

Association between Optical Signal Derived Aortic Augmentation Index and Cardiovascular Risk Factors in Healthy Volunteers

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Abstract

Background: The aim of this study was to determine whether the photoplethysmographic signal derived Aortic Augmentation Index (PPGAI_{ao}) can be used as an alternative method for cardiovascular risk estimation. The relationship between PPGAI_{ao} and the traditional cardiovascular risk factors were investigated on apparently healthy subjects. **Methods:** The Photoplethysmographic (PPG) signal was registered from right hand index finger of healthy volunteers. The Arteriograph device was used as a reference for the pulse wave analysis parameters and aortic pulse wave velocity measurements. The HDL-cholesterol, LDL-cholesterol, total cholesterol and triglycerides from collected peripheral venous blood specimens were measured. The relationships between the results of arterial stiffness related parameters and the traditional cardiovascular risk factors were analyzed. **Results:** Our data showed the strong correlation between Arteriograph and PPG signal derived augmentation indices ($r=0.78$). The PPGAI_{ao} values were averagely 7% higher than Arteriograph estimated aortic Augmentation Index (AI_{ao}). The PPGAI_{ao} and AI_{ao} showed positive correlation or did not correlate with other cardiovascular risk parameters. Both derived augmentation indices were higher in case of higher SCORE risk chart values and in case of subject groups with higher age. **Conclusion:** It can be assumed that the optically estimated PPGAI_{ao} could be considered in the future as one method for augmentation index and cardiovascular risk estimation. Future studies have to be carried out on actual patients, to improve the PPG waveform registration method.

Keywords: Arterial Stiffness; Augmentation Index; Cardiovascular Risk Factors; Photoplethysmography; Pulse Wave Analysis; Pulse Wave Velocity

Introduction

It is known that mortality from Cardiovascular Diseases (CVD) is a leading cause of mortality in all developed countries, including Estonia. In this regard, one of the priorities of healthcare is early detection of atherosclerotic vascular lesions and giving adequate treatment to patients at high risk of cardiovascular complications. Prevention and treatment of the circulatory system diseases is an important task to both healthcare and the society as a whole.

Systemic Coronary Evaluation (SCORE) risk chart for screening fatal cardiovascular complications, recommended by the

ESC experts, has a limited set of variables, and does not include the parameters that characterize the vascular wall [1]. The consensus document that unifies the opinions of European experts on using arterial stiffness parameters for diagnosis and treatment (published at the end of 2006) states that measuring arterial stiffness related parameters has significant advantages over the evaluation of classical risk factors, as it directly reflects the factual damage of the vascular wall [2]. Currently, it has been proven that the stiffness of the major arteries determined by Pulse Wave Velocity (PWV) is an independent predictor of cardiovascular mortality, fatal and nonfatal coronary events in patients with arterial hypertension or Type 2 diabetes, as well as elderly patients and total population as a whole [3-5].

Augmentation Index (AIx) is considered to be a measure of systemic arterial stiffness and is calculated from the central and radial pressure waveforms. Aortic Augmentation Index (AI_{ao}) is

related to the mechanical properties of the artery through changes in PWV. In case of elastic arteries, the reflected waves from the peripheral sites arrive back to the aortic root during diastole part of the heart cycle. Increased arterial stiffness raises the PWV and causes the early arrival (during systole part of the heart cycle) of reflected waves. This phenomenon augments the systolic and pulse pressure in aorta, increases wall stress, raises risk of atherosclerosis development and elevates left ventricular afterload [6]. However, in addition to the stiffness of the arteries, the AIx_{ao} is influenced as well by the characteristics of the left ventricle ejection profile and amplitude of the reflected waves [7,8]. An increased AIx have been associated with increased cardiovascular risk [9,10]. In addition, in the study by Schram, et al. [11] an increased AIx was reported in patients with type 2 diabetes or impaired glucose tolerance. Furthermore, AIx_{ao} has been shown to have independent predictive values for cardiovascular mortality in patients with end-stage renal disease [12]. AIx has been in focus for mechanistic analyses in therapeutics, pharmacology and pathophysiology, nevertheless more investigations are needed before it can be recommended to introduce it into routine clinical use [13].

From the scientific community and industry, there has been much interest in developing non-invasive methods and devices for cardiovascular system status evaluation [2]. SphygmoCor and Complior devices are considered as “Gold standard” for the measurement of aortic pulse wave velocity and central blood pressure. SphygmoCor enables to estimate AIx_{ao} , which is used as an indicator of aortic stiffness [14]. Aortic PWV, AIx_{ao} and central blood pressure can also be obtained Arteriograph device that has been validated with invasive methods [15]. In earlier study, three devices used to measure PWV were compared [16]. It was found that the differences were primarily caused by the differences in measuring traveled distance of the pulse wave. In current study, the Arteriograph device is used to estimate PWV and AIx_{ao} .

Previous studies have shown that Photoplethysmographic (PPG) method, which is an optical method, can offer an alternative approach for the estimation of AIx_{ao} [17]. PPG method registers the blood volume and velocity changes in the examined tissue using mainly red or infrared light. Registered light intensity changes are related to the pulse wave, which is propagating in the arterial tree [18]. The aim of this study was to determine whether the PPG signal derived aortic augmentation index ($PPGAIx_{ao}$) can be used as an alternative method for cardiovascular risk estimation. Therefore, the relationship between $PPGAIx_{ao}$ and the traditional cardiovascular risk factors were investigated on apparently healthy subjects. The Arteriograph device was used as a reference for the pulse wave analysis parameters and aortic PWV measurements.

Methods

Study Population

The present study included 54 asymptomatic volunteers (29 men and 25 women) without known heart and vascular diseases. All subjects in this study were asked to provide their written consent. The subjects were divided into three groups on the basis of their age: 1 (age: 21 - 39 years, n=20), 2 (age: 40 - 53 years, n=25), 3 (age: 56 - 73 years, n=9). The study was carried out in North Estonia Medical Centre in collaboration with the Department of Biomedical Engineering, Tallinn Technical University. This study was approved by the Tallinn Ethics Committee on Medical Research.

Cardiovascular Risk Factors

Information on demographic and anthropometric characteristics and cardiovascular risk factors was collected on the day when the measurements with the non-invasive devices were carried out. We administered a structured questionnaire to obtain information on each subject: age, body mass index (was calculated), smoking status (yes/no), use of medications (had not received treatment with statins), and medical history. The WHO classification of Body Mass Index (BMI) was used to classify the patients as underweight (BMI < 18.5 kg/m²); normal (BMI 18.5 - 24.9 kg/m²); overweight (BMI 25.0 - 29.9 kg/m²); and obese (BMI > 30 kg/m²) [19]. Results of laboratory tests were recorded.

Laboratory Methods

All parameters were analyzed during the same day using standard methodology in an accredited laboratory. Peripheral venous blood specimens were collected, centrifuged, and biochemical measurements such as HDL-cholesterol, LDL-cholesterol, total cholesterol and triglycerides were completed by Cobas-600-c501 (Roche Diagnostics GmbH, Mannheim, Germany) using commercial kits.

Arteriograph Parameters

The central Systolic Blood Pressure (SBP_{ao}), Central Pulse Pressure (PP_{ao}), Aortic Augmentation Index (AIx_{ao}), and aortic Pulse Wave Velocity (PWV_{ao}) were estimated using an Arteriograph device (TensioMed, Budapest, Hungary) [20]. The distance between jugulum (sternal notch) and symphysis (pubic symphysis), two characteristic anatomical points, was measured in a straight line and it was ensured that the tapeline was not following the curves of the body. Second, the Arteriograph measurement was carried out. In all measurements the cuff size was set in accordance with the manufacturer’s recommendation and placed tightly around

the left upper-arm. Third, the measurement with the Arteriograph was carried out. Initially, the device measured the blood pressure using an oscillometric method. Next, the pressure waveform measurements were performed when the cuff pressure exceeded systolic blood pressure by 35mmHg, with a completely occluded brachial artery. The pressure wave signal was recorded for 10 seconds. The quality of the signal was carefully examined after each measurement and if needed, the measurement was repeated.

The SBP_{ao} , PP_{ao} , AIx_{ao} and PWV_{ao} were calculated automatically by the TensioClinic version 1.10.1.1 (TensioMed, Budapest, Hungary) software. The Arteriograph calculates the central SBP_{ao} and PP_{ao} on the basis of the brachial systolic blood pressure (SBP_{brach}) and the recorded pressure waveform. The brachial augmentation index (AIx_{brach}) was calculated from the recorded pressure waveform. The AIx_{ao} was calculated using the linear model between AIx_{brach} and AIx_{ao} [15]. The transit time is the return time (S35) calculated by the Arteriograph from the recorded pressure waveform, which is the difference in milliseconds between the initial and the reflected systolic waves. The PWV_{ao} was calculated as the ratio between the distance of jugulum-symphysis and the return time. As the pulse wave travelled to the bifurcation and back, the distance was multiplied by two for PWV_{ao} calculation.

Experiment Setup and Measurements

The measured and calculated parameters and used methods are summarized in Table 1. PPG signal was registered using experimental measurement complex [21]. The PPG signal was registered from an index finger of right hand using Envitec F-3222-12 finger clip sensor (Honeywell, Germany). The infrared LED (880nm) of the sensor was used. The sensor was connected to the lab built module, where it was possible to set the current of the LED and gain of the signal. The LED worked in pulsed mode. The lab built module was connected to the data acquisition card PCI MIO-16-E1 (National Instruments, USA), where the analogue signal was digitized with sampling frequency of 1kHz. The PPG signal was monitored and recorded during the experiment, using the LabVIEW (National Instruments, USA) environment developed program.

All the experiments were carried out by trained personnel in a quiet room with constant temperature ($23 \pm 1^\circ C$). Firstly, the subject was asked to be in supine position. The PPG sensor was attached to the index finger of the subject and the current of the LED and gain of the signal were set in order to achieve the quality of the PPG signal. The maximum current of the LED in pulsed mode was 47mA. It was ensured that the LED of the sensor would not cause any heating effect to the finger. After at least 20 minutes, the measurements with Arteriograph were carried out and the parameters were calculated as previously explained. The supine

position remained constant also during the one-minute-long PPG signal registration.

Parameter	Method
Age	Questionnaire
BMI	Calculated
Waist circumference	Measuring tape
S-Chol	Cobas-600-c501 commercial kit
S-HDL-Chol	Cobas-600-c501 commercial kit
S-LDL-Chol	Cobas-600-c501 commercial kit
fS-Trigl	Cobas-600-c501 commercial kit
DBP_{brach}	Arteriograph measured
SPB_{brach}	Arteriograph measured
SPB_{ao}	Arteriograph calculated
PP_{ao}	Arteriograph calculated
PWV_{ao}	Arteriograph calculated "Gold standard" parameter
AIx_{ao}	Arteriograph calculated
$PPGAIx_{ao}$	Proposed method in this study

Table 1: Measured and calculated parameters and methods used.

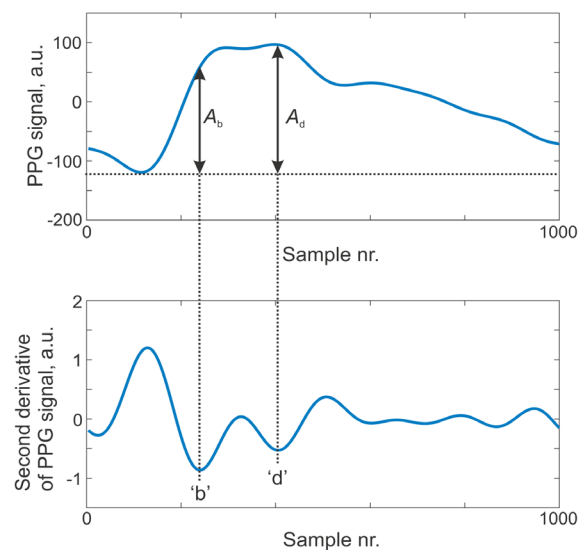


Figure 1: One period long PPG signal, which is filtered and normalized in length (upper graph) and the amplitudes A_b and A_d are detected at the locations of corresponding second derivative PPG signal peaks of 'b' and 'd' (lower graph).

Data Analysis and Statistical Methods

The PPG signal analysis was carried out using MATLAB (The MathWorks, USA). For each subject, the periods of the PPG signal were filtered and normalized in length according to our previous study [17]. From the second derivative PPG signal the distinct peaks ‘b’ and ‘d’ were detected and the PPG signal amplitudes at these locations were measured (Figure 1). The PPGAI index was calculated according to the following equation:

$$PPGAI = \frac{A_d}{A_b} \quad (1)$$

where A_d and A_b are the amplitudes of the normalized PPG signal at the locations of distinctive peaks ‘d’ and ‘b’ of second PPG derivative signal, respectively. The aortic augmentation index ($PPGAIx_{ao}$), given in percentages, was calculated from the PPGAI index using in the previous study [17] developed model:

$$PPGAIx_{ao} = 57.19 \cdot PPGAI - 55.69 \quad (2)$$

Statistical analysis was carried out with IBM SPSS statistics

version 20. Data normality was analyzed using the Shapiro-Wilk test. The results are expressed as mean \pm standard deviation or as median (25th-75th percentile) for skewed data. The difference between variables was tested using the Mann-Whitney test. Spearman’s correlation coefficients were calculated to test the association between arterial stiffness related parameters and risk factors. Statistical significance was considered if $p < 0.05$.

Results

Characteristics of Study Subjects and Assessment of Risk Factors

Subjects’ age was between 21 and 73 years, with mean \pm SD age being 43 ± 13 . The subjects were divided into three groups on the basis of their age: 1 (21 - 39 years), 2 (40 - 53 years), 3 (56 - 73 years). The mean BMI was $23.5 \pm 3.2 \text{ kg/m}^2$, $25.9 \pm 3.4 \text{ kg/m}^2$, $24.9 \pm 2 \text{ kg/m}^2$. There was no significant difference in waist circumference between groups. The levels of total cholesterol, LDL cholesterol were lower in group-1 than in group-2 and group-3, which was statistically significant ($p < 0.05$). The peripheral systolic blood pressure was lower in group-1 than in group-2 and group-3, which was statistically significant ($p < 0.05$). The main characteristics of the study subjects are shown in Table 2.

	All (n=54)	Group-1 (n=20)	Group-2 (n=25)	Group-3 (n=9)	P ^a	P ^b	P ^c
Age range (years)		21-37	40-53	56-73			
Anthropometric parameters							
BMI (kg/m ²)	24.8 \pm 3.3	23.5 \pm 3.2	25.9 \pm 2	24.9 \pm 2	0.021	0.43	0.23
Waist (cm)	89 \pm 9	86 \pm 9	92 \pm 10	90 \pm 4	0.34	0.42	0.15
Laboratory parameters							
S-Chol (mmol/L)	5.4 \pm 1.0	4.9 \pm 0.9	5.6 \pm 1.1	5.8 \pm 0.7	<0.01	0.72	<0.01
S-HDL-Chol (mmol/L)	1.68 \pm 0.6	1.7 \pm 0.7	1.8 \pm 0.6	1.4 \pm 0.5	0.46	0.15	0.42
S-LDL-Chol (mmol/L)	3.3 \pm 0.9	2.9 \pm 0.9	3.5 \pm 0.9	3.9 \pm 0.6	<0.01	0.27	<0.01
fS-Trigl (mmol/L)	1.20 \pm 0.6	1.05 \pm 0.4	1.16 \pm 0.6	1.67 \pm 1.0	0.46	0.07	0.02
Peripheral arterial blood pressure measurements							
DBP _{brach} (mmHg)	80 (78 - 90)	80 (74 - 80)	86 (80 - 91)	80 (70 - 90)	<0.01	0.263	0.501
SPB _{brach} (mmHg)	122 (114 - 131)	118 (110 - 122)	130 (117 - 135)	128 (123 - 136)	0.013	0.759	0.011

^a Comparison between group-1 and group-2.

^b Comparison between group-2 and group-3.

^c Comparison between group-1 and group-3.

Table 2: Characteristics of study subjects.

Arterial Stiffness Related Parameters

Table 3 and Figure 2 summarize the results of the aortic stiffness related parameters. The PWV_{ao} was, on average, lower in group-1 (6.8m/s (varied between 6.3m/s and 7.3m/s)) than in group-2 (7.0m/s (varied between 6.6m/s and 8.6m/s)) and group-3 (9.8m/s (varied between 8.3m/s and 12.1m/s)). The differences between the groups were statistically significant ($p < 0.05$). The SBP_{ao} , PP_{ao} and AIx_{ao} were higher in group-3 than in group-1 ($p < 0.05$).

The AIx_{ao} and $PPGAIx_{ao}$ were higher for females than males (AIx_{ao} : 24% vs 14%, $p = 0.07$ and $PPGAIx_{ao}$: 20% vs 9%, $p < 0.01$, Figure 3).

	All (n=54)	Group-1 (n=20)	Group-2 (n=25)	Group-3 (n=9)	P ^a	P ^b	P ^c
Age range (years)		21 – 37	40 – 53	56 – 73			
Aortic stiffness parameters							
SBP_{ao} (mmHg)	113 (105 - 136)	111 (105 - 115)	126 (104 - 139)	144 (105 - 177)	<0.05	0.163	<0.05
PP_{ao} (mmHg)	39 (35 - 50)	37 (33 - 44)	44 (37 - 54)	54 (38 - 77)	<0.05	0.231	<0.05
AIx_{ao} (%)	19 (12 - 35)	13 (8 - 18)	24 (13 - 36)	36 (31 - 48)	<0.01	0.060	<0.05
PWV_{ao} (m/s)	7.1 (6.6 - 8.5)	6.8 (6.3 - 7.3)	7.0 (6.6 - 8.6)	9.8 (8.3 - 12.1)	<0.05	<0.05	<0.01
$PPGAIx_{ao}$ (%)	15 (7 - 22)	8 (-2 - 16)	17 (7 - 26)	22 (20 - 31)	<0.05	0.081	<0.01

^a Comparison between group-1 and group-2.

^b Comparison between group-2 and group-3.

^c Comparison between group-1 and group-3.

Table 3: Arterial stiffness related parameters in the study subjects.

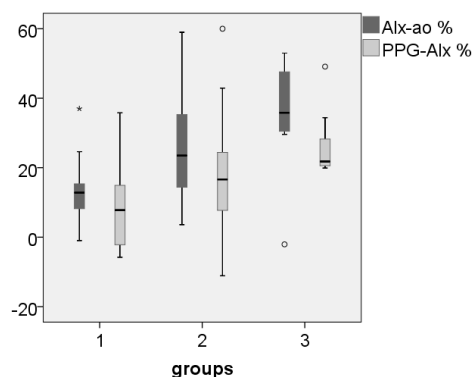


Figure 2: Differences of AIx_{ao} and $PPGAIx_{ao}$ for all study groups. Median (bold line), upper quartile (upper edge of gray box), lower quartile (lower edge of gray box), maximum (upper bar), minimum (lower bar) and outlier (circle) values of AIx_{ao} (%) and $PPGAIx_{ao}$ (%) are given.

Arterial Stiffness Related Parameters and Cardiovascular Risk Factors

PPGAI_{ao} positively correlated with age ($r=0.54$, $p<0.01$) and has low correlation with systolic blood pressure ($r=0.32$, $p<0.05$), HDL-cholesterol ($r=0.16$, $p=0.25$), and LDL-cholesterol ($r=0.13$, $p=0.36$). Similarly, AI_{ao} positively correlated with age ($r=0.55$, $p<0.01$) and again has low correlation with systolic blood pressure ($r=0.27$, $p<0.01$), HDL-cholesterol ($r=0.28$, $p<0.05$), or LDL-cholesterol ($r=0.30$, $p=0.05$). Likewise, PWV_{ao} also positively correlated with age ($r=0.55$, $p<0.01$) and has low correlation with systolic blood pressure ($r=0.36$, $p<0.01$), HDL-cholesterol ($r=0.24$, $p<0.05$) or LDL-cholesterol ($r=0.31$, $p<0.05$). Triglyceride level did not correlate with any of the arterial stiffness related parameters.

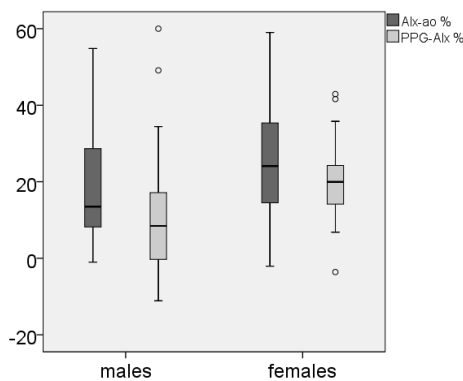


Figure 3: Variation of PPGAI_{ao} and AI_{ao} by gender.

On the basis of the SCORE risk chart, all subjects were classified into risk levels (Table 4 and Figure 4). Positive correlation was revealed between SCORE and AI_{ao} ($r=0.51$, $p<0.001$), however weak positive correlation was found between PPGAI_{ao} ($r=0.39$, $p<0.001$) and SCORE.

SCORE		n	AI _{ao} (%)	PPGAI _{ao} (%)
Low Risk	<1%	39	19	14
Moderate Risk	≥1% and <5%	13	27	20
High Risk	≥5% and <10%	2	48	33

Table 4: Arterial stiffness related parameters in the study subjects according to SCORE.

Increased SBP_{brach} > 135mmHg was found in 19% of subjects. Subjects with increased SBP_{brach} had higher PPGAI_{ao} (20% vs 15%) and AI_{ao} (28% vs 21%) than subjects with SBP_{brach} < 135mmHg. Positive correlation was found between PPGAI_{ao} and

Arteriograph estimated AI_{ao} ($r=0.78$, $p<0.01$), which is illustrated with Bland-Altman plot in Figure 5.

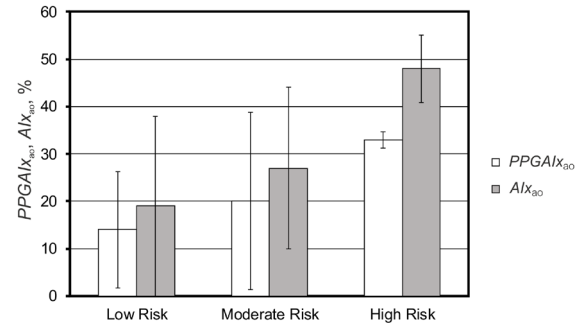


Figure 4: Average values with standard deviations of PPGAI_{ao} and AI_{ao} according to SCORE.

Discussion

In this study, the aortic AIx was estimated using the non-invasive optical technique for pulse wave registration from index finger and new offline waveform analysis algorithm. The Arteriograph device was used as a reference for the pulse wave analysis parameters and PWV measurements. The main objective was to investigate the relationship between PPGAI_{ao} and the traditional cardiovascular risk factors in apparently healthy subjects.

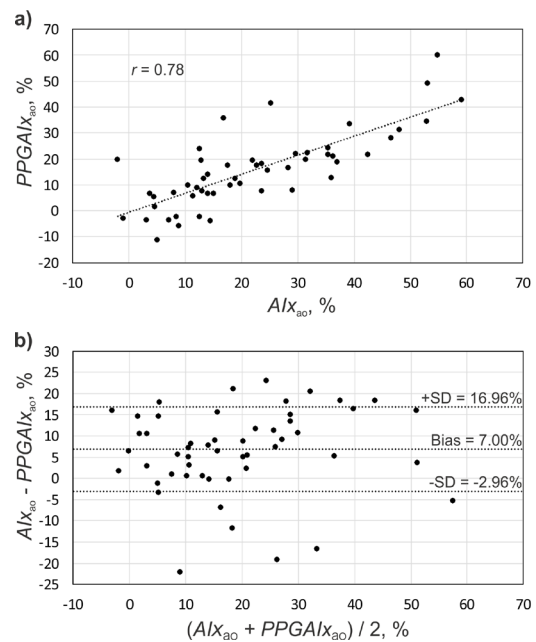


Figure 5: a) The relation between the PPGAI_{ao} and the AI_{ao} with the regression line and the correlation coefficient. b) Bland-Altman plot of the PPGAI_{ao}.

Positive correlation ($r=0.78$) was found between PPGAI_{ao} and AI_{ao}. The results are similar to our previous study [17], where strong correlation was found between PPGAI_{ao} and SphygmoCor derived AI_{ao} ($r=0.85$). In line with a previous study [22], our results showed that the augmentation index was higher for women.

According to the Bland-Altman plot (Figure 5b), the PPGAI_{ao} values are on average higher (7%) than Arteriograph estimated AI_{ao} values. Outliers can be found as well, which cause the high standard deviation in Bland-Altman plot. The differences can be explained by various factors – the measurements are not carried out simultaneously, the source of the signal differs in the physical (different type of sensor) and physiological point of view (different locations in arterial tree).

The PPG signal is optical signal, which represents the blood volume changes in the microvascular bed of tissue. The Arteriograph and SphygmoCor devices register the signal, related to the pressure wave. The volume-pressure relationship is non-linear and the volume wave depends on the transmural pressure, which is the difference between the internal pressure and any additional externally applied pressure of the blood vessel [23]. Therefore, the PPG signal amplitude and the waveform [24] depend on the applied pressure by the sensor. In this study, all the PPG signal registrations were carried out with the same sensor. However, the blood pressure, as well as the circumference of the finger varied, which caused the change in the transmural pressure. It can be debated that the influence is minimal, nevertheless, in the future studies this effect should be taken into account and the influence on estimated PPGAI_{ao} should be investigated.

Positive correlation of SCORE values with AI_{ao} and weak positive correlation between SCORE values and PPGAI_{ao} were found, according to Figure 4 the average PPGAI_{ao} and AI_{ao} tend to increase with the SCORE values. Due to the small number of the subjects in the “High risk” group the statistical differences between the groups were not possible to investigate. As the population in Estonia is relatively small (about 1.3 million people), it is very difficult to find elderly and at the same time healthy subjects. In addition, in Table 4 does not include “Very high risk” (>10%) group according to the SCORE risk chart, because subjects were apparently healthy and no one fit into this category. SCORE is the European cardiovascular disease risk assessment model, which has several cardiovascular risk factors (gender, age, total cholesterol, systolic blood pressure and smoking status) as input parameters. The positive tendency in the increase of PPGAI_{ao} and AI_{ao} together with SCORE values indicates an increased risk of cardiovascular events with a possible increase in arterial stiffness. It is also supported by the study done by Rhee, et al. [14], where the alterations in AI_{ao} and PWV_{ao} are associated with the structural changes of atherosclerosis. It may be suggested that the vascular wall is a target organ for exposure to risk factors mentioned at the

SCORE scale. It is notable that compared to the previous study [25], the PPGAI_{ao} and AI_{ao} showed weak positive correlation with the systolic blood pressure, HDL- and LDL-cholesterol. In addition, PWV_{ao} showed positive correlation with age, but weak associations were found with systolic blood pressure, HDL-cholesterol and LDL-cholesterol, which is similar to the PPGAI_{ao} and AI_{ao}.

Moreover, this study did not show any association between triglyceride level and increase in parameters associated to the arterial stiffness. However, the relation between triglycerides and arterial stiffness is controversial. Our findings differ from those of Sliem, et al. [26], which demonstrated that aortic stiffness is in direct association only with triglycerides, when the components of the lipids are considered separately. Another study [27] in Greece has found that serum triglyceride levels are associated with indices of arterial stiffness. Our findings are in agreement with a study by Razman, et al. [28], which found no significant association between triglyceride level and AI_{ao}.

The results from our study suggest that PPGAI_{ao}, AI_{ao}, PP_{ao}, PWV_{ao}, and SBP_{ao} are lower in young adults as compared to elderly subjects. Our findings are in close agreement with a previous study that reported a positive correlation between increased arterial stiffness and age and systolic blood pressure [29].

Conclusions

According to the results, the PPGAI_{ao} index, derived from PPG registered pulse waveform, correlates significantly with Arteriograph estimated AI_{ao} in case of healthy subjects. The PPGAI_{ao} values were averagely higher compared to the AI_{ao} values. In addition, PPGAI_{ao} and AI_{ao} correlate only little or not at all with other cardiovascular risk parameters. Furthermore, the PPGAI_{ao} values are higher, similarly to AI_{ao}, for subjects with higher SCORE values and groups with higher age. Therefore, it can be assumed that the optically estimated PPGAI_{ao} could be considered in the future as one method for augmentation index and cardiovascular risk estimation. However, more studies are needed to carry out on patients and as well to improve the PPG waveform registration method.

Conflicts of interest

The authors have no conflicts of interest related to this study.

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