Original Research Article

Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity

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ABSTRACT

Pulse wave velocity (PWV) is commonly used for assessing arterial stiffness and it is a useful and accurate cardiovascular mortality predictor. Currently, many techniques and devices for PWV measurement are known, but they are usually expensive and require operator experience. One possible solution for PWV measurement is photoplethysmography (PPG), which is convenient, inexpensive and provides continuous PWV results. The aim of this paper is validation of a new device for PPG sensor-based measurement of multi-site arterial PWV using a SphygmoCor XCEL (as the reference device) according to the recommendations of the Artery Society Guidelines (ASG). In this study, 108 subjects (56 men and 52 women, 20–91 years in 3 required age groups) were enrolled. The multi-site PWV was simultaneous measured by 7 PPG sensors commonly used in pulse oximetry in clinical settings. These sensors were placed on the forehead, and right and left earlobes, fingers and toes. Pulse transit time (PTT) was measured offline as the difference of time delay between two onsets of the pulse wave determined by the intersecting tangent method. The PWV was calculated by dividing the distance between PPG sensors by PTT. During PPG signals measurement, reference carotid to femoral PWV (cfPWV) was performed with a SphygmoCor XCEL system. The Pearson correlation coefficient (r) between the obtained PWV results was calculated. The Bland-Altman method was used to establish the level of agreement between the two devices. Mean difference (md) and standard deviation (SD) were also calculated. The multi-site PWV was highly correlated with accuracy at the ASG-defined level of "Acceptable" (md < 1.0 m/s and SD $\leq$ 1.5 m/s) with cfPWV: forehead - right toe (r = 0.75, md = 0.20, SD = 0.97), forehead - left toe (r = 0.79, md = 0.18, SD = 0.91), right ear - right toe (r = 0.79, md = 0.11, SD = 0.96), left ear - left toe (r = 0.75, md = 0.43, SD = 0.99), right ear - left toe (r = 0.78, md = 0.40, SD = 0.93), left ear - right toe (r = 0.78, md = 0.11, SD = 0.96), right finger - right toe (r = 0.66, md = 0.95, SD = 1.29), left finger - left

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toe (r = 0.67, md = 0.68, SD = 1.35). This study showed that PWV measured with the multi-site PPG system, in relation to the obtained numerical values, correlated very well with that measured using the commonly known applanation tonometry method. However, it should be noted, that the measured PWV concerns the central and muscular part of the arterial tree while the cfPWV is only for the central one. The best results were obtained when the proximal PPG sensor was placed on the head (ear or forehead) and the distal PPG sensor on the toe. PPG sensors can be placed in many sites at the same time, which provides greater freedom of their configuration. Multi-site photoplethysmography is an alternative method for PWV measurement and creates new possibilities for the diagnostics of cardiovascular diseases.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally [1,2]. Classic risk factors for CVD development are divided into non-modifiable ones i.e. age and family history of heart diseases, as well as modifiable risk factors, such as hypertension, hyperlipidemia, smoking, diabetes and obesity [3]. Arterial stiffness [4] has been shown to have an independent predictive value for cardiovascular events in people with hypertension, diabetes [5], and end-stage renal disease [6], in the elderly [7,8], and in the general population. In addition, there are discussions as to whether increased arterial stiffness is the result or perhaps the cause of hypertension. While the "secondary" increase in large artery stiffness is attributable to an increase in mean pressure that occurs in hypertension, evidence now exists that the "primary" increase in large artery stiffness that accompanies aging gives rise to an increase in large vessel stiffness that proceeds an elevation of arterial pressure [8]. Aortic stiffness is an independent predictor of fatal stroke in patients with essential hypertension [9]. A review of PVW as a measure of arterial stiffness in patients with familial hypercholesterolemia was presented in [10].

Pulse wave velocity (PWV) measurement is an established method of assessing arterial stiffness and it is a useful and accurate cardiovascular mortality predictor [11]. The prognostic value of the aortic PWV measurement was also reflected in the guidelines of the European Society of Cardiology and the European Society of Hypertension [12]. PWV measurement may refer to both the aorta and the peripheral segments of the arteries [13]. The carotid to femoral PWV (cfPWV) is indicative of the stiffness in the central-elastic artery, while the carotid to radial PWV (crPWV) can provide information about the peripheral-muscular arteries [14]. In a review [15], authors provide an overview of the numerous methods and underlying technologies within devices that claim to measure arterial stiffness in humans and demonstrate advantages and disadvantages of methods aiming to measure aortic PWV and local arterial stiffness. Despite devices dedicated to PWV measurement (for example, SphygmoCor, Complior, Artegiograph [16,17]), the possibilities of assessing arterial stiffness are analyzed by tools commonly used in radiology - such as magnetic resonance [18], ultrasound [19] or a promising technique used in cardiological ultrasonography - two-dimensional speckle tracing [20]. Assessment of arterial compliance may be done by fusion of oscillometry and PWV information also [21]. Besides to the PWV measurement, attention should be paid to the additional information from Pulse Wave Analysis (PWA), which parameters allow estimation of cardiac output based on continuous analysis of the arterial blood pressure waveform tested according to many algorithms [22].

The study of PWV and factors influencing PWV is still an important and current topic. The impact of heart rate (HR) on cfPWV was investigated in [23] under a simulated case. It has been shown that relatively small HR changes may only slightly affect cfPWV. In turn, it was shown in [24,25] that the brachial to ankle PWV (baPWV) could be a useful screening tool for the early detection of adverse cardiac features among untreated hypertensive patients. In [26] it was shown that both an orthostatic blood pressure drop and rise were associated with elevated PWV. The usefulness of baPWV in the detection of diabetic changes was investigated in [27] and indicated that baPWV may be a convenient, noninvasive, and reproducible method for detecting early diabetic nephropathy. In [28] was shown that baPWV is associated with plasma fibulin-1 level in patients with asymptomatic hyperuricemia. A positive association between baPWV and white blood cells counts in patients with hypertension was revealed in study [29]. In addition to the classic cfPWV measurement and the more peripheral baPWV [24], studies of other indicators of arterial stiffness are being undertaken, such as the measurement of heart-femoral PWV (hfPWV) [30] or completely new assessment methods that correlate with PWV, such as neutrophil-to-lymphocyte ratio (NLR) [31]. Research is growing in the field of PWV's algorithms as well. In [32] various methods of coronary PWV determination in anesthetized pigs were examined. The tangent intersection method applied to the backward waves and template matching method has been shown to be the most appropriate for clinical studies. Machine learning (ML) algorithms used to measure the PTT and PWV by analyzing PPG signal waves acquired by a digital camera recording two regions were presented in [33]. In [34] was presented an approach using ML pipelines to estimate the cfPWV from the peripheral pulse wave measured at a single site (e.g. the radial pressure wave). Once more, a solution where cfPWV is combined with crPWV

and ML for estimating aortic characteristic impedance and arterial compliance is presented in [35]. All these above-mentioned studies indicate the need for further work in the field of PWV.

PWV can be measured by several techniques: invasive methods, applanation tonometry, cuff-based oscillometry, magnetic resonance imaging, photoplethysmography, using piezoelectric mechanotransducers and ultrasound techniques. An overview of the above-mentioned techniques has been described in previous works [36–39]. The invasive technique is the most accurate, is considered as the gold standard but its use is very limited, usually only during an angiography procedure. The most commonly used and developed methods are non-invasive. Several commercial devices using non-invasive techniques are available and largely used worldwide: SphygmoCor CvMS-PWV, SphygmoCor XCEL, PulsePen, Complior, Arteriograph, Vicorder. Also, there are known non-commercial solutions as custom or individual designs. An approach based on two multiplexed fiber-optic Fabry-Perot interferometric sensors was presented in [40], based on a piezoelectric sensor array in [41], magnetic transducers in [42,43], MEMS-based sensors (pressure and accelerometer) in [44–46]. A combined phonocardiographic (PCG), impedance cardiographic (ICG), electrocardiographic (ECG) and PPG approach was presented in [47]. A method based on ECG and two blood pressure measuring cuffs was presented in [48]. An aortic PWV measurement may be also realized by inductive plethsymography [49]. For easy-to-use PWV measurement miniaturized handheld laser Doppler vibrometer arrays in silicon photonics platform was presented in [50].

Photoplethysmography technique is extensively used in pulse oximetry and for determining other cardiovascular parameters [51,52]. A PPG sensors are usually placed in one site or in multi-site simultaneously [53,54]. Photoplethysmography can be used for PWV assessment as a non-invasive, inexpensive and easy-use technique also. For PWV measurement it requires two sensors, placed in different sites and containing a light source (usually a LED diode) and a photodetector (usually a photodiode). Examples of use of PPG sensors for PWV measurement are known in the literature. In [55] was presented a device called pOpmètre containing a PPG sensor positioned on the finger and the toe. PWV was calculated using pulse transit time (PTT) between the toe and the finger. The distance covered by the pulse was estimated using subject height. A similar solution was used in [56] but the distance was the difference between the distance measured from the sternal notch to the toe and from the sternal notch to the finger. In [57] a custom probe was presented containing two PPG sensors placed at constant distance of 23 mm. The probe was tested on the carotid artery. For PWV assessment a local PTT was used (i.e. between two PPG sensors on the probe). A low cost measurement system for local PWV assessment was presented in [58]. It consist two PPG sensors placed at radial artery (at wrist). In [59] was presented an approach using two synchronized, wireless reflectance PPG sensors placed on the wrist and finger of the same hand at a constant distance of 224 mm. A local PWV can be also assessed with the multi-photodiode array technique [60]. There are also examples of calculating the PWV based on the time delay between the peak of the ECG R wave and the foot of the PPG

pulse wave [61–63]. In [64] was presented a concept of a new method to approximate central PWV based on pulse arrival time (PAT) segmentation into cardiac isovolumic contraction and vascular PTT. PAT refers to the interval between the ECG R-peak and the systolic foot identified in a peripheral pressure waveform, typically acquired by a PPG sensor. The paper [33] describes the development and evaluation of a new contactless cardiovascular monitor, which can measure PTT and PWV by analyzing the PPG signal obtained by an RGB camera's green channel.

In this article we present a measure method and obtained results of simultaneous and continuous PWV measurement using seven PPG sensors placed on many sites of the body. According to the authors' knowledge, this is the first paper presenting the validation of a synchronous and multi-site PWV measurement using PPG signals. This article is continuation of our preliminary work presented in [65].

2. Materials and methods

2.1. Multi-site measurement system

For multi-site arterial pulse wave velocity measurements, we used a custom made system called MPPT. The MPPT is a precise, multi-site system for the simultaneous, real-time, synchronous measurement of photoplethysmographic and electrocardiographic signals as well as simultaneous NiBP (non-invasive blood pressure) pressure assessment. This system was described in detail in [66]. It was validated with the Fluke ProSim 8 patient simulator. For multi-site PWV measurement, we used 7 PPG sensors as shown in the MPPT configuration diagram (Fig. 1). Also localization of the SphygmoCor XCEL sensors (tonometer and cuff on right body site) is shown in Fig. 1.

A significant problem in simultaneous measurement of many signals is data synchronization. As described in detail in [66], all PPG channels use the same AFE (analog-front-end) i.e. AFE4490 by Texas Instruments. The clock input of all these AFEs was connected to the common central clock of the microprocessor system. Therefore, the PPG data synchronization error is less than one sampling period. The circuits of the AFE applied include a LED driver, a transimpedance amplifier for a photodiode and a high-resolution 22-bit analog–digital converter. No filters (analog or digital) in the MPPT device were used.

The PPG sensors, manufactured by Unimed, were used i.e. transmission clamps on fingers, toes (type U410-01) and earlobes (type U910-01) and a reflectance sensor on the forehead (type U803-01V). Each of these sensors has one RED diode (wavelength 660 nm) and one IR diode (wavelength 905 nm). According the recommendations for validation of new devices, presented in [67], the MPPT sampling frequency has been increased to 1 kHz. The MPPT device was connected to a computer via a galvanic separation USB interface. Dedicated computer software was responsible for control, online data transfer and visualization of raw (unprocessed) signals as well as data archiving. Signal processing and calculation of PWV was performed after completed measurements (offline mode).
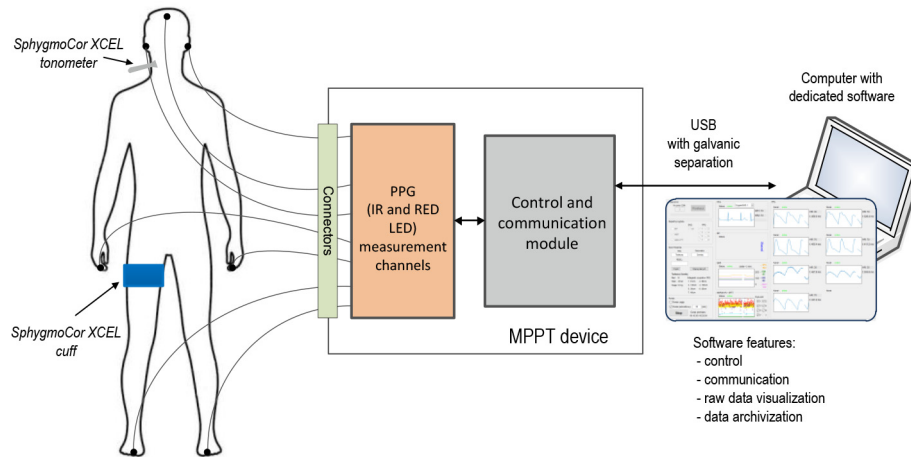
Fig. 1 – Block diagram of MPPT system configured for multi-site PWV measurement (with SphygmoCor XCEL sensors).

2.2. Reference devices

The reference PWV measurement (marked as cfPWV) was performed with a SphygmoCor (XCEL version) device by ATCOR. The SphygmoCor has been validated as per the ARTERY PWV validation guidelines [67–69] and it is most widely used and considered as the noninvasive gold standard technique. The SphygmoCor XCEL device simultaneously acquires a carotid pulse through applanation tonometry and femoral pulse by volumetric displacement within a cuff around the upper thigh [70]. Then, the device calculates the pulse transit time (cfPTT) between the feet of the carotid and femoral pulse. The path length (distance) to determine cfPWV was obtained with the subtraction method. The single measurement recording time was 10 s. For each subject (person) we performed usually three or more cfPWV measurements with an interval of approximately 3 min. We reported the cfPWV as the median of the measurements.

2.3. Study population

The study population meets the required criteria specified in [67]. Characteristics of the study group are shown in Table 1.

2.4. Path length measurement

Due to the short pulse transit time in the vessels, the correct determination of the path length is of great importance for the PWV measurement result. The basic rule is to determine the length of the blood flow path between two measurement sites. The direction of the blood flow should also be taken into account. Various methods of determining the path length are known and it is described in detail in the [71,72]. As recommended in [67], in our validation work we used the subtraction method. For path length determination we defined some distances as shown in Fig. 2.

In the reference measurement (cfPWV) with the use of SphygmoCor XCEL, the path length (d_{SC}) was calculated according to operator's manual (Revision 4.0):

$$d_{SC} = d_2 - d_1 - d_3 \tag{1}$$

where:

d_1 – distance from the carotid artery measurement site (on the neck) to the sternal notch,
d_2 – distance from sternal notch to the top edge of the femoral cuff,
d_3 – distance from femoral artery to the top edge of the femoral cuff.

Table 1 – Characteristics of the study group.	
Variable	Mean (SD) [Min–Max] or number
Number of subject	108
Sex, male/female	56/52
Age, years old	48 (21) [20–91]
<30 years group	31
30–60 years group	42
>60 years group	35
Height, cm	171 (12) [146–196]
Weight, kg	72.6 (12.0) [46–100]
Body Mass Index - BMI, kg/m^2	24.8 (2.5) [18.4–30.0]
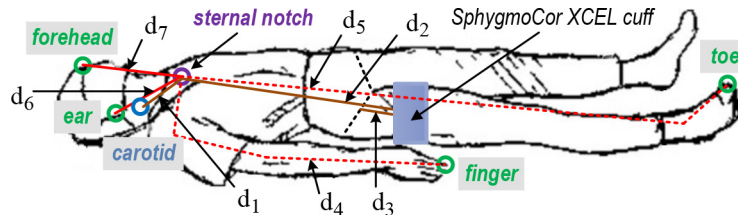
Fig. 2 – The distances used to calculate the PWV in the SphygmoCor XCEL (d$_1$, d$_2$, d$_3$) and the MPPT system (d$_4$, d$_5$, d$_6$, d$_7$).

All the distances were obtained directly with a tape measure with a reading accuracy of ±0.5 cm.

Multi-site PWV calculation required several other distance measurements. As for the SphygmoCor XCEL device, the starting point was the sternal notch. Moreover, we assumed that the distance between the sternal notch and the left or right measurement point is the same. The distances were measured with a tape, in a straight line (ear – d$_6$, forehead – d$_7$) or a broken line (finger – d$_4$, toe – d$_5$):

d$_4$ – distance from the sternal notch to the center of the PPG sensor placed on the right finger, obtained as sum of the three lines (as shown in Fig. 2),

d$_5$ – distance from the sternal notch to the center of the PPG sensor placed on the right toe, obtained as sum of the two lines (as shown in Fig. 2),

d$_6$ – straight line distance from the sternal notch to the center of the PPG sensor placed on the right ear,

d$_7$ – straight line distance from the sternal notch to the center of the PPG sensor placed on the center of the forehead.

The path length for PWV measurements in MPPT were defined as:

d$_{HT}$ - path length for MPPT forehead-toe PWV (htPWV),
d$_{ET}$ - path length for MPPT ear-toe PWV (etPWV),
d$_{FT}$ - path length for MPPT finger-toe PWV (ftPWV),

$$d_{HT} = d_5 - 1.9 \times d_7 \tag{2}$$

$$d_{ET} = d_5 - d_6 \tag{3}$$

$$d_{FT} = d_5 - d_4 \tag{4}$$

The real length of the blood vessels between the sternal notch and the sensor in the forehead is much bigger than the direct d$_7$ measurement. The d$_7$ shows the shortest path between the measurement points in a straight line, while the arteries, due to their flexibility and the location between other tissues of the body (muscles, tendons, bones), do not run in straight lines, but have a physiological tortuous location among other structures of the body and are therefore naturally longer. Therefore, for the calculation of d$_{HT}$, we proposed a length correction to $1.9 \times d_7$. This correction coefficient was selected experimentally on the basis of the obtained results. Path length results for our study group are shown in Table 2.

**Table 2 – Characteristics of the path length.**

Parameter	Mean (SD) [Min–Max]
d$_{SC}$, cm	50.1 (3.7) [42.0–62.0]
(d$_{SC}$/height) $\times$ 100, %	29.4 (2.1) [25.3–36.4]
d$_{HT}$, cm	112.9 (8.9) [93.2–132.3]
(d$_{HT}$/height) $\times$ 100, %	66.1 (2.2) [59.2–71.6]
d$_{ET}$, cm	137.5 (9.9) [118.0–158.0]
(d$_{ET}$/height) $\times$ 100, %	80.5 (1.7) [76.8–86.8]
d$_{FT}$, cm	65.6 (5.6) [52.0–81.0]
(d$_{FT}$/height) $\times$ 100, %	38.4 (1.5) [34.4–42.0]

The shortest path lengths are for d$_{SC}$ ([42.0–62.0] cm). It should be noted that the shorter the path, the greater the impact of accuracy of the distance on the PWV result. Therefore, all distance measurements were made with great care.

2.5. The validation protocol

108 volunteers were qualified for the validation studies. They had been informed of the purpose and procedure of the study before the measurements. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Bioethics Committee at the National Institute of Geriatrics, Rheumatology and Rehabilitation in Warsaw (Doc number: KB 4/1/2017 and KB 1/9/2019). Before inclusion in the study, all the participants were made to provide a written informed consent.

The tests were carried out during the day, in a separate and quiet room, at about 22–24 °C. Measurements were made in the supine position after about 15 min of supine rest on a medical settee (height 75 cm). It should be stressed that the reference measurements with the SphygmoCor XCEL (cfPWV) device were performed simultaneously with the measurements with the MPPT device, as shown in Fig. 3.
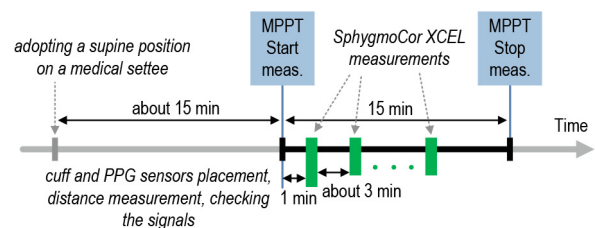

Fig. 3 – Timeline of the measurement protocol.

All measurements were performed by the same operator. The MPPT device measured the signals continuously for 15 min. The recording duration was adopted so that several cfPWV measurements could be performed. The PPG sensors were in the fixed sites. The number of cfPWV reference measurements depended on the quality of the signal obtained from the carotid artery (signal quality was shown by the SphygmoCor XCEL software). In some cases, it was difficult to get the required carotid signal quality. For one person, the cfPWV measurement was not correctly performed. This person was not included in the results of this study.

2.6. Signal processing

Signal processing only concern to the MPPT measurement system. As previously mentioned, signal processing and PWV calculation were performed offline, in MATLAB environment (version R2019a), after all 15-minute recordings had been completed. The primary goal of the signal processing algorithms was to indicate the onset of the pulse wave (Fig. 4), calculate the appropriate PTT times and then calculate the PWV.
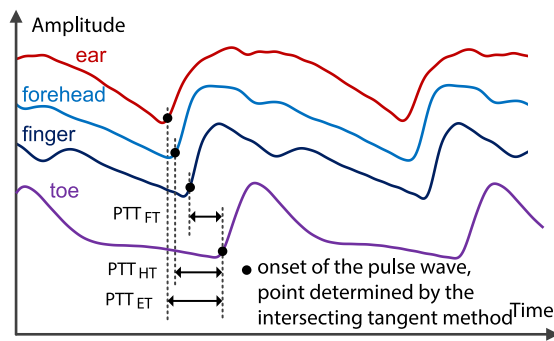
Fig. 4 – Sample of signals from PPG sensors and PTT delays for multi-site PWV calculation.

For PWV calculation we used PPG signals from IR diodes, because they usually have a greater amplitude than the signals from the RED diodes [73]. A Butterworth bandpass ([0.5–15] Hz) filter of order 4 was used to filter the PPG signals. Such a filter is a maximally flat magnitude filter that rolls off slower and without ripples around the cutoff frequency [52,74] which is especially important when determining the onset of the pulse wave. Each PPG signal was filtered with the same method and, in addition, zero-phase digital filtering was used ("filtfilt" function of the MATLAB). As a result, there were no delays between signals due to signal processing. After filtration, for each of the PPG signals (forehead, ears, fingers, toes), the onset of the pulses wave was determined using the intersecting tangent method [39,67,75].

Next, the pulse transit times were calculated between the forehead and toe (PTT_{HT}) for left and right leg, the ear and toe (PTT_{ET}) for left and right site and the finger and toe (PTT_{FT}) for left and right site. Multi-site PWVs were defined as:

$$htPWV = d_{HT}/PTT_{HT} \tag{5}$$

$$etPWV = d_{ET}/PTT_{ET} \tag{6}$$

$$ftPWV = d_{FT}/PTT_{FT} \tag{7}$$

where:

htPWV – pulse wave velocity calculated from the signals of the forehead and toe sensors,
etPWV – pulse wave velocity calculated from the signals of the ear and toe sensors,
ftPWV – pulse wave velocity calculated from the signals of the finger and toe sensors.

The applied signal processing takes approximately 0.4 s (Matlab 2019a, Core i7-3770K @3.5 GHz, 16 GB RAM) to calculate one PWV variant (e.g. forehead-toe) for a 15-minute PPG signal. Signal filtration and determination of onset points of the pulse wave takes the longest time (about 99% of the processing time).

2.7. Data analysis

The calculated multi-site PWV values are momentary values calculated for each heart beat. The final multi-site PWV (htPWV, etPWV, ftPWV) value was calculated for each subject as the mean of the 15-minute recording. Apart from the mean value, standard deviation was determined. Likewise, for each subject the average of the all SphygmoCor XCEL cfPWV readings was calculated and used in the subsequent analysis.

In order to compare the results reference PWV (cfPWV) and multi-site PWV values were determined for each subject. Subjects with the number of multi-site momentary PWV values smaller than 50 (in a 15 min recording) and SD >2 m/s were excluded from the analysis. The analysis of the results was performed using the Bland-Altman methodology and relationship (linear regression) between cfPWV and multi-site PWV for various PPG sensor variants. The linear equation (y) showing the relationship can be written generally as: $y = ax + b$, where a represents the slope and b intercept. For each of the analyzed multi-site variants, the values of a and b were determined. For the relationship, the Pearson correlation coefficient (r) and p-value (p) based on the "corrcoef" function of MATLAB were computed also.

In order to analyze the proportional bias, according to the recommendation [76], a linear regression line was fitted to the Bland–Altman plots.

3. Results

The obtained results are presented in the relationship and Bland-Altman plots with additional analysis of the proportional bias and summary in the table. The analysis of the proportional bias (PB) is marked on the Bland-Altman plots with the red lines (the relationship line is marked in thick, the 95 % prediction interval is marked thin). In the presented below, the symbols mean:

n – number of valid data pairs	SD – standard deviation
r – Pearson correlation	CV – coefficient of
RMSE – root mean squared error	variation (SD of mean
y – relationship linear equation	values in %)
	PB – proportional bias

3.1. Comparison between cfPWV and forehead - right toe htPWV (variant no. 1)

In this variant, signals from PPG sensors placed on the forehead and right toe were processed. htPWV was calculated based on Eq. (5). The results are shown in a relationship plot (Fig. 5a) and a Bland-Altman plot (Fig. 5b).

3.2. Comparison between cfPWV and forehead - left toe htPWV (variant no. 2)

In this variant, signals from PPG sensors placed on the forehead and left toe were processed. htPWV was calculated based on Eq. (5). The results are shown in a relationship plot (Fig. 6a) and a Bland-Altman plot (Fig. 6b).

3.3. Comparison between cfPWV and right ear - right toe etPWV (variant no. 3)

In this variant, signals from PPG sensors placed on the right ear and right toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 7a) and a Bland-Altman plot (Fig. 7b).

3.4. Comparison between cfPWV and left ear - left toe etPWV (variant no. 4)

In this variant, signals from PPG sensors placed on the left ear and left toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 8a) and a Bland-Altman plot (Fig. 8b).

3.5. Comparison between cfPWV and right ear - left toe etPWV (variant no. 5)

In this variant, signals from PPG sensors placed on the right ear and left toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 9a) and a Bland-Altman plot (Fig. 9b).

3.6. Comparison between cfPWV and left ear - right toe etPWV (variant no. 6)

In this variant, signals from PPG sensors placed on the left ear and right toe were processed. etPWV was calculated based on Eq. (6). The results are shown in a relationship plot (Fig. 10a) and a Bland-Altman plot (Fig. 10b).

3.7. Comparison between cfPWV and right finger- right toe ftPWV (variant no. 7)

In this variant, signals from PPG sensors placed on the right finger and right toe were processed. ftPWV was calculated based on Eq. (7). The results are shown in a relationship plot (Fig. 11a) and a Bland-Altman plot (Fig. 11b).

3.8. Comparison between cfPWV and left finger- left toe ftPWV (variant no. 8)

In this variant, signals from PPG sensors placed on the left finger and left toe were processed. ftPWV was calculated based on Eq. (7). The results are shown in a relationship plot (Fig. 12a) and a Bland-Altman plot (Fig. 12b).

Based on the graphs presented above, it can be seen that for each of the variants similar results were obtained. Table 3 summarizes these results. Table 3 also shows the results for variants where the distal PPG sensor was placed on the head (ear or forehead) and the proximal PPG sensor was placed on the finger (variants no. 9–12).

For these variants, the correlation coefficient r has a very small value which may indicate a lack of correlation with the cfPWV. This matter is considered in the Discussion section.

A high value of the Pearson correlation coefficient (r) was obtained (variants no. 1–8). It ranges from 0.66 to 0.79. The RMSE error is ≤ 0.8 m/s for variants no. 1–6 and the maximum is 1.34 m/s for variant no. 8. For our results, the linear regression parameter a is in the range [0.52–0.85] and the parameter b is in the range [0.45–3.8]. The mean difference between
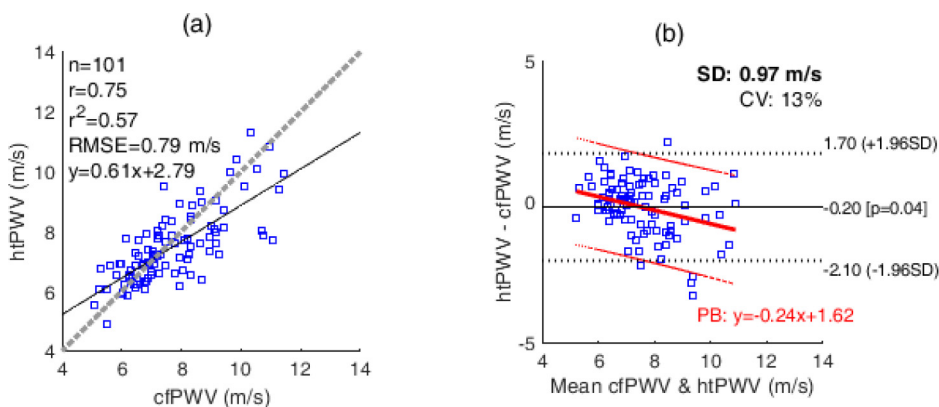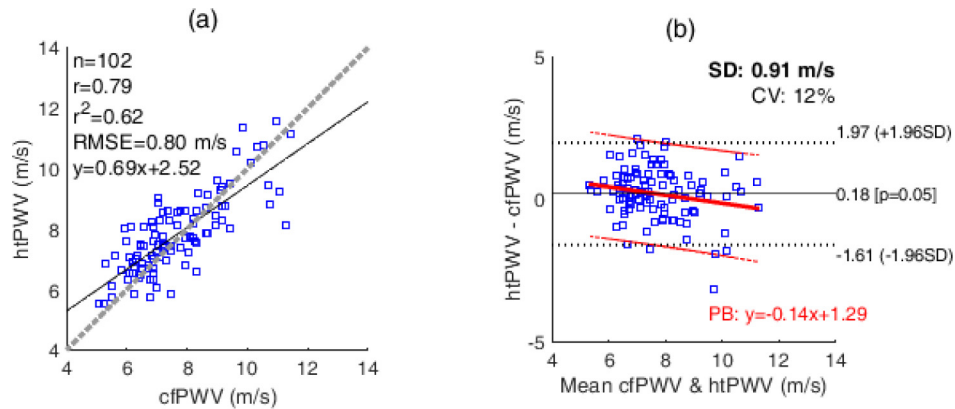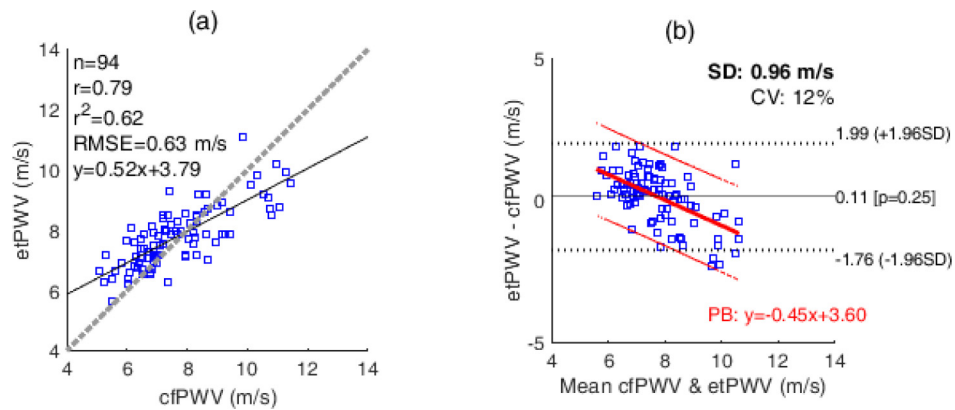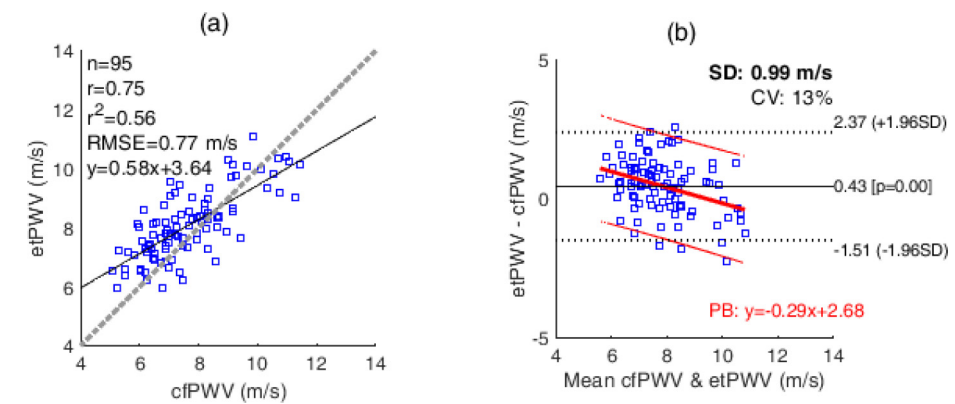

Fig. 5 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (htPWV). MPPT measurement site: forehead - right toe.

Fig. 6 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (htPWV). MPPT measurement site: forehead – left toe.

Fig. 7 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: right ear - right toe.

Fig. 8 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: left ear - left toe.

cfPWV and multi-site PWV is within the range [0.11–0.95] and it is the smallest for variants no. 3 and 6 and the highest for variant no. 7. Standard deviation (SD) is <1 m/s for variants no. 1–6 and <1.4 m/s for variants no. 7 and 8. The variability of the obtained results of PWV measurement, represented

by the coefficient of variation (CV), is ≤13% for variants no. 1–6 and ≤19% for variants no. 7 and 8.

The most important parameters for validating of the new device are mean difference and SD [67]. The PWV results for our MPPT device obtained, for each of the variants (no. 1–8)

Fig. 9 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: right ear – left toe.
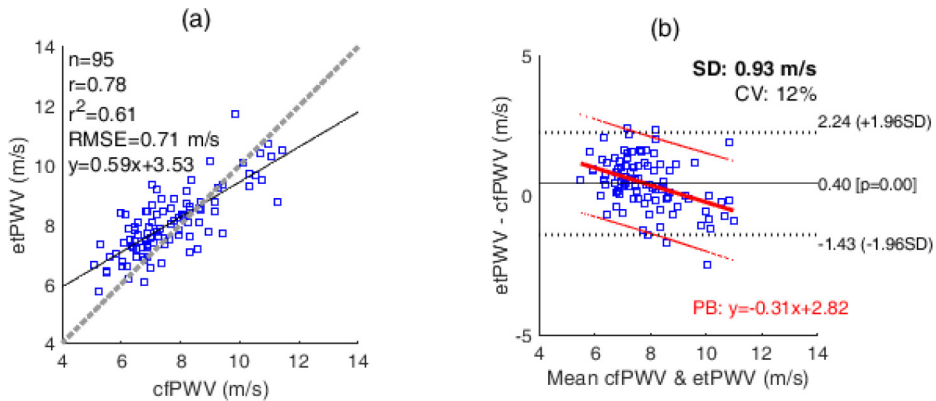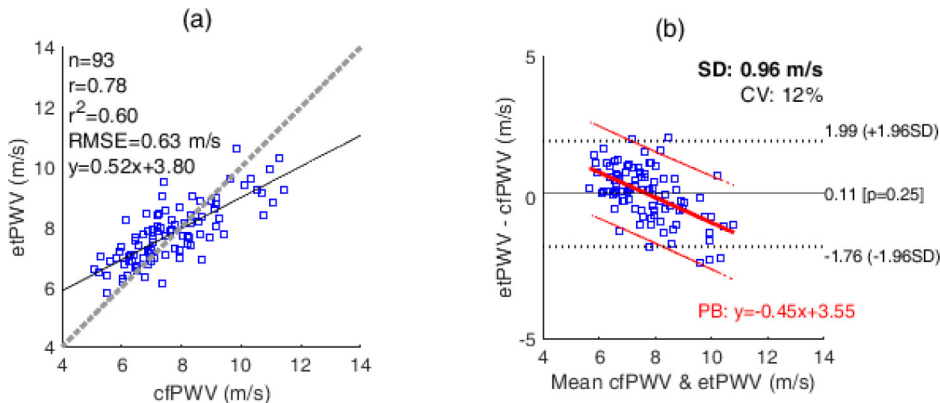

Fig. 10 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (etPWV). MPPT measurement site: left ear - right toe.

Fig. 11 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: right finger - right toe.

meet the accuracy criteria at the level of Acceptable (mean difference <1.0 m/s and SD ≤1.5 m/s).

In order to increase the accuracy of the measurement, it is also possible to average the PWV results obtained from selected variants. The mean PWV obtained after averaging the results from variants no. 1–6 are shown in Fig. 13 (a - relationship plot, b - Bland-Altman plot).

After the averaging of the results from variants no. 1–6 (msaPWV), a higher value of the correlation coefficient (r = 0.89), a smaller mean difference (0.12) and a smaller stan-
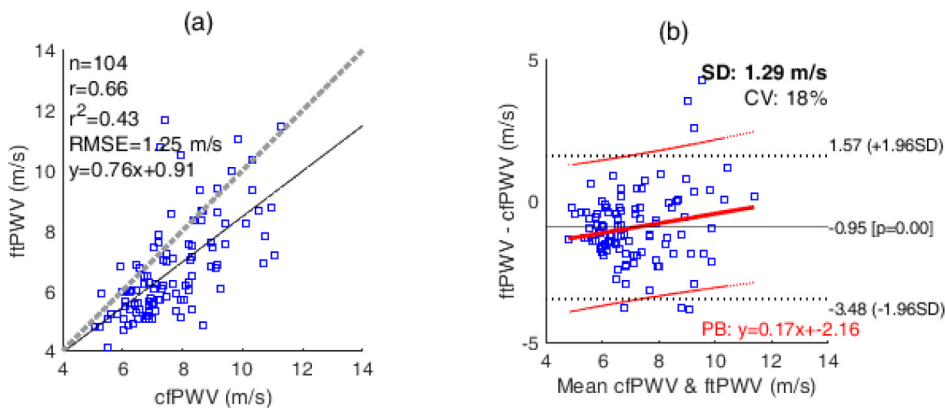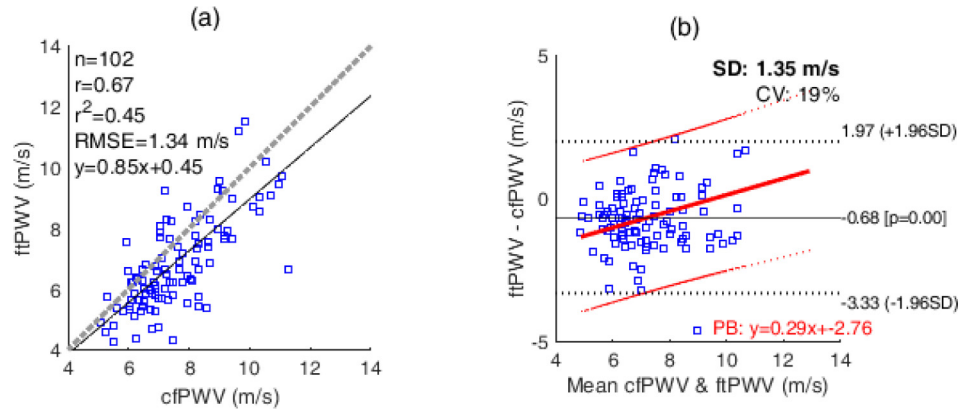
Fig. 12 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and MPPT device PWV (ftPWV). MPPT measurement site: left finger - left toe.

dard deviation (SD = 0.72) were obtained. This result, in relation to the obtained numerical values, meets the requirements of "excellent" accuracy level with reference cfPWV (according to [67]). However, the measured arterial tree in msaPWV differs from the central cfPWV and these results should require commentary. More about this was considered in the Discussion section.

4. Discussion

4.1. Reference PWV measurement

In our study, the SphygmoCor XCEL device was used for the reference PWV measurement, similarly to the other works. To the SphygmoCor as reference the oscillometric technique (the Arteriograph [16], Vicorder [77] and Mobil-O-Graph [78] devices) and piezoelectric mechanotransducer (the Complior [79] and Aortic [80] devices) were validated. Although the SphygmoCor device (the first CvMS-PWV version and newest - XCEL version) is commonly considered as the noninvasive gold standard, its PWV measurement method is different from that of the validated MPPT device. The SphygmoCor XCEL uses a tonometer on the carotid and a cuff on the femoral artery, whereas the MPPT device only uses the photoplethysmographic sensors. As far as the signal recorded by the tonometry technique is similar to that from the PPG technique [52,81,82], the auscultatory signal in the cuff (pressure changes in the cuff caused by the flowing pulse wave) is different from the PPG signal. Other methods of acquiring the signal of the validated reference device may cause slight differences in the obtained results. Moreover, it is obvious that each device has its own measurement error. However, the most important factor influencing the obtained differences in the results is different location of the sensors (measurement site). In the case of SphygmoCor, these sites were the right carotid artery (proximal site) and the right femoral artery (distal site). For the MPPT device, the right ear and forehead were closest to the right carotid artery (distance from over a dozen to tens of cm), while the corresponding sensor for the right femoral artery was only on the right toe (distance of even 1 m). For this reason, the regional reference value

(cfPWV) could differ from the regional PWV value measured by the MPPT device.

4.2. Analysis of own PWV results

According to the above remark, regarding the reference PWV measurement, it is worth noting that the best agreement with the reference cfPWV was achieved with the variant (no. 3) of the PPG sensor placed on the right ear and right toe (r = 0.79 and mean difference = 0.11 m/s). It should be noted, that the greatest dispersion of MPPT PWV measurements was obtained for variants no. 7 and 8, in which the PPG sensor was placed on the fingers and toes. For these variants, the lowest values of the correlation coefficient r and the highest RMSE, mean difference and SD were obtained. Concurrently, for these variants, the highest value of the slope (a) and the smallest value of the intercept (b) describing the relationship linear equation (y) were obtained. These results show that fingers and toes can be good and easy-to-use sites for measurements with PPG sensors (like [55]). Moreover, for fingers and toes we can use widespread transmission pulse oximeters clamps.

As shown in Table 3, for variants no. 9–12, in which the distal PPG sensor was placed on the head and the proximal PPG sensor was placed on the finger, no correlation was obtained between the measured PVW and the reference cfPWV. It should be noted that for these variants the measurement of the arterial path does not include the central arterial path used by the SphygmoCor XCEL. Moreover, the lack of correlation can be explained by the physiology of the arteries because the results from variants no. 9–12 mostly cover the velocity in the peripheral arteries - physiologically built of muscles, not the central arteries which are elastic. As regards the physiological blood flow and vascular structure - cholesterol and calcium deposits are mainly deposited in large, elastic arteries made of fibers, which also explains the greater difference in velocity in these arteries than in less stressed peripheral arteries made up mainly of muscles.

In relation to the physiological context, the measurements consistent with the cfPWV (assessing PWV predominantly in the elastic central artery - the aorta) are measured with the

Table 3 – Summary of comparison between cfPWV and MPPT multi-site PWV measurement.

Variant no.	PPG sensor localization	n	r	RMSE [m/s]	relationship linear equation	Mean difference	p-value	SD [m/s]	CV [%]	Accuracy level [67]
1	forehead - right toe	101	**0.75**	0.79	y = 0.61x + 2.79	**0.20**	0.04	**0.97**	13	Acceptable
2	forehead - left toe	102	**0.79**	0.80	y = 0.69x + 2.52	**0.18**	0.05	**0.91**	12	Acceptable
3	right ear - right toe	94	**0.79**	0.63	y = 0.52x + 3.79	**0.11**	0.25	**0.96**	12	Acceptable
4	left ear - left toe	95	**0.75**	0.77	y = 0.58x + 3.64	**0.43**	0.00	**0.99**	13	Acceptable
5	right ear - left toe	95	**0.78**	0.71	y = 0.59x + 3.53	**0.40**	0.00	**0.93**	12	Acceptable
6	left ear - right toe	93	**0.78**	0.63	y = 0.52x + 3.80	**0.11**	0.25	**0.96**	12	Acceptable
7	right finger- right toe	104	**0.66**	1.25	y = 0.76x + 0.91	**0.95**	0.00	**1.29**	18	Acceptable
8	left finger- left toe	102	**0.67**	1.34	y = 0.85x + 0.45	**0.68**	0.00	**1.35**	19	Acceptable
9	right ear - right finger	92	**0.06**	1.37	y = 0.05x + 9.28	**2.02**	0.00	**1.98**	23	Poor/no correlation
10	left ear - left finger	89	**0.12**	1.37	y = 0.11x + 9.08	**2.21**	0.00	**1.91**	23	Poor/no correlation
11	forehead - right finger	101	**0.01**	1.90	y = 0.01x + 9.48	**1.94**	0.00	**2.39**	28	Poor/no correlation
12	forehead - left finger	94	**0.01**	1.58	y = 0.01x + 9.98	**2.27**	0.00	**2.16**	25	Poor/no correlation

n – number of valid data pairs (sample size); r – Pearson correlation; RMSE – root mean squared error; SD – standard deviation, CV – coefficient of variation (SD of mean values - relative standard deviation - in %).
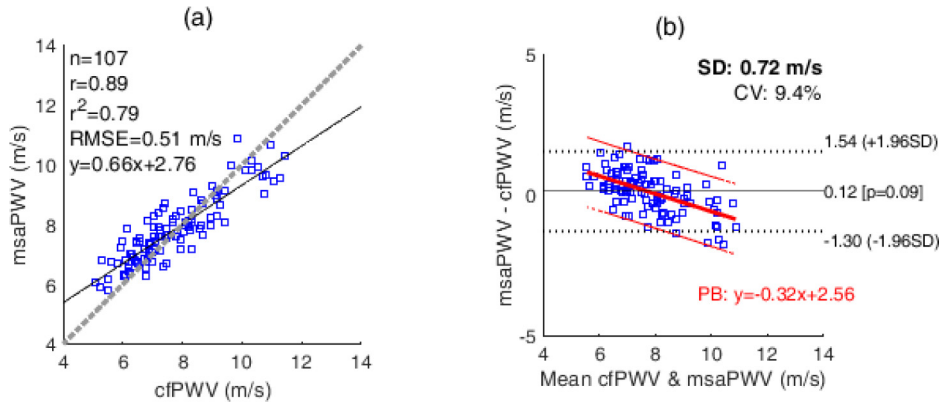
Fig. 13 – Relationship (a) and difference (b) between carotid-femoral PWV (cfPWV) and average MPPT device PWV (msaPWV). msaPWV is the mean of variants no. 1–6.

MPPT device for variants no. 1–6. This is consistent to a lesser extent for variants no. 7–8 because these variants contain a connection of peripheral flow in the entire upper limb (peripheral - mainly muscular arteries, then from the brachial - elastic) as well as the flow in the aorta (elastic). In contrast, variants no. 9–12 measure mainly PWV in peripheral arteries with a naturally different physiological structure. Therefore, the measurement method where PPG sensors are only on the head and finger (variants no. 9–12) should not be used to assess the central PWV.

Another important issue observed in the Bland-Altman plots is the proportional bias, i.e. the difference from the reference value depends on the value of the mean value. This effect shows up for variants no. 1–8 (in the Figs. 5 to 12) and is most evident for variants no. 3,5,6 (in Fig. 7,9 and 10). For variants no. 1–6, the Bland-Altman plots highlighted a negative proportional bias, showing an underestimation of the measured PWV at the highest PWV values. However, for variants 7 and 8, Bland-Altman plots highlighted a positive proportional bias, showing an overestimation of the measured PWV at the highest PWV values. The negative proportional bias occurs in variants where the proximal PPG sensor was placed on the head and the distal PPG sensor on the toe. This is because arterial stiffness arises primarily in the aorta and large arteries, and to a small extent in muscular arteries. For variants no. 1–6 there is a long common arterial path, i.e. the d_2 (see Fig. 2) is within the d_5, so between the cuff on the femoral artery and the toe there are increasingly thinner peripheral arteries and, finally, only muscular arteries. Thus, in these variants there was an underestimation of the measured PWV compared to the cfPWV. For variants no. 7–8 there is also a long common path, (the d_2 is within the d_5), but there is also a long d_4 path with peripheral arteries. In this case, the length of the peripheral arteries path is greater than that of the central ones, so in these variants there was an overestimation of the measured PWV compared to the cfPWV. Small PWV indicates low arterial stiffness, low cardiovascular risk and low risk of atherosclerosis. If there is no atherosclerosis and cholesterol does not accumulate in the central arteries, it will not be deposited in the peripheral arteries that build muscle tissue. Other values, higher for close to central

measurements (variants no. 1–6), lower for peripheral (variants no. 9–12) are physiologically explainable by the structure of the arteries - naturally greater stiffness of the arteries with an elastic structure.

Next issue in the multi-site PWV measurement is averaging the results obtained from different sites. The basic criterion for selecting PWV results for averaging were similar sites of the proximal PPG sensors and similar sites of the distal PPG sensors. This is important as the PWV values may vary depending on the measurement site [83,84]. Another criterion was to obtain a similar arterial path as for the reference device. Note that the forehead/ear-to-toe arterial path includes the carotid-to-femoral path used by the Sphygmo-Cor. For the above-mentioned reasons, only the variants where the proximal PPG sensor was placed on the head and the distal PPG sensor on the toe were taken into account (i.e. variants no. 1–6). Although our averaged results, in relation to the obtained numerical values, show an "excellent" accuracy level with the SphygmoCor they should be interpreted with caution. This is because the reference cfPWV is central and MPPT-based is central and muscular arteries PWV. For healthy young people, who usually have low PWV, the difference between central and peripheral PWV is small, whereas for older people (usually with a higher PWV) this difference will be greater. This can be seen in Fig. 15a), where SDavg represents the dispersion between the results. Therefore, the claim of excellence agreement is uncertain and cannot be accepted.

The applied averaging of the results allowed to determine the final proportional bias described by the equation (see Fig. 13b):

$$y = -0.32x + 2.56 \quad (1)$$

The Eq. (1) and Fig. 13 show that for small PWV there is a slight overestimation of the measured PWV with respect to cfPWV, while for large PWV there is an underestimation of the measured PWV with respect to cfPWV. This underestimation is disadvantageous because it occurs with the PWV range which that is more clinically relevant. The obtained Eq. (1) can be treated as a correction equation when calculating the PWV for each of the variants no. 1–6. Then the proportional bias will decrease while good compliance with cfPWV is main-

tained. Moreover, the slope (0.32) of the Eq. (1) can be taken as the quantitative contribution of peripheral stiffness of the legs to central arterial stiffness. However, in order to confirm this conclusion, studies on a larger group are necessary.

It is commonly known that PWV increases with age as a result of increasing vascular stiffness. The relationship between the msaPWV (after averaging variants no. 1–6) and age is shown in Fig. 14. Similar results were obtained also in the studies [62,85].
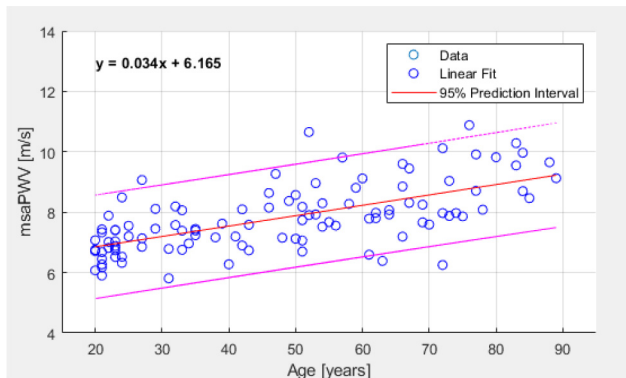
Fig. 14 – Relationship between the msaPWV and subject age.

The stiffness of the vessels may be unequal on the whole arterial tree. This can be manifested by larger differences between PWV measured at different sites. For our multi-site PWV results (variant no. 1–6) we calculated standard deviation (SDavg). The obtained SDavg results, depending on the age and cfPWV, are shown in Fig. 15.

The obtained plots confirm an increase in the spread between site-dependent PWV values with age (similar to the study [85]) or with a greater PWV value.

An important factor affecting the PWV result is also the measurement of the path length [71]. For example, if the pulse transit time is 125 ms, then for the path length measurement error of ±1 cm, the PWV measurement error is approx. ±0.1 m/s. However, for smaller PTT values (caused e.g. a larger PWV or shorter path length), the impact of the accuracy of the path length measurement on the PWV is even greater. For example, for PTT = 50 ms and path length error equal ±2 cm, the PWV measurement error is ±0.4 m/s. Thus, the shorter the path length or the smaller the expected PTT time, the more attention should be paid to the accuracy of the path length measurement. The error in measuring the path length is

influenced not only by the accuracy of the reading from the measuring instrument (e.g. a tape measure) but also by the body surface variability, which is particularly important for people with an increased BMI index.

Although 108 subjects participated in the study (see Table 1), the number of valid data pairs (n) is smaller for each of the variants (see Table 3). The main reason for this is that the quality of the PPG signals was not always good enough. This sometimes occurred for ears where the PPG signals obtained were usually of too low amplitude and low perfusion index. However, in each variant, the minimum sample size required by the recommendations [67] was met. In the photoplethysmography method, it should be taken into account that besides the measurement site, the PPG signal is influenced by external factors that may reduce its quality, e.g. ambient light, nail polish, sensor pressure, poor perfusion and motion artifacts [86,87]. Moreover, regardless of the measuring apparatus, PPG signals are characterized by a quasi-periodic course. The repeating "pulses" may naturally differ from one another. Additionally, skin temperature can significantly affect the value of the PPG signal. The above-mentioned factors are a limitation of the PWV measurement using photoplethysmography.

4.3.   *Comparison with other related works*

Comparison of the other devices validation results was shown in Table 4. For an appropriate comparison under similar measurement conditions, the studies with SphygmoCor as reference PWV measurement were shown. We used the newest version of SphygmoCor XCEL to validate our MPPT device. It is a version compatible with the previous one using the ECG signal [68,69].

In the presented related works, a different number of subjects were examined, in study [89] and [79] even more than in our case, however only our and for Aortic devices [80] study subjects respected requirements ARTERY recommendation [67]. The best agreement ("excellent" accuracy level according recommendation [65]) was only obtained for the piezoelectric mechanotransducer (for Aortic [78] and Complior [77] devices). It is worth noting, that this sensor is differ then the PPG. Some of the other studies ([46,89,92]) listed in Table 4 showed a high correlation coefficient (similar to MPPT) also, but the level of accuracy according to [65] was lower or not assessable.
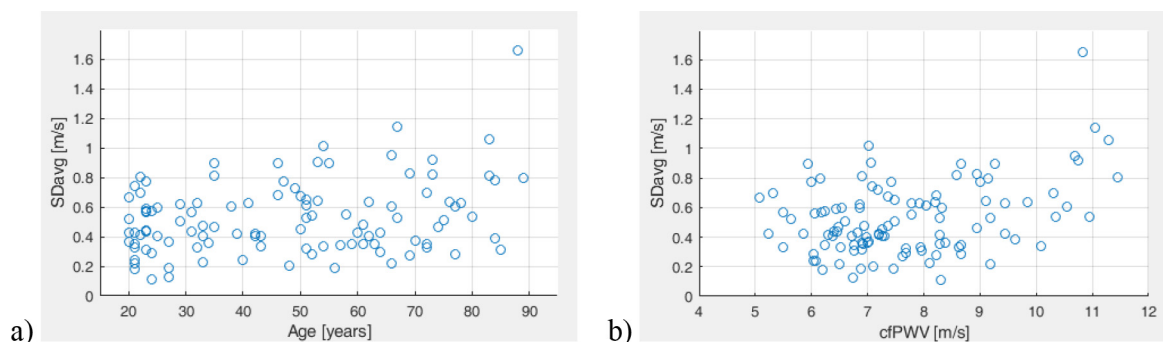
Fig. 15 – The relationship between the SDavg and subject age (a) and cfPWV (b).

Device	Meas. method used in device	Reference device	No of subjects	Age/Age ranges	Multi-site	Mean PWV difference	r	Accuracy level according [67]	Reference, year
MPPT (*our design*)	PPG	SphygmoCor (cuff based - XCEL)	108	48 ± 21 [20–91][a]	Yes	[0.11–0.95][b] ± [0.91–1.35][b]	[0.66–0.79][b]	acceptable (for all valid variants)	*this work*
Athos	MEMS force sensors	SphygmoCor (ECG-gated)	10	45 ± 14 [21–63]	No	0.2 ± 0.34	0.93	not assessable	[46], 2021
pOpmètre	PPG	SphygmoCor XCEL	24	5.9 ± 1.4 [4–8]	No	0.36 ± 0.96	NA	not assessable	[88], 2020
Mobil-O-Graph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	234	53 ± 10 [27–78]	No	NA	0.58	not assessable	[89], 2019
			83	50 ± 13 [20–80]	No	0.6 ± 1.3	0.39	acceptable	[78], 2012
pOpmètre	PPG	SphygmoCor (ECG-gated)	101	59 ± 15 NA	No	0.35 ± 0.8	0.76	acceptable	[90], 2017
			86	53 ± 20 NA	No	0.22 ± 2.46	0.43	poor	[55], 2015
Aortic	Piezoelectric mechanotransducer	SphygmoCor (ECG-gated)	85	46 ± NA [18–80][a]	No	0.02 ± 0.84	0.89	excellent	[80], 2015
Complior	Piezoelectric mechanotransducer	SphygmoCor (ECG-gated)	112	47 ± 15 [16–83]	No	0.0 ± 0.7	0.93	excellent	[79], 2014
Arteriograph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	63	48 ± 15 [20–69]	No	1.1 ± 2.05	0.54	not assessable	[16], 2014
			33	54 ± 15 [24–85]	No	1.3 ± 2.75	NA	not assessable	[91], 2011
Vicorder	Cuff-based oscillometry	SphygmoCor (ECG-gated)	30	65 ± 8 NA	No	0.01 ± 0.54	0.67	not assessable	[92], 2013
Mobil-O-Graph	Cuff-based oscillometry	SphygmoCor (ECG-gated)	83	50 ± 13 [20–80]	No	0.6 ± 1.3	0.39	acceptable	[78], 2012

NA – not available.
[a] – respected requirements for three age groups (<30, 30–60, >60) [67].
[b] – for detail see Table 3.

Due to the measurement method, which uses PPG signals, the most similar to the MPPT device is the pOpmètre [90]. However, pOpmètre only measures one PWV value based on two PPG sensors (finger and toe). Our MPPT device used seven PPG sensors located in many sites on the body (forehead, ears, fingers, toes). Thanks to this, we can obtain several PWV results simultaneously or we can use sensors only in selected sites, e.g. ear-toe. We can also perform averaging the results. However, it should be noted that there is some limitation on PPG sensor placement. The PPG signals received from the fingers, toes, and forehead are usually of appropriate amplitude and have a high perfusion index, while PPG signals obtained from the earlobes often have low and variable amplitude and low perfusion index. However, to obtain a better PPG signal from the ear, a different sensor design could be used, e.g. similar to the E1® Ear Sensor from Masimo which is placed securely in the cavum conchae (the deep hollow near the ear canal opening). Another limitation is that it is more difficult to put the sensor on the forehead than on the fingers, toes or ears. In addition, a reflectance sensor must be used on the forehead, which sometimes requires little tuning (i.e. repositioning the sensor).

As mentioned in the Introduction, many studies are related to new PWV measurement methods. However, validation of those new solutions did not always done with the SphygmoCor as reference device. In [33] for validation of video-based PPG system a CARDIOS Dyna-MAPA + device was used. However, the results do not include the PWV values, only the Pearson correlation coefficient with the aortic PTT (r = 0.77). Also, the study was conducted with 36 subjects. In study [47] the combined ICG and PCG with multichannel reflective PPG device at the sternum was used to detect the PTT and PWV calculation. The study was conducted with 29 subjects and the results were validated with the Complior as reference device. The following results were obtained: r = 0.88, md = 1.1 m/s, SD = 2.39 m/s for cfPWV as reference and r = 0.72, md = 0.5 m/s, SD = 2.43 m/s for crPWV as reference. In study [48] a custom device with 4 cuffs (2 on the arms and 2 on the legs) was validated with a VaSera VS-1500 device. Authors studied 113 subjects and correlation between the two devices was of 0.93. Validation result of PPG-based multi photodiode array (MPA) with Biopac-system based on a PPG and ECG signals was presented in [60]. The 30 subjects participated in the study and were divided into two groups: young and old. The following results were obtained: r = 0.94, md = 2.2 m/s, SD = 1.22 m/s for young and r = 0.83, md = 2.6 m/s, SD = 0.46 m/s for old group. Although standard deviation is not very large, the value of mean difference is high. With our MPPT device more successful results were achieved. In study [63] a custom module with PPG finger and ECG sensor was validated with the Mobil-O-Graph for assessment of PWV for 80 subjects. Good results have been achieved (r = 0.92, md = 0.3 m/s), which indicate (similar to our MPPT device) that the measurement of PWV obtained from the PPG is a reliable method.

4.4. Measurement site dependent PWV

PWV is slightly different in the central - elastic and peripheral - muscular arteries. In addition to the classic cfPWV, the use of other measuring points is also explored. One of the most interesting is baPWV, which measures the longer arterial pathway and is a combination index reflecting the stiffness of the central and peripheral arteries. An Asian meta-analysis found that people with high baPWV had a 2.5-fold higher risk of cardiovascular events, a 2.6-fold higher risk of cardiovascular mortality, and a 1.7-fold higher risk of all-cause mortality than patients with low baPWV [24]. In a study conducted among untreated hypertensive patients, the PWV measurement was related to the parameters of LV remodeling and diastolic function [25]. Interesting conclusions can be drawn from studies conducted among people with diabetes, in which multivariate regression analysis showed that the strongest influence on baPWV was the level of hs-CRP and the duration of diabetes. It should be emphasized that diabetes leads to the destruction of both central (aortic atherosclerosis) and peripheral (nephropathy, retinopathy) vessels, therefore in this group of patients it seems important to examine the condition of the arteries throughout their course [27]. With regard to our MPPT device, the measurement of variants no. 7 and 8 can be considered a measurement similar to the baPWV, with the emphasis that these include even a longer component of peripheral vessels than the classic baPWV. Interesting recent reports on the prognostic effect of baPWV - according to Japanese guidelines, recognized as a study for the detection of vascular damage [93], suggest that clinical assessment of the prognostic value will be crucial in various PWV measurements made with our MPPT in different patient groups.

Several new PWV measurement sites are being tested in the MPPT. It should be emphasized that, in contrast to the classic cfPWV and the baPWV with a more peripheral component, the more central hfPWV seems to be an interesting indicator. The current findings indicate that acute changes in cfPWV are strongly associated with hfPWV [30]. The hfPWV may be a simple alternative to cfPWV in the indication of cardiovascular risk in clinical and epidemiological settings. The hfPWV is estimated from the Cardio-Ankle Vascular Index device (VaSera-1500) by combining phonocardiogram with pulse signals detected by thigh cuffs and is noninvasive measurement. The hfPWV can be automatically measured in an operator-independent manner with cuff-based systems.

In understanding and researching the influence of the measurement site on the PWV result, very useful can be the [94] study. The researchers created a database of pulse waves (PW) simulated by a computer to span a range of CV conditions, representative of a sample of healthy adults. Much attention was also paid to the analysis of PW in the entire arterial tree, i.e. also for the central and muscular arteries. The simulating photoplethysmogram PWs was also performed and issues related to the value of PWV were also discussed. A non-linear relationship between aortic PWV and the arterial stiffness index was also shown. This is especially noticeable for higher aortic PWV values. With regard to our results, this confirms that cfPWV may differ from PWV measured in other sites and other arterial path.

4.5. Importance of PWV measurement

Studies on the assessment of arterial stiffness appear to be an important value in predicting cardiovascular risk. The

attempt to compare the estimated cardiovascular risk assessed by PWV with other risk scales, e.g. the recognized SCORE scale, is noteworthy. For example, in the Polish population the calculated cfPWV cut-off point of 11.7 m/s allowed us to classify participants of the study as a high CVD risk group with optimal sensitivity and specificity [95]. When analyzing the parameters of arterial stiffness, one should critically look at the repeatability and reproducibility of the results and the dependence of their possible changes on the measured blood pressure [96]. Despite the studies discussed in the course showing an association of increased PWV with diseases that increase cardiovascular risk, single indicators should be critically assessed and their optimization should be sought - often by creating complex models. An example of the above is in the meta-analysis among patients with familiar hypercholesterolemia (FH) who do not show a significantly altered PWV compared to the control group. Meanwhile, a sub-analysis of studies in which there was intima-media thickness (IMT) is increased in FH patients when compared with controls [10]. The correlations between the increased PWV value and the severity of atherosclerosis assessed using the IMT value were also examined [97]. As well, arterial stiffness was compared parameters in the stratification of patients with peripheral arterial disease, where decreased ankle-brachial index is associated with an increase in cfPWV i decreased subendocardial viability ratio, indicating an important connection between the peripheral arteries and the coronary circulation. Pulse wave propagation is different with clogging peripheral vessels causing the pulse to return earlier wave towards the heart and affect its workload and perfusion [98]. Ambilateral peripheral PWA and PWV measurements are potential new clinical applications, beside duplex sonography, also to assess and monitor functions in non-physiologically altered vessels such as RCF radiocephalic fistula (RCF) [99].

In addition to PWV measurements performed with the use of dedicated devices, attempts are also made to measure it using magnetic resonance [18,100,101], Doppler echocardiography [30,85], or speckle tracking [20]. PWV measurements carried out with classical radiological techniques are already assessed in specific groups of patients. Reference values of carotid PWV for ultrafast ultrasound imaging stratified by sex and age were determined for the first time. Age, blood pressure (BP), and BMI were the dominant determinants of carotid PWV on ultrafast, ultrasound imaging, which should be considered in clinical practice [19]. Measuring carotid PWV using a single slice oblique-sagittal phase contrast MRI is a potential utility in assessment of carotid stiffness and evaluation of cerebroarterial aging and age-related neurovascular disorders [18].

Besides assessment of arterial stiffness PWV can also be used for BP estimation. In [102], an evaluation of the analytical model showing the relationship between BP and PWV was presented. The utility of the PWV measurement for continuous, cuffless, and noninvasive BP monitoring has been demonstrated. In [57] was shown that carotid local PWV and brachial BP were kind correlated (r = 0.82 for diastolic BP, r = 0.69 for systolic BP, r = 0.83 for mean arterial pressure). In the clinical application review [36] the authors indicate, that in recent years there have been tremendous technological advances in regional PWV-based approaches for cuffless evaluation of arterial BP parameters. In turn, interesting results are shown in study [103], where the PAT (determined from the PPG and ECG sensor) time was used for the BP estimation. The proposed model, based on deep learning approach, provided a highly accurate prediction of the systolic (mean difference 2.398 ± 5.623 mmHg) and diastolic BP (mean difference −2.497 ± 3.785 mmHg) compared to arterial line measurements. Note that, the PAT time is also related to the PTT used to calculate the PWV, therefore the PWV as measured by PPG technique can also be useful for continuous cuffless BP imputation.

In the future, apart from classic PWV measurements, other indicators are also sought that can predict an increase in vessel stiffness - such as molecular or genetic tests. Currently there are new studies of markers such as NLR with positive correlation with PWV and increased arterial stiffness [31]. The NLR is used as a marker of subclinical inflammation. It is calculated by dividing the number of neutrophils by number of lymphocytes, usually from peripheral blood sample, but sometimes also from cells that infiltrate tissue, such as tumor. Genome-wide association analysis of PWV traits provide new insights into the causal relationship between arterial stiffness and blood pressure [104]. In performed research it was possible to identify a new locus for arterial stiffness and successfully replicate an earlier proposed locus. PWV shares common genetic architecture with BP and coronary artery disease. BP causally affects PWV. Larger studies are required to further unravel the genetics determinants and effects of PWV [104].

The presented research shows that it is important to create new devices that measure the pulse wave velocity in a multifactorial and multifaceted way.

5. Conclusions

A novel photoplethysmographic device (named MPPT) providing measurement of multi-site pulse wave velocity has been presented. This device has been validated with carotid-femoral PWV using the SphygmoCor XCEL System. The reference cfPWV measurements were performed simultaneously with the MPPT device, which resulted in greater reliability of the validation study. In our study, each variant of multi-site PWV, in relation to the obtained numerical values, strongly correlates with cfPWV („acceptable" accuracy level according to the guide in [67]). However, it should be noted that, the measured MPPT-based PWV concerns the central and muscular part of the arterial tree while the cfPWV is only for the central one. For this reason, the obtained validation results should be interpreted with caution. Our analysis of the results showed that the impact of the contribution of the muscular arteries to the measured PWV can be approximately 30%. However, in order to confirm this finding, further studies are necessary.

The best results were obtained when the proximal PPG sensor was placed on the head (ear or forehead) and the distal PPG sensor on the toe. Placing the PPG sensors on the finger and toe is easier than on the ear or forehead, and usually provides more stable signals, but at the same time, lower correlation with reference cfPWV.

The use of a tonometer to PWV assessment requires a lot of operator experience. This is especially important for the new version of the SphygmoCor (XCEL version) where the correct signal from the carotid artery must be maintained during the inflation of the femoral cuff and next during the final measurement stage. The entire measuring process takes several dozen seconds. At this time, in some cases, there occurred carotid "hiding" and the signal was too small to complete the measurement. PWV measuring by photoplethysmographic method is easier, rapid and convenient for the patient. Moreover, PPG sensors can be placed in many sites at the same time, which provides greater freedom of their configuration and increases diagnostic possibilities. However, not all of these sensors need to be used at the same time. There must be at least two, but a greater number of sensors enables the simultaneous measurement of many PWV channels and averages the results, but it is not obligatory. Simultaneous measurement in the multi-site mode allows for the most reliable comparison of results obtained from different sites.

Photoplethysmography is a cheap, easy to use, and alternative method of pulse wave velocity measurement. Multi-site PWV measurements create new possibilities for the diagnostics of cardiovascular diseases.

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CRediT authorship contribution statement

Tadeusz Sondej: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition. **Iwona Jannasz:** Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Krzysztof Sieczkowski:** Conceptualization, Software, Investigation, Resources, Data curation. **Andrzej Dobrowolski:** Conceptualization, Supervision, Project administration, Funding acquisition. **Karolina Obiała:** Data curation. **Tomasz Targowski:** Resources, Supervision. **Robert Olszewski:** Conceptualization, Investigation, Resources, Supervision.

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