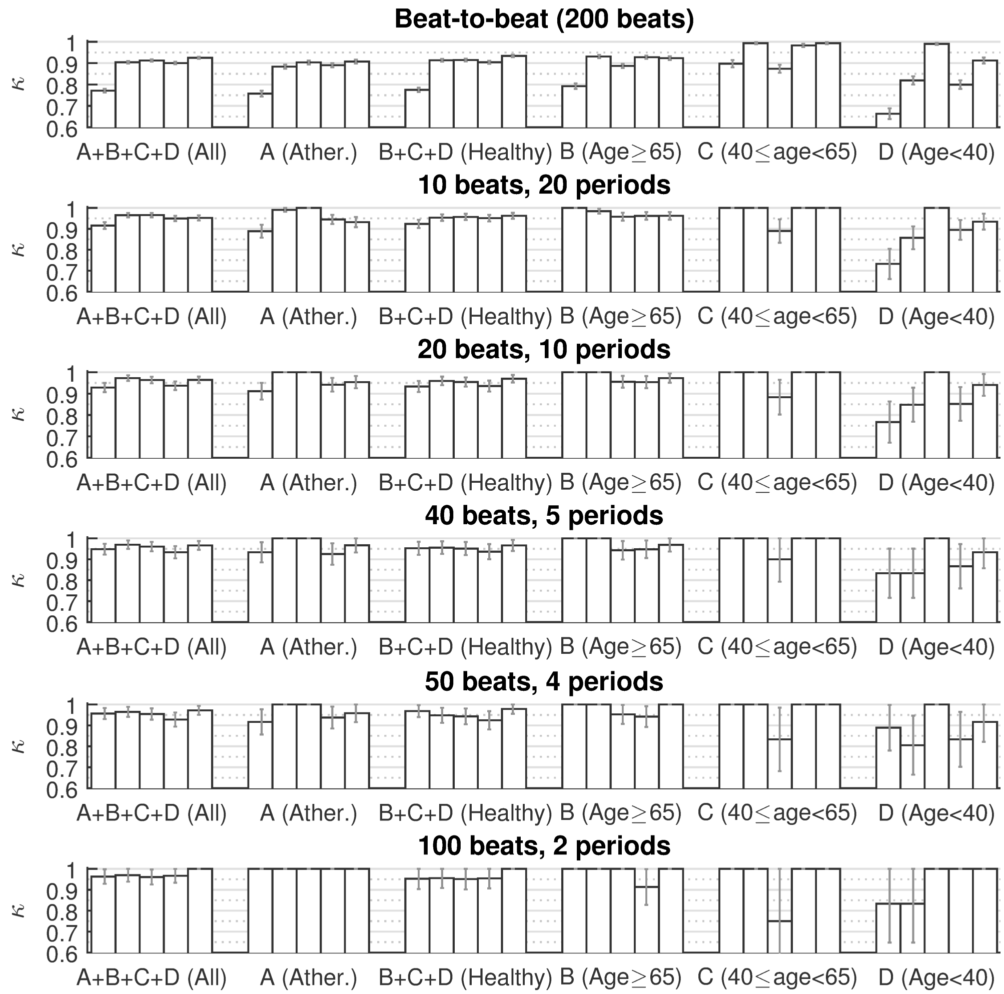

Figure 7. Free-marginal multirater κ with 95% confidence limits for the averages based on different numbers of PWs and for different study groups. The order of bars in each group of 5 bars: wrist/ankle, wrist/toe, cubital fossa/ankle, cubital fossa/toe, finger/toe.

3.3. Multiple linear regression

The results of multiple linear regression (Table 3) show that 3 out of 5 area ratios are dependent on both age and diagnosed atherosclerosis which is also partially seen in Fig. 3, but not linearly dependent on several confounders or other major cardiovascular risk factors. This indicates that the method is not necessarily dependent on mediasclerosis which is a significant confounder with ABI in diabetic patients. However, a significant limitation related to this conclusion is that the promising outcome may be a result of the fact that the atherosclerotic patients have a miscellaneous combination of different risk factors which decreases the significance of an individual risk factor. In addition, there are few control subjects having cardiovascular risk factors. The age dependency was an expected result since the arteries stiffen due to aging and because many other PW parameters have clear correlations with the age [17, 23, 8]. This suggests that

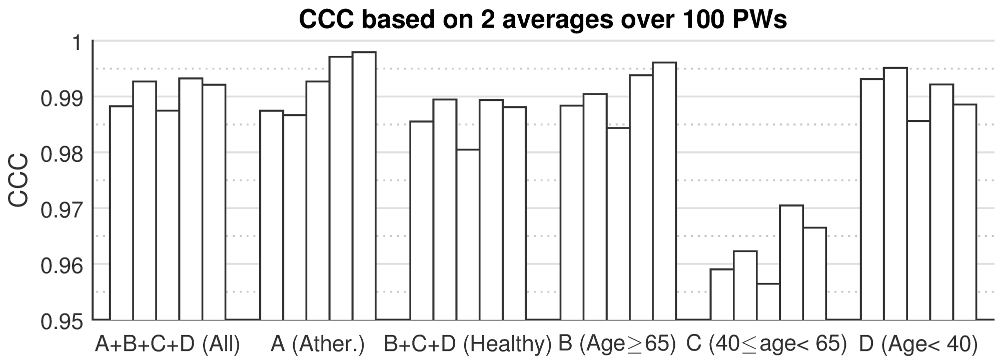

Figure 8. CCC for different study groups, based on 2 averages per each test subject (100 PWs per period). The order of bars in each group of 5 bars: wrist/ankle, wrist/toe, cubital fossa/ankle, cubital fossa/toe, finger/toe.

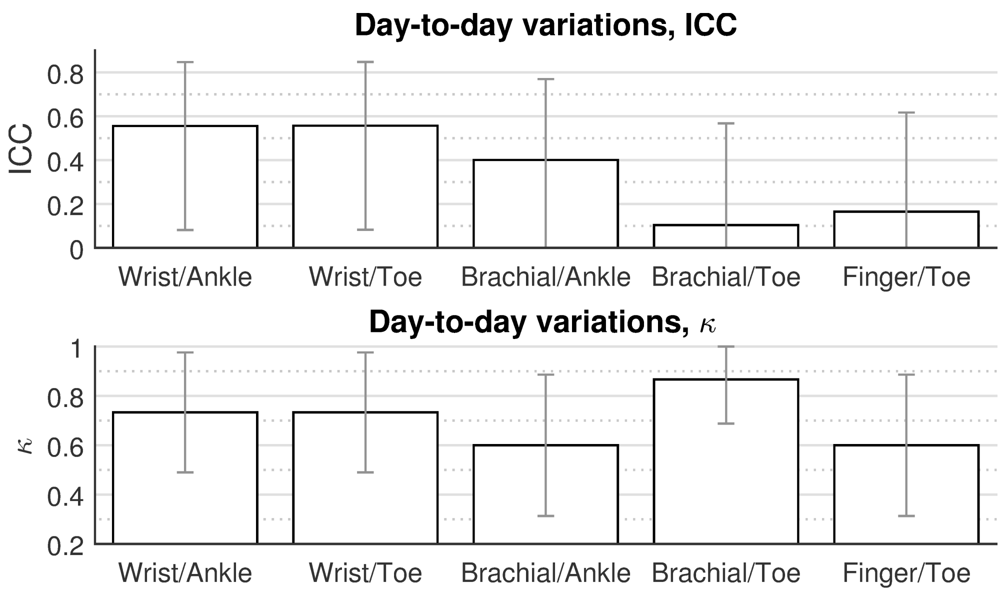

Figure 9. ICCs with 95% confidence intervals and κ values for the measurements conducted on different days.

Table 3. Results for multiple linear regression analysis.

	Wrist/Ankle		Wrist/Toe		Cubital fossa/Ankle		Cubital fossa/Toe		Finger/Toe	
Variable	β	Significance	β	Significance	β	Significance	β	Significance	β	Significance
(Intercept)	1.141	p<0.0001	1.317	p<0.0001	1.332	p<0.0001	1.663	p<0.0001	1.477	p<0.0001
Atheroscl.	-0.104	NS	-0.197	p<0.01	-0.198	p<0.05	-0.306	p<0.01	-0.196	p<0.001
Age	-0.003	p<0.05	-0.003	p<0.025	-0.002	NS	-0.004	p<0.05	-0.004	p<0.001
Heart rate	0.002	NS	0.000	NS	-0.001	NS	-0.003	NS	-0.001	NS
Diabetes	-0.080	NS	-0.072	NS	-0.030	NS	-0.049	NS	-0.021	NS
Dyslipidemia	0.016	NS	-0.004	NS	0.036	NS	-0.000	NS	0.018	NS
Smoking	0.012	NS	0.071	NS	-0.019	NS	0.106	NS	0.051	NS
Rheum. arth.	-0.039	NS	-0.103	NS	0.085	NS	-0.069	NS	-0.043	NS
Hypertension	-0.034	NS	0.010	NS	-0.019	NS	0.000	NS	0.048	NS
Gender	-0.016	NS	-0.054	NS	0.038	NS	-0.061	NS	0.018	NS

NS = not significant (i.e. $p > 0.05$)

when assessing the vascular status based on the area ratios, the age must be taken into account.

Still, the area ratios in atherosclerotic group differ significantly ($p < 0.003$ and $p < 0.03$ before and after Holm-Bonferroni correction, respectively) from the corresponding values found for the group of elderly control subjects (group B).

4. Discussion

4.1. Classification performance

In terms of classification performance, the proposed area ratios perform better than features derived directly from the PWs. In a comparative study with the same data[8], the AUC values for directly PW derived features (second derivative based aging index AGI [9], different reflection indices [10] and augmentation index AIx [11]) varied from 0.65 to 0.88 with the parameters having statistically significant ($p < 0.05$) differences between the atherosclerotic patients and control subjects. For the finger and toe PPGs and a simple machine learning technique based method, the AUCs of 91.6% $\pm$ 5.6% (mean$\pm$standard deviation over different datasets) were found in [24].

To authors' knowledge, this is the first study evaluating the results for the ratios of the areas under PW curves as a diagnostic tool. In the field of PW analysis, better results have been reported for a parameter called shape index which differs from our method in such a way that it compares the hallux PPG with apparently proprietary reference PW considered as normal-shaped PW: sensitivities of 88.9%–92.7%, specificities of 89.3%–90.6% and accuracies of 90.2%–90.5% have been found with the study populations of 44–48 control subjects and 63 atherosclerotic patients older than 40 years [12, 13]. In the present study, the ratios of the areas under amplitude normalized PW contours were analyzed and the comparison of the PW contours was performed at intra-subject level.

4.2. Repeatability

In terms of repeatability, ICCs over 0.80 were widely found in this study for the beat-to-beat area ratios and over 0.95 for the area ratios based on averages of different numbers of PWs. These correspond to the κ agreements mostly higher than 0.75 (beat-to-beat) and 0.90 (averages based on different numbers of PWs). For comparison, within-visit ICCs for the commonly used ABI are reported to be 0.72–0.93 [25, 26, 27]. There are also many studies showing that the differences of the ABI values between different measurements can be $\pm$0.1 ABI points in Doppler-based manual ABI measurement [28, 29, 30, 31]. This makes e.g. value at the threshold of ABI=0.9 questionable in vascular screening.

Related to the other PW parameters, the ICC of 0.84 has been reported for the index finger PPG based AGI [32] and ICCs of 0.93–0.96 have been reported for the radial artery tonometry based AIx [3]. In [8], ICCs mostly over 0.80 were found for the values of AGI, AIx, and different reflection indices based on beat-to-beat series. The results based on 10 periods of averages over 20 PWs per subject improved the results: ICCs mostly over 0.95 were found [8]. Based on this and a previous study [8], even a shorter than one-minute measurement (e.g. 10–40 PWs) provides enough data for reliable measurement in the repeatability point of view, and in case of large uncertainty of a previous finding, a short-term measurement is quick to repeat.

In this study, (Fig. 9), day-to-day ICCs of 0.5–0.8 were found for most of the parameters. Between-visit ICCs of 0.48–0.87 have been reported for ABI in [26, 33].

Demir *et al* have reported that 12% of the sample displayed differences higher than 0.15 ABI points in three measurements conducted within one week and ICCs of 0.808 single measurement and 0.927 averaged measurements [34].

In comparative study [8], direct PW-derived indices were extracted from the data recorded as PPG signals from index finger and second toe as well as dynamic pressure PWs from cubital fossa, wrist and ankles (posterior tibial artery) and the parameters having the best day-to-day repeatability provided ICCs of 0.7–0.8. Endes *et al* report ICCs of 0.59 for the peripheral augmentation index [35]. The results found for the day-to-day or between-visit repeatability are in the same level in the present study, but limited by low number of only healthy subjects.

4.3. Multiple linear regression

The area ratios containing PWs from the ankles are less consistently dependent on age or atherosclerosis (Table 3). This may be a result of lower signal-to-noise ratios of ankle PW signal, especially with the atherosclerotic patients having poor circulation in the legs. This is seen also as pretty high number of patients missing useful ankle PW signal. Because of these problems, area ratios containing PWs from the ankles are less reliable than those ones containing toe PWs recorded with PPG probes. With other area ratios, the age dependency was an expected result since arteries stiffen due to aging and because many other PW parameters have clear correlations with the age [8, 17, 23]. This suggests that when assessing the vascular status based on the area ratios, the age of the subject should be taken into account.

4.4. Study limitations

The sensitivity, specificity and other classification performance indicators reported in this study are based on the partition value obtained by weighting all of the performance metrics equally. If any one of these indicators is weighted differently, the results shown in Figs. 5, 6, 7 and 9 will change. By weighting all the indicators equally in the selection of the partition value, the proposed area ratios become more specific than sensitive (Fig. 5). One reason may be the study population consisting of smaller number of atherosclerotic patients (30) than control subjects (52). The most optimal partition values are possible subjects of further studies, since e.g. the positive and negative predictive values are dependent on the disease prevalence and since the requirements may be different for different applications.

In practice, we noticed that the missing or disturbed EMFi signals may also be a result of the measurement event: computation of one area ratio requires signals only from two measurement points whereas in the measurement event, there were unpractically large number of sensors attached on the test subject concomitantly since we aimed to find out which measurement points provide the best results for the detection of atherosclerotic changes. The high number of attached sensor and time taken to find the best locations for the force sensors may have made the test subjects to feel uncomfortable increasing the amount of motion artefacts. In the worst case, the force sensors may have moved away from the best location. Concentrating on fewer number of sensors per measurement event may make subjects to feel more relaxed, producing the signals with better quality.

In addition to the young healthy test subjects, factors that may cause uncertainty to the results of day-to-day repeatability measurements is that the daily activities of the test subjects was not restricted and the room temperature, which may affect peripheral vascular resistance and peripheral microcirculation, was not controlled. Also the exact contact pressures of the sensors were not controlled, but the operator checked the quality and shape of the signals visually and ensured by asking the test subject that the sensors do not make him or her to feel uncomfortable. In further studies, the effect of these factors should be taken into account.

Even the reported performance of a diagnostic test ABI<0.9 has wide variation from study to study (SE: 15%–79%, SP: 83.3%–99.0%, AC: 72.1%–89.2%, +PV: 36.4%–99.0% and -PV: 40.7%–98.0%) [4]. This is also a limitation of our study. The subjects classified as atherosclerotic patients had most probably true atherosclerotic changes since they had abnormal ABI and at least one risk factor or symptoms of cardiovascular diseases and were treated or medicated due to the cardiovascular problems. However, a more problematic issue is that the exclusion of atherosclerosis was based on the ABI measurement and a careful cardiovascular risk factor survey. In future, a study comparing the presented method with established gold standard, such as angiographic examination, pulse wave measurement or intima-media thickness, in earlier phase of the atherosclerosis is required for confirming the results.

5. Conclusions

The primary objective of this study was to propose a new method based on the ratios of the areas under the PW curves for finding the atherosclerotic alterations and evaluate and compare its performance to other PW derived indices. The study shows that simple ratios of areas under PWs recorded from different points in upper and lower limbs could provide an additional diagnostic tool with high repeatability for finding the atherosclerotic changes. The proposed area ratios have better classification performance than the features derived directly from the PWs. The presented method could be a useful tool for finding the asymptomatic patients having atherosclerotic changes and thus suitable aid as a part of risk stratification of cardiovascular diseases. Although our findings in this proof of concept study may facilitate development of early diagnostic approaches and preventive strategies against atherosclerosis and cardiovascular events, further studies with higher sample size, with more reliable reference method, and possibly in earlier phase of the atherosclerosis should confirm the results.

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