Photoplethysmographic signal waveform index for detection of increased arterial stiffness

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Abstract
The aim was to assess the validity of the photoplethysmographic (PPG) waveform index \textit{PPGAI} for the detection of increased arterial stiffness. For this purpose, PPG signals were recorded from 24 healthy subjects and from 20 type II diabetes patients. Recorded PPG signals were processed with the analysis algorithm developed and the waveform index \textit{PPGAI} similar to the augmentation index (AIx) was calculated. As a reference, the aortic AIx was assessed and normalized for a heart rate of 75 bpm (AIx@75) by a SphygmoCor device. A strong correlation ($r=0.85$) between the \textit{PPGAI} and the aortic AIx@75 and a positive correlation of both indices with the age were found. Age corrections for the indices \textit{PPGAI} and AIx@75 as regression models from the signals of healthy subjects were constructed. Both indices revealed a significant difference between the groups of diabetes patients and healthy controls. However, the \textit{PPGAI} provided the best discrimination as the standard deviation of the regression model constituted 39\% from the average difference of the diabetes patient group. The waveform index \textit{PPGAI} based on the inexpensive PPG technology can be considered as a perspective measure of increased arterial stiffness estimation in clinical screenings.

Keywords: Arterial stiffness, photoplethysmography, diabetes mellitus, signal processing, augmentation index

1. Introduction
It is important to detect and diagnose the early signs of cardiovascular disease in order to apply effective prevention and treatment (Perk \textit{et al} 2012). Premature increase in arterial stiffness has been considered a risk factor for cardiovascular disease. The arterial stiffness of a subject increases with age, hypertension, and diabetes mellitus in addition to other factors (Lee and Park 2013). Different methods and devices are used to estimate arterial stiffness (Laurent \textit{et al} 2006, Woodman \textit{et al} 2005).

Introduced by Murgo \textit{et al} (Murgo \textit{et al} 1980) the augmentation index (AIx) has been used as a surrogate parameter for arterial stiffness (Mitchell \textit{et al} 2004, Schram \textit{et al} 2004). Previous studies have shown that aortic AIx increases with age due to the increase in the stiffness of the arteries (Safar and London 2000). Among other devices (Laurent \textit{et al} 2006, Woodman 2005), SphygmoCor can be used to estimate aortic Alx from a radial artery pulse waveform. The pulse waveform from radial artery is recorded by applanation tonometry. However, this method of pulse waveform recording is often time-consuming and requires a trained operator. To estimate arterial stiffness, we need a simple screening method, which is user independent, non-invasive, inexpensive, and rapidly performed. The photoplethysmographic (PPG) waveform analysis method may fulfill these criteria (Millasseau \textit{et al} 2006).

PPG is an optical non-invasive method that can be used to detect blood flow and volume changes in peripheral vessels and smaller arteries at different body locations (Allen 2007). The PPG sensor consists of a light source, which is often a red or an infrared light emitting diode (LED), and a
photodetector. In the transmission mode, the photodetector is placed at the opposite side of the measured volume. In the reflection mode, the photodetector is adjacent to the light source. The light is emitted from the light source to the skin, where it is absorbed, reflected and scattered in the tissue and blood. A small fraction of back scattered (reflection mode) or transmitted (transmission mode) light intensity changes is received by the photodetector.

The PPG signal consists of a large and slowly varying DC component and about ten times smaller pulsating AC component. The pulsations in the AC component of the PPG signal are synchronous with the heart rate and depend on the changes in the pulsatile pressure and pulsatile blood volume. The AC component of the PPG signal is characterized by systolic and diastolic phases, which are separated by a notch or an inflection point (Chan et al. 2007). Though origins of the pulsatile waveform components of the PPG signal have been studied; the phenomenon is still not fully understood (Allen 2007). Generally, it has been accepted that the AC component of the PPG signal can provide valuable information about the cardiovascular system.

It has been found that the PPG signal waveform depends on the location where the sensor is attached on the body (Allen and Murray 2003). In addition, the waveform changes are dependent on the biological age of the subject, which can be associated with the stiffness of blood vessels (Millsassee et al. 2002, Hlimonenko et al. 2003, Pilt et al. 2012). The finger PPG signal waveform changes caused by aging have been studied on a frequency domain (Sherebrin and Sherebrin 1990).

Changes in the finger PPG signal waveform can be characterized through the amplitudes of distinctive points, which can be determined from period to period and subject to subject. As the PPG signal waveform is smooth compared to the pressure waveform, the early and late systolic inflection points cannot be easily detected. Within one period, a PPG signal has several convexes and concaves, visualized through the second derivative PPG (SDPPG) signal (Takazawa et al. 1998). In our earlier study, an improved SDPPG waveform analysis algorithm was introduced for the arterial stiffness estimation (Pilt et al. 2013a). Furthermore, in our pilot study, the normalized amplitudes at the locations of the SDPPG signal peaks were calculated and used as indices for cardiovascular aging (Pilt et al. 2013b). In this study, the PPG waveform augmentation index (PPGAI) similar to the aortic augmentation index is calculated based on the normalized amplitudes for the discrimination of the subjects with higher arterial stiffness. The purpose is to compare the proposed PPG waveform PPGAI index with the SphygmoCor derived aortic AIx and to show that PPGAI index can be used for detection of premature cardiovascular ageing among diabetes patients. The study has been carried out on healthy subjects and diabetes patients with probable increase in arterial stiffness.

2. Methods

2.1 Subjects
We studied 24 healthy subjects between the age of 21 and 66 years (14 males and 10 females with a mean age of 41 years) and 20 type II diabetic patients (5 males and 15 females with a mean age of 44 years) between the age of 27 and 66 years. Nineteen healthy volunteers were engaged in some physical training or activity at least once a week. For healthy subjects, the blood pressure and body mass index had to be lower than 140/90mmHg and <30kg/m², respectively. As different from healthy subjects, all the diabetes patients had glycohemoglobin above the normal level (5.9%).

The subject was in the supine position for at least 20 minutes before the blood pressure measurements. The supine position remained constant during the radial artery waveform recording with a SphygmoCor device. After that during one minute the PPG and ECG signals were recorded. PPG signals were recorded from the index finger of the left hand. The room temperature was kept constant at around 23 ± 1 degrees Celsius.

This study has been approved by the Tallinn Ethics Committee on Medical Research at the National Institute for Health Development, Estonia. All the subjects gave written informed consent to participate in this study.

2.2 Determination of aortic AIx
The SphygmoCor device (AtCor Medical, Australia) was used to assess arterial stiffness. The peripheral pulse waveforms were recorded from the radial artery at the wrist by using applanation tonometry. The operator had passed SphygmoCor measurements training and had completed several hundred recordings. After the waveform was stabilized, the 10-second signal was recorded with a sampling rate of 128Hz. About 10 recurrences per subject were used in the analysis of the pulse
waveform. According to the recommendations from the manufacturer, only the recordings with an operator index above 85 (in the scale of 0 to 100) were used. The aortic waveform is generated from the radial artery waveform by using validated generalized transfer function (Chen et al 1997). AIx is derived from the aortic pulse waveform, as shown in figure 1. The AIx is expressed in percentages is calculated as follows:

\[
AIx = \frac{P_1 - P_2}{PP} = \frac{AP}{PP}
\]

where \(PP\) is the pulse pressure and \(AP\) is the augmentation pressure. As the AIx depends on the heart rate, the index has been normalized for the heart rate of 75bpm (Wilkinson et al 2000). The normalized AIx value is denoted as AIx@75. The AIx and AIx@75 values typically increase with age as the arteries turn out to be stiffer.

\[\text{Figure 1. The augmentation pressure (AP) and the pulse pressure are determined from an average aortic pressure waveform and used for the AIx calculation.}\]

2.3 Instrumentation

The PPG and ECG signals were registered by an experimental measurement complex described in our earlier paper (Pilt et al 2010). The commercially available Envitec F-3222-12 finger clip sensor (Honeywell, Germany) was connected to the lab-built PPG module. The PPG signal was recorded by the infrared LED of the sensor at the wavelength of 880nm. The single channel ECG signal was recorded synchronously with the PPG signal. The signals were digitized with a National Instruments PCI MIO-16-E1 data acquisition card (National Instruments, USA). The sampling frequency was set to 1kHz. The signals were monitored and recorded in the LabVIEW (National Instruments, USA) written program.

2.4 Analysis of PPG signal waveform and PPGAI

The PPG signal waveform was analyzed according to the algorithm described in our earlier studies (Pilt et al 2013a, Pilt et al 2013b). Briefly, a recorded PPG signal is filtered with a FIR high- and low-pass filter. Filters are designed using the window method, with the Hamming window function and the cut-off frequencies are selected 0.5Hz (filter order: 4000) and 30Hz (filter order: 500), respectively. The beginning and ending points of each recurrence in the PPG signal are detected by using R-peaks of the ECG signal. Thereafter, the PPG signal is differentiated for two and four times.
As it follows here, all the recurrences of the PPG signal are limited equally with six harmonic components. For that purpose, the PPG signal is resampled such that one of the selected recurrence lengths is 1 s (1000 samples), which corresponds to the pulse frequency of 1 Hz. The resampled signal is filtered with a Parks-McClellan low-pass filter with an edge frequency of 6 Hz and a transition band of 1Hz. The maximum allowable errors, i.e. ripples, for the pass- and stop-band were set at 0.001. The
The selected recurrence is now limited with six harmonic components and a copy of it is placed into the matrix. The copy of the selected recurrence is aligned in the matrix with other filtered recurrences from this PPG signal. The 50 per cent level of the PPG signal raising front is used as the reference point for the alignment of the recurrences in the matrix. The next recurrence is then selected from the PPG signal and the resampling, filtering and alignment process previously described is completed. Similarly, the recurrences are processed from the derivative signals and the matrices with recurrences are constructed. The constructed matrices for one PPG signal are illustrated in figure 2.

The fourth derivative waveform was used to detect the peaks from the SDPPG waveform. The SDPPG waveform peaks are looked up in the zones between two consecutive zero crossings from the fourth derivative PPG signal. The four wave peaks ‘a’, ‘b’, ‘c’, and ‘d’ are detected from each of the SDPPG waveform, as shown in figure 2. The amplitudes of the characteristic points $A_b$ and $A_d$ are measured from the PPG waveforms in the locations of the SDPPG waves ‘b’ and ‘d’, as indicated in figure 2. The characteristic amplitudes $A_b$ and $A_d$ are normalized with the PPG signal amplitude $A$, named as $PPGb$ and $PPGd$, respectively. The PPG waveform $PPGAI$ index is calculated as follows:

$$PBGAI = \frac{A_d}{A} = \frac{PPGd}{PPGb}$$

The matrices are constructed for each recorded PPG signal separately. The wave peaks are detected and the $PPGAI$ index is calculated for each waveform from the PPG signal. The $PPGAI$ values are averaged and the standard deviations are calculated.

The waveform analysis algorithm described above was implemented in MATLAB (The MathWorks, USA). The function ‘resample’ was used in MATLAB to resample the signals. The one-minute long signals were processed offline after the experiments.

3. Results

Physiological parameters of the healthy subjects and diabetes patients are summarized in Table 1. The age, body mass index (BMI), systolic blood pressure (BP), diastolic BP, and heart rate are given as average values with a standard deviation (SD) for the controls and the diabetes patient group.

PPG signals were processed by using the waveform analysis algorithm described in the previous section. The linear relationship between $PPGAI$ and $AIx@75$ investigated is illustrated in figure 3. In the analysis all the data points (44 altogether) from both subject groups were used and the Pearson’s correlation coefficient was calculated. In addition, the regression model was calculated.

<table>
<thead>
<tr>
<th>Table 1. Summary of the characteristic parameters of the subjects</th>
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<tr>
<td>Healthy subjects</td>
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<tr>
<td>No. of subjects</td>
</tr>
<tr>
<td>Male/female</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>BMI (kg·m$^{-2}$)</td>
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<tr>
<td>Systolic BP (mmHg)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td>Heart rate (bpm)</td>
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As the cardiovascular age of the subject can be associated with the stiffness of blood vessels, the relationship between the age and the $PPGAI$ is illustrated in figure 4a. Each data point in figure 4a represents the average value of the index for one subject. In addition, figure 4b shows the relationship between the SphygmoCor calculated $AIx@75$ and the age. The linear model was constructed for both indices by using the data points from healthy subjects. The standard deviation $SD_x$ was calculated for both models based on the data from healthy subjects. Pearson’s correlation coefficient $r$ was calculated in order to investigate the linear relationship between the indices and the age.
The differences denoted as $\Delta$ between the data points and the constructed model were calculated for PPGAI and AIx@75 (e.g., $\Delta_{\text{PPGAI}} = y_{\text{PPGAI}} - \text{PPGAI}$). The differences were averaged for data points from healthy subjects and diabetes patients and denoted as $\Delta_h$ and $\Delta_d$, respectively. $\Delta_h = 0$ for PPGAI and AIx@75 as the models were constructed on the basis of data points from healthy subjects. For both indices, the data point differences from the proposed model were compared between the healthy and the diabetes patients groups. A paired t-test (Two-Sample Assuming Unequal Variances) was performed in MS Excel with $\alpha = 0.05$. The P-values from the t-test were $P<0.0001$ for both indices. Figure 5 shows averaged differences $\Delta_h$ and $\Delta_d$ as well as standard deviation bars of the model for both indices.
4. Discussion

The proposed PPGAI is strongly correlated ($r=0.85$) with aortic AIx@75 and it shows that the proposed PPG waveform index is related to the arterial stiffness. Similarly, Takazawa group found high correlation ($r=0.86$) between the invasive aortic pressure wave and the PPG signal augmentation indices. However, the PPG signal processing and the calculation of AIx in this study differ from the study by Takazawa group. Figure 3 reveals deviations from the regression line, which are mainly caused by the different origin of the signals. The PPG signal is related to the arterial pressure pulse, although the waveform is not the same (Millasseau et al 2000). In addition, the peripheral blood flow in finger depends on the activity of the sympathetic nervous system and the temperature, which may cause deviations in the PPG waveform (Nitzan et al 1998, Hertzman and Orth 1942, Pilt et al 2013c).

As the cardiovascular age of the subject can be associated with the stiffness of blood vessels (Millasseau et al 2002, Lee and Park 2013), the relations between the PPGAI, AIx@75 and the age are shown in figure 4. Relatively high correlation ($r=0.77$) was found between the PPGAI and the age. In addition, the data points from healthy subjects are situated close to the regression line. It is visible that data points from diabetes patients have noticeably higher values than those of healthy subjects. However, some data points from diabetes patients are situated close to the regression line. It can be assumed that the stiffness of the arteries has not increased for some of the diabetes patients due to the short duration of the disease or their active life styles. The SphygmoCor assessed AIx@75 data points from healthy subjects are more dispersed around the regression line. However, all the data points from diabetes patients are with higher values compared to the regression line.

In order to discriminate the subjects with increased arterial stiffness from healthy persons, the regression model was constructed for the age correction. For both indices the group differences were significant ($P<0.0001$). Figure 5 reveals that the average differences in the diabetes patient group from the constructed models are larger than the standard deviation of the given models. However, the standard deviation of the model $y_{AIx@75}$ constitutes 84% from the average difference of the diabetes patient group $\Delta_{d}$. The same ratio for the PPGAI is 39%, which is more than two times lower. As a result, the subject can be discriminated better by using the index PPGAI.

5. Conclusions

This study has shown that the PPG waveform index PPGAI calculated by the analysis algorithm developed earlier can be applied to discriminate the subjects with raised arterial stiffness from healthy persons. The PPGAI was compared with the recognized stiffness index AIx@75, which was obtained with a SphygmoCor device. Strong linear relation was found between the two indices. To discriminate the subjects, the age correction model was constructed for both indices. The largest difference between the standard deviation of the model and the average difference of the diabetes patient group was achieved with the PPGAI index. It can be assumed that the changes in the index finger PPG signal caused by the stiffening of the arteries can be detected with the waveform index PPGAI.

Acknowledgments

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