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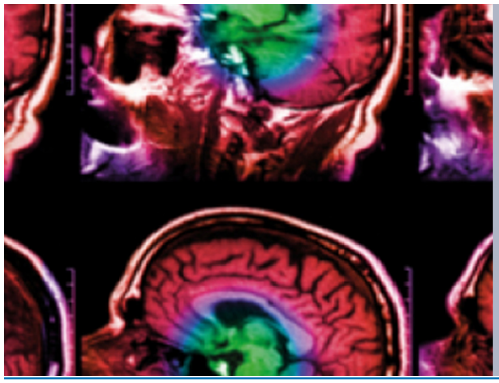

Biomedical Physics & Engineering Express

PAPER

Measuring pulse wave velocity with a novel, simple sensor on the finger tip: a feasibility study in healthy volunteers

Marit H N van Velzen[1,2], Sjoerd P Niehof[1], Egbert G Mik[1] and Arjo J Loeve[3]

[1] Department of Anesthesiology, Laboratory of Experimental Anesthesiology, Erasmus MC University Medical Center Rotterdam, the Netherlands
[2] Department of Medical Information Communication Technology MICT, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands
[3] Department of BioMechanical Engineering, Faculty 3mE, Delft University of Technology, Delft, the Netherlands

E-mail: m.v.velzen@jbz.nl

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Abstract

Objective: The speed of pressure pulses traveling through the blood, the pulse wave velocity (PWV), is a metric that provides substantial information about the passive and active elasticity of the blood vessels. Therefore, PWV is a valuable parameter in the diagnosis of cardiovascular and vessel-related neurological diseases. The purpose of this study was to investigate whether a novel, simple, easy-to-use, photoplethysmography-based Multi Photodiode Array (MPA) provides PWV measurements that agree with measurements done with more complicated and harder-to-use systems currently used in clinical practice. *Methods:* An often-used vascular perturbation that changes the conduit artery vasomotor tone during reactive hyperemia was imposed on thirty healthy volunteers. The MPA was used alongside and its results compared to those of a commonly used measurement device, the Biopac-system, during flow-mediated dilation (FMD). This way it was investigated if measurements with these systems, measuring over two different, but partly overlapping vessel trajectories agree. *Results:* The baseline absolute PWV values were significantly lower for the MPA as compared to the Biopac-system. Additionally, Bland-Altman plots and Pearson's correlation tests suggested good agreement between the two PWV measurement techniques during the FMD. *Conclusion:* Measuring PWV with the MPA in clinical practice is feasible and provides reliable data. *Significance:* The MPA may substantially simplify PWV measurements and may enable long-term PWV monitoring as long as one is aware of the relation between PWV and the vascular trajectory over which it is measured.

1. Introduction

Globally, the number one cause of death is cardiovascular disease (CVD). Smoking, unhealthy diet, physical inactivity and excessive use of alcohol are the most important behavioural risk factors for CVDs. Consequently, individuals may develop atherosclerosis, diabetes, heart failure or hypertension, most of which being related to a change in arterial stiffness. Arterial stiffness is deducted from the relationship between a change in blood pressure inside the artery and the successive change of arterial expansion [1]. Therefore, arterial stiffness, or its inverse the arterial compliance, is a reliable prognostic indicator of cardiovascular morbidity and mortality in the adult population [2–4]. When arterial stiffness increases, the speed with which pressure pulse waves (PWs) travel through the vessels, the pulse wave velocity (PWV) [5, 6], increases. Blood vessels should have good arterial stiffness, because the elastic walls of the arteries attenuate the systolic pressure wave of each heartbeat. During the diastole, the potential energy stored in the elastic vessel walls is used to continue to propel the blood between successive heartbeats [1]. The pulse wave velocity is widely considered to be one of the major standards for non-invasive measurement of arterial stiffness and the PWV over the carotid-femoral trajectory has been shown to provide particular value for the assessment of risk of cardiovascular events [7]. The PWV is inversely related to arterial distensiblility [8–10] and directly related to the incremental elastic modulus $E_{inc,vessel}$ and vessel wall thickness h_{vessel}, and inversely related to the vessel radius

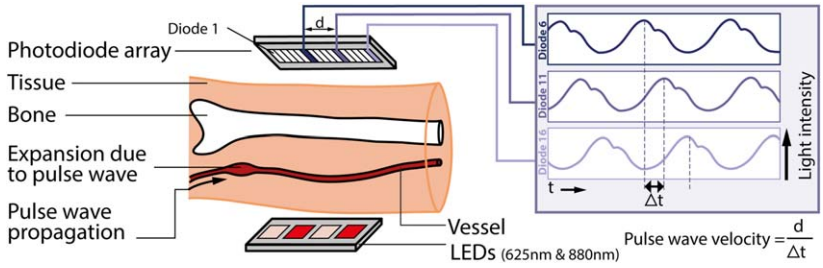

Figure 1. Schematic overview of the multi photodiode array (MPA) and illustration of the calculation of the pulse wave velocity.

r_{vessel} by the Moens-Korteweg equation (with ρ_{blood} the density of blood) [11]:

$$PWV = \sqrt{\frac{E_{inc,vessel} \cdot h_{vessel}}{2r_{vessel} \cdot \rho_{blood}}} \quad (1)$$

The PWV is generally measured as an average speed of a PW between two locations on the body. Note that PWV is not the speed of blood, but of the pressure pulse traveling through the moving blood (comparable to a sound wave). The PWV can be measured both invasively and non-invasively and is highly reproducible [12]. However, available PWV measurement systems require quite advanced devices and highly trained operators and have several disadvantages in terms of usability. This was also described [13], where several non invasive techniques for measuring PWV were mentioned, originating from [14–16]:

- the SphygmoCor system (AtCor Medical, West Ryde, Australia), measuring PWV between carotid and thigh, using a tonometry sensor on the neck and a pressure cuff on the thigh,
- the Arteriograph system (Tensiomed, Budapest, Hungary), continuously using a pressure cuff on the upper arm,
- and the Complior system (Alam Medical, Saint Quentin Fallavier, France), using piezo-electronic pressure transducers placed at the neck and at the groin.

The authors previously developed a device, further called the Multi Photodiode Array (MPA), that enables peripheral, non-invasive PWV measurements along a trajectory of 12.0 mm, without having the drawbacks of the currently available alternatives [13]. The MPA has been designed and validated to enable comfortable measurements with a single, simple device without requiring highly trained operators. The MPA is based on photoplethysmography (PPG): a widely used non-invasive optical technique for measuring volumetric expansion and contraction of vessels (figure 1) [17] and was shown to measure the PWVs with a maximum uncertainty of 3% for velocities up to 45 m s^{-1} [13]. This uncertainty was determined including all variations, tolerances and clearances in both the test setup and the MPA itself. Although the length of the trajectory over which the PWV is measured is more accurately known for the MPA than for any of the other available techniques, even small absolute errors in determining this rather short distance may cause rather large PWV measurement errors, as these errors are large in relative sense and translate linearly to the calculated PWV. However, it is expected that this still outperforms the uncertainty in lengths of the trajectories over which other systems measure the PWV, as these are estimated by approximating the curved vasculature inside the body with a straight line between the two measurement locations.

The maximum volumetric expansion at any point along a vessel occurs when the peak of a PW passes that point. Therefore, the PWV can be calculated using the time differences between the detection of the PW peaks at successive points along the vessel spaced a known distance apart. The technical functioning and measurement accuracy of the MPA have previously been validated [13]. However, because the MPA is utilized to measure PWV locally on a finger, it has yet to be investigated to what extent these local PWVs correspond with PWVs measured in conventional ways.

The goal of this study was to investigate whether the MPA results correspond with PWV measurements obtained in clinical practice. To that purpose, the MPA was used synchronously with and its results compared to those of a commonly used measurement device, the Biopac-system (Biopac Systems, Inc. Goleta, USA). The Biopac-system measures PWV using photoplethysmography and ECG and measures PWV over the trajectory of the heart-fingertip vasculature. So both systems may provide similar information of vascular condition through measurement of PWV variation, but at different absolute values, as the trajectories over which they measure PWV partly overlap. The MPA and the Biopac-system were compared during a well-known inducible physiological effect to investigate to what extent measurements with these systems and over those two different vessel trajectories agree.

2. Materials and methods

To investigate whether the MPA can measure physiological effects of the human body, an often used vascular perturbation that changes the conduit artery vasomotor tone during reactive hyperemia [18, 19] was imposed on healthy volunteers. Reactive hyperemia can be measured using flow mediated dilation (FMD) [20], a technique that reflects the bioavailability of nitric oxide (NO) [21]. Characterized by reduced NO bioavailability, the endothelial dysfunction contributes to the progression of cardiovascular diseases, such as hypertension, diabetes, heart failure or atherosclerosis [22, 23]. The observed decline in PWV during vasodilation after ischemia might be used as a marker of arterial distensiblility and endothelial function [18, 19]. A quantitative change of the dilation of the artery can be measured with ultrasound. However, disadvantages of this technique are limited availability and requirement of a skilled operator. Moreover, the diameter and velocity are commonly measured with high-resolution B-mode and duplex ultrasound with the same transducer, which have competing requirements for an optimal measurement [24]. Alternatively, PWV measured with MPA could be easily measured continuously and without special training.

2.1. Study population

This study was approved by the medical ethics committee of Erasmus University Medical Center Rotterdam, the Netherlands (MEC-2017-453). A total of thirty healthy volunteers were included and then divided into two groups. The participants were between 19–63 years old without any known history of atherosclerosis associated diseases (such as diabetes mellitus, hypertension, coronary artery disease, stroke, renal disorder, arrhythmia) or injuries at the upper limbs. The healthy volunteers were included in this study after obtaining written informed consent from the subject. To determine the effect of age on the PWV in two relatively extreme conditions, the study population was divided into 2 groups: a young group of participants aged between 18 and 35 years ($n = 20$) and an older group aged above 55 years ($n = 10$).

2.2. Protocol

The transit time of a PW traveling from within the heart to easily accessible locations, such as the extremities or the neck, consists of 2 components: the PW propagation-time from the heart through the artery to the PW measurement location, and the isometric contraction time of the heart (pre-ejection period, PEP). The PEP is known to vary with cardiac preload and heart rate [25–27]. Therefore, all measurements were conducted in a quiet room under tranquil conditions at a room temperature of 22.4 °C (SD 0.5 °C). To further minimize any influences of a varying PEP or cardiac output during the measurement, the subjects were instructed not to talk or move during the measurement. Before the start of the measurement the subject's blood pressure and arm length (from the left middle finger to the sternoclavicular joint) was measured. The subjects were sitting on a chair with both hands resting on a pillow. To attain a cardiovascular steady-state before starting the measurement, the subjects had rested for at least 10 min in an upright sitting position.

A sphygmomanometer cuff was placed on the left upper arm for the FMD.

PWV was simultaneously measured using two systems: the new MPA and the Biopac-system. The Biopac-system consisted of a measurement device and analysis software. The measurement device contained a PPG-sensor (TSD200 with PPG100C amplifier, Biopac Systems, Inc, Goleta, USA), placed on the left middle finger, and three external ECG-leads (ECG100C amplifier, Biopac Systems, Inc, Goleta, USA) (see figure 2). The three ECG-leads were placed on the subject's both wrists and left hip. The PPG- and ECG-signals were simultaneously converted to digital signals using AcqKnowledge version 3.7.3 software (Biopac Systems, Inc, Goleta, USA), at a sampling frequency of 2 kHz. The MPA-system contained the MPA-sensor, consisting of an array of 4 red and infrared LEDs and an array of 16 photodiodes of which 4 were active. The left index finger was placed on the MPA using the setup shown in figure 2. The MPA-system read out 4 photodiodes (numbers 6, 8, 10, and 12 in the array, all spaced 1.6 mm apart) and converted the data to digital signals through a NI-USB 6229 Multifunction Data Acquisition system and LabVIEW 2010 software (both: National Instruments, Austin, TX, USA).

Before the start of the FMD the baseline PWV at rest was measured for 1 min. Then reactive hyperaemia was induced by blocking the arterial blood supply with the sphygmomanometer cuff around the upper arm. The cuff was kept inflated for 5 min to approximately 50 mmHg above systolic blood pressure. This arterial occlusion activates the endothelium-dependent vasorelaxation, whereas after releasing the pressure in the cuff ischemia and shear stress on the endothelial cells of the blood vessel is induced. After 5 min, the cuff was rapidly deflated to 0 mmHg and the reactive hyperaemia was measured for 5 min. Summarizing, the PWV was recorded during a 1 min baseline measurement, for 5 min during occlusion and 5 min after occlusion, see figure 3.

2.3. Pulse wave analysis

After obtaining the data, Matlab R2010a (The MathWorks, Inc., Matick, MA, USA) was used to analyse the data and to calculate the PWV from the signals received by the Biopac-system and MPA. All PPG-signals were filtered with a fourth-order low-pass Butterworth filter with a cut-off frequency of 9 Hz.

The PWV_{Biopac} was determined by dividing the distance between the PPG-sensor on the left middle

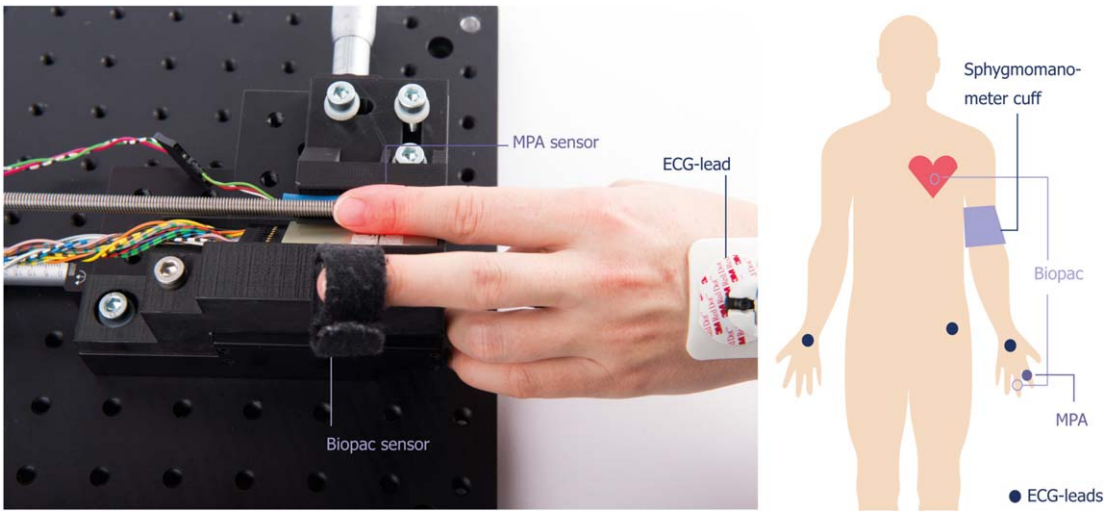

Figure 2. Photograph and schematic view of placement of the both measurement systems and the sphygmomanometer cuff. MPA = Multi Photodiode Array; ECG = Electrocardiogram.

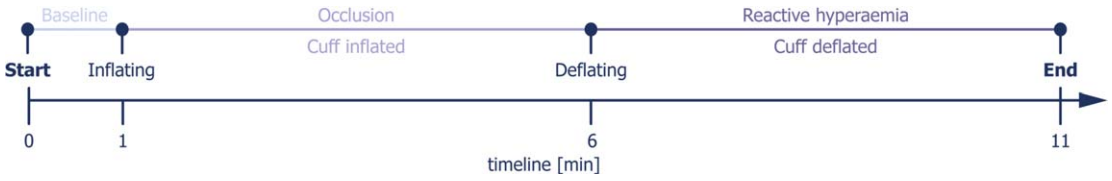

Figure 3. Schematic representation of the measurement protocol used in the study comparing the MPA and the Biopac-system.

finger and the sternoclavicular joint (D) by the calculated time-difference between the time instance of the R-peak of the ECG ($t_{ECG\ R\text{-}peak}(n)$) and the foot of the PW measured at the left index finger tip ($t_{PPG\ foot}(n)$):

$$PWV_{Biopac}(n) = \frac{D}{t_{PPG_{foot}}(n) - t_{ECG_{R-peak}}(n)} \quad (2)$$

where n is the sequence number of the heartbeats (figure 4). The feet of the PWs (PPG_{foot}) were defined as the maximum of the second derivative of each PW [28–32]. The R-peaks in the ECG were found using the off-the-shelf Matlab function 'R-peakdetect' [33].

The PWV_{MPA} was determined for each pair of photodiodes i and j by dividing the distance between the photodiodes by the time-difference between the arrival of the PPG signals' peaks at the locations of these successive photodiodes:

$$PWV_{MPA,i-j}(n) = \frac{D_{i-j}}{t_i(n) - t_j(n)} \quad (3)$$

where n is the sequence number of the heartbeats (figure 4), $D_{i\text{-}j}$ is the distance between two photodiodes and $t_i(n)$ and $t_j(n)$ are the times at which the foot of the PWs of heartbeat n arrived at those respective photodiodes. This was done for each combination of any two of the used photodiodes (photodiodes pairs 6–8, 8–10, 10–12, 6–10, 8–12, 6–12).

The utilized PPG-sensors were quite sensitive for motion and positioning artefacts, which sometimes distorted the shapes of the PWs in a way that they were rendered unsuitable for further analysis. Therefore, a custom-made Matlab algorithm, called '7Step PW-Filter', was implemented in the data analysis to filter out any PWs that strongly deviated in shape from a suitable PW [34]. Occasionally the PWV data showed inexplicably and unrealistically high or low PWV-values (e.g. $>\pm 100\ m\ s^{-1}$). These extreme outliers were removed using the Matlab function 'Hampel'. The final $PWV_{MPA}(n)$ was calculated as the median PWV of all $PWV_{MPA,i\text{-}j}$ over all combinations of any pair of photodiodes used.

The median PWV after occlusion was calculated for each 30 s interval ($\tilde{P}WV_{30s,i}$) starting from the first PW after occlusion. The FMD for each 30 s interval ($FMD_{30s,i}$) was expressed as the relative change in PWV following hyperemia, expressed as a percentage of the median baseline PWV ($\tilde{P}WV_{baseline}$):

$$FMD_{30s,i} = \frac{\tilde{P}WV_{30s,i}}{\tilde{P}WV_{baseline}} \cdot 100\% \quad (4)$$

These $\tilde{P}WV_{30s,i}$ were calculated for the MPA as well for the Biopac-system. Because in a few subjects the values seemed to be heavily distorted (suspected to be caused by hand motion or strong coughing during the measurements), strong outliers (mean ±3 SD) were removed.

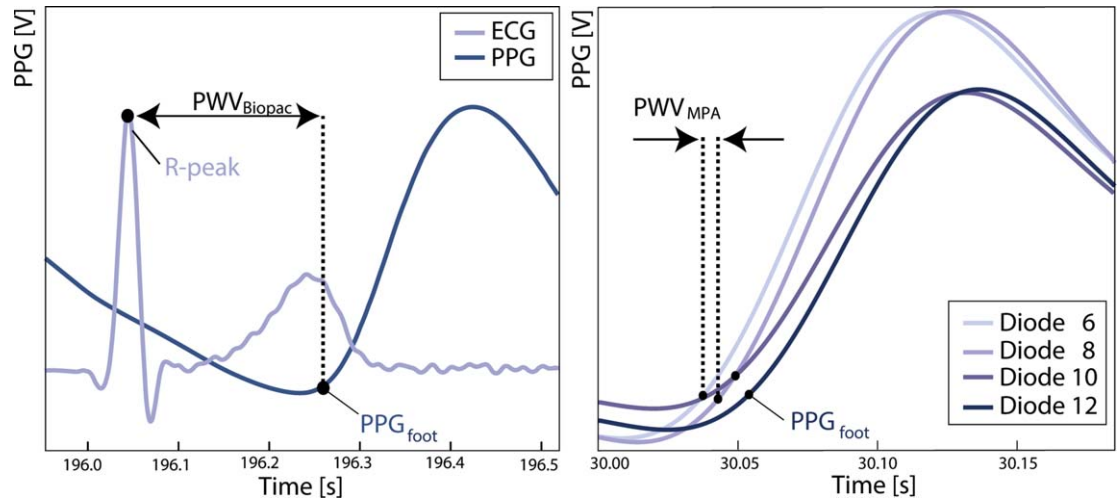

Figure 4. Exemplary signals for both the MPA and the Biopac, and the time delays used to calculate the PWV. PPGfoot is the onset of the upward slope of the next pulse and is defined as the maximum of the second derivative of that PW. PPG = Photoplethysmography; MPA = Multi Photodiode Array; ECG = Electrocardiogram.

2.4. Statistical analysis

The mean PWV ± standard deviations (SD) for the baseline were calculated. A Shapiro-Wilk test was used to check if the data were normally distributed. An independent samples t-test was used to assess any differences between the heart rates of the two age groups during the baseline measurements. A two-way ANOVA was used to test for any effects of the age groups and of the measurement system used on the PWV during baseline. Correlation between the two measurement systems during reactive hyperaemia was analysed for each age group using a Pearson correlation test. A paired samples t-test was used to assess the differences between the PWV_{Biopac} and PWV_{MPA} for each 30 s post-occlusion interval. Bland-Altman plots were used to assess the agreement between the PWV_{Biopac} and PWV_{MPA} for the baseline and for each 30 s post-occlusion interval. The limits of agreement were set at +/−1.96 SD. Hence, agreement was deemed good when the differences between PWV_{Biopac} and PWV_{MPA} consistently were within a 95% bandwidth around their mean difference. The analysis was performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA) and Matlab. The significance level adopted was $p < 0.05$.

3. Results

Thirty subjects (13 male, 17 female) were included in this study. Table 1 presents the characteristic of the study population. The data of one male (Old group) and one female subject (Young group) were excluded from the analysis because there was too much noise in the signals to obtain any usable PWs. Another male (Old group) had strong arrhythmia and was therefore excluded. For another female (Old group) the protocol appeared to not have been properly followed with regard to the positioning of the finger and was therefore excluded. Outlier removal removed most of the data of these subjects with irregularities due to coughing or moving and none of the subjects in whom no irregularities were observed, which further confirmed that these were in fact exceptions.

Table 1. Characteristics of the study population. Values are means ±SD or number (%) of participants.

Variable	Young group (n = 20)	Old group (n = 10)
Gender (male), no.(%)	8 (40)	5 (50)
Age [years]	27 ± 4	58 ± 3
Weight [kg]	77 ± 18	77 ± 15
Height [m]	1.72 ± 0.10	1.71 ± 0.05
Body mass index [kg m^{-2}]	25.9 ± 5.6	26.1 ± 4.0
Blood pressure [mmHg]		
Systolic	132 ± 12	136 ± 17
Diastolic	87 ± 9	82 ± 11
Heart rate [bpm]	77 ± 15	69 ± 9
Smoker (yes), no. (%)	1 (5)	0 (0)
Distance from sternoclavicular to fingertip [cm]	85 ± 5	87 ± 5

Table 2 presents the mean PWVs and heart rates for the baseline. For the heart rate, there was no significant difference between the two groups ($t(24) = 1.276$, $p = 0.214$). For the baseline measurements there was a significant effect of the measurement system used ($F(1,48) = 374.05$, $p = 0.000$) on the PWV measured, there was no significant effect of the age group ($F(1,48) = 3.25$, $p = 0.078$), and there was no significant interaction ($F(1,48) = 1.77$, $p = 0.190$).

The Bland-Altman plots in figure 5 show that almost all data falls within the set limits of agreement. The absolute PWV values were significantly higher when measured with the Biopac-system than with the MPA, as indicated by the bias lines.

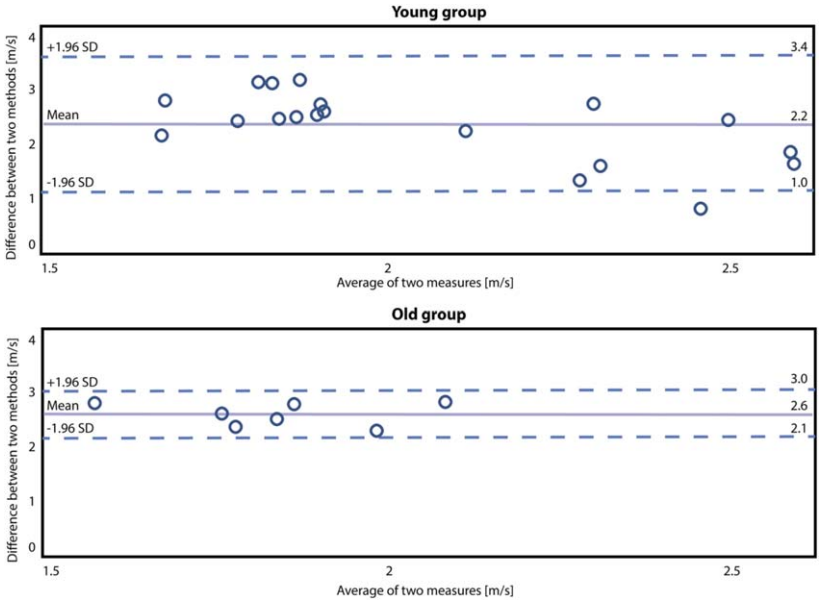

Figure 5. Bland-Atman plots of the PWV_{Biopac} and PWV_{MPA} during baseline. The dotted lines represent the 95% limits of agreement and the solid lines represent the mean difference (bias) between PWV_{Biopac} and PWV_{MPA}.

Table 2. The PWV (Pulse Wave Velocity) values measured during baseline using the Biopac-system and MPA, and heart rate during the baseline measurements. MPA = Multi Photodiode Array.

	Young group [mean ± SD]	Old group [mean ± SD]
PWV_{biopac} Mean [m s^{-1}]	3.2 ± 0.3	3.1 ± 0.2
PWV_{MPA} Mean [m s^{-1}]	0.9 ± 0.6	0.6 ± 0.2
Heart rate Mean [bpm]	75 ± 10	70 ± 9

The results of the paired samples t-test done to assess the differences between the FMD_{Biopac} and FMD_{MPA} for each 30 s post-occlusion interval are given in table 3. Figure 6 shows the median PWV for the baseline and for each 30 s post-occlusion interval for both groups and both systems.

There were no significant differences between the relative PWV values measured by the two measurement systems following reactive hyperaemia after occlusion, except for the time-interval 30–60 s in the Young group ($p = 0.042$). The Pearson correlations between the Biopac and MPA were 0.940 ($p < 0.0001$) for the Young group and 0.834 ($p = 0.0014$) for the Old group. The Bland-Altman plots showed to be consistently between the 95% limits of agreement, suggesting that the two PWV measurement techniques agreed within the desired limits (figures 5 and 7).

4. Discussion

This study compared PWV values measured in healthy volunteers over a 4.8 mm short peripheral vascular trajectory in the left index fingertip using the MPA system with PWV values measured between the R-peak of the ECG and the arrival of the PW in the left middle fingertip using the Biopac-system during reactive hyperaemia. The PWV_{MPA} and PWV_{Biopac} measurements showed good agreement, as shown by the Bland-Altman plots in figure 5 and the Pearson's correlation tests, but also a systematic difference. The PWV_{MPA} was consistently and considerably lower than PWV_{Biopac}. Looking at equation (1) this difference may be explained by vessels being more compliant and thinner, yet also being smaller in diameter, closer to the periphery. This agrees with the results of van Velzen *et al* showing higher PWVs for the trajectory of the carotid-radial artery than for the heart-fingertip trajectory [35]. This confirmed that when the PWV is measured towards the periphery, the PWV decreases.

When eyeballing the results in figure 6, it may seem as if there is a rather large difference between the relative change of PWV measured with the Biopac system and that measured with the MPA. Yet, these seemingly present differences were not statistically significant. This may have been a consequence of the standard deviations in the PWV_{MPA} results being relative large compared to those for the PWV_{Biopac}. The accuracy of the MPA has previously been shown to be within 3% [36]. The accuracy of the Biopac is unknown, but it does seem to have a higher precision than the MPA. The distance between the photodiodes on the MPA is 12 mm +/−0.25 mm between the first

Table 3. FMD per time interval for the MPA and the Biopac-system for both age groups. Values are given as mean ± SD. FMD = flow mediated dilation; MPA = Multi Photodiode Array.

	FMD [%] Young group			FMD [%] Old group		
Time interval [s]	Biopac-system	MPA	Paired samples t-test	Biopac-system	MPA	Paired samples t-test
0–30	94.7 ± 2.9	78.1 ± 31.4	t(15) = 2.071 p = 0.056	96.8 ± 2.1	91.6 ± 32.3	t(6) = 0.418 p = 0.691
30–60	95.1 ± 3.0	81.4 ± 25.4	t(16) = 2.214 **p = 0.042**	96.9 ± 1.5	90.7 ± 28.2	t(6) = 0.566 p = 0592
60–90	96.0 ± 2.8	85.4 ± 22.5	t(16) = 1.921 p = 0.073	98.0 ± 2.2	87.9 ± 19.2	t(5) = 1.192 p = 0.287
90–120	96.5 ± 2.7	86.8 ± 21.2	t(15) = 1.737 p = 0.103	98.0 ± 2.2	90.6 ± 15.2	t(5) = 1.087 p = 0.327
120–150	97.0 ± 2.6	88.5 ± 21.7	t(15) = 1.504 p = 0.153	97.7 ± 2.3	91.6 ± 16.0	t(5) = 0.939 p = 0.391
150–180	98.6 ± 2.7	89.9 ± 16.5	t(13) = 2.131 p = 0.0.53	98.0 ± 2.3	91.8 ± 18.5	t(5) = 0.792 p = 0.464
180–210	99.1 ± 1.8	90.1 ± 20.4	t(13) = 1.592 p = 0.135	98.4 ± 2.1	93.7 ± 18.8	t(5) = 0.642 p = 0.549
210–240	99.0 ± 2.7	93.4 ± 19.0	t(14) = 1.207 p = 0.247	99.1 ± 1.8	98.3 ± 18.5	t(5) = 0.131 p = 0.901
240–270	99.5 ± 3.0	98.1 ± 24.3	t(14) = 0.795 p = 0.795	99.2 ± 2.0	98.6 ± 20.2	t(5) = 0.105 p = 0.920
270–300	100.2 ± 3.0	95.3 ± 22.6	t(13) = 0.750 p = 0.466	99.8 ± 3.4	97.2 ± 17.2	t(5) = 0.457 p = 0.667

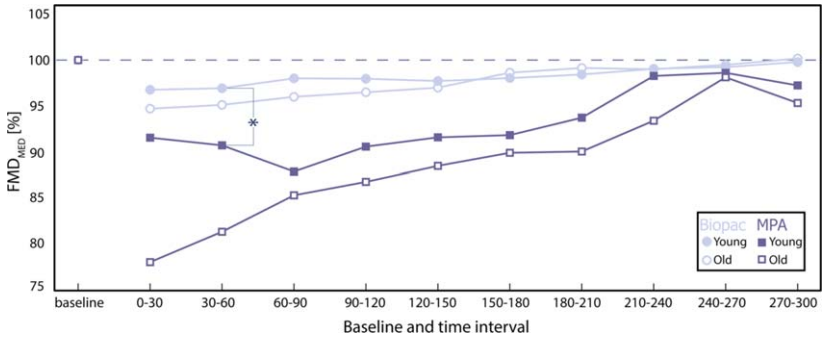

Figure 6. Relative PWV per post-occlusion interval after FMD. FMD_{MED} is the median PWV as percentage of the baseline PWV. Changes in PWV following hyperaemia were averaged per 30 s interval for each group, starting from the first PW after cuff release. *) $p < 0.05$ for difference between both systems.

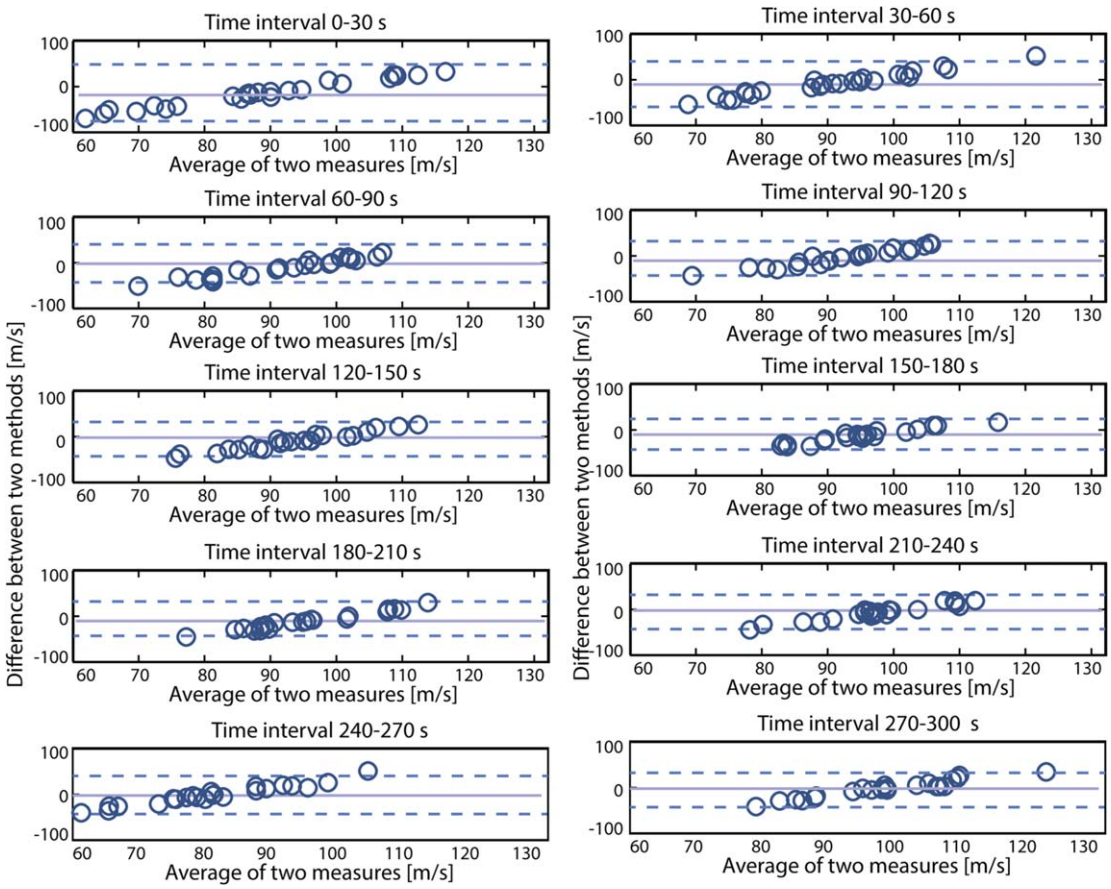

Figure 7. Bland-Atman plots for the agreement between the PWV_{Biopac} and PWV_{MPA}. PA per post-occlusion interval. The dotted lines represent the 95% limits of agreement and the solid lines represent the mean difference (bias) between PWV_{Biopac} and PWV_{MPA}.

and last diode, suggesting a tolerance of about 0.02 mm on the distance of 0.8 mm between successive diodes. This is unlikely to contribute more than about 0.25% to the measurement accuracy of the MPA. Furthermore, because the distance between diodes cannot vary during the measurements, sensor variations are not expected to contribute to the stochastic variation in the PWV either. Therefore, this larger variability in PWV when using the MPA may have several causes, but the most likely cause (based on observations during the measurements) was that the MPA readings were quite sensitive to positioning and pressure of the finger on the sensor. Because this sensitivity was known in advance, all fingers were placed at the same spot on the sensor and kept in place using an elastic textile band with a gentle, standardized pre-tension. However, due to subject motion and slight variations in placement, variations may still occur. Therefore, the MPA sensor should be further developed into a user friendly device that facilitates standardized and stable placement of the MPA on the finger.

The FMD results in this study agreed with those of Cauwenberghs *et al* when applying 5 min occlusions: a change in PWV with a maximum of −14.6% was found for the first 30 s post-occlusion time interval [37]. In that study, the PWV was measured over the brachial-radial trajectory by use of two oscillometric cuffs. As the Biopac-system measured the PWV over the heart-fingertip trajectory and the MPA over a mere 4.8 mm in the fingertip, it is fitting that the Cauwenberghs *et al* result of 14.6% lies between the corresponding values for the Biopac-system (−5.3%) and for the MPA (−21.9%). When using the Biopac-system, the measured PWV includes the PEP. The PEP is known to vary during position changes. PEP variations caused by subject movement or stress were avoided as good as possible during the current study. Still, Kortekaas *et al* showed a variability of the PEP in healthy volunteers at rest of 58.5 ± 13.0 ms [26]. Within the distances travelled by the PWs in the current study, these PEP durations could account for no more than 1 m s^{-1} of the PWV_{biopac}. Consequently, PEP variations are unlikely to explain any variations in this study.

Considering the relatively small sample size, the findings should be validated in a larger cohort of randomly recruited subjects. Furthermore, the study population mainly included healthy, Caucasian European participants, potentially limiting the generalizability of the findings to other ethnicities and patients. Furthermore, the utilized PPG sensor in the Biopac-system and the PPG sensor array in de MPA-system were quite sensitive to motion and positioning disturbances. This sensitivity to disturbances poses a potential limitation on the usability of these techniques in clinical practice. Although the '7Step PW-Filter' algorithm used to eliminate distorted PWs functioned well, the availability of a MPA sensor less sensitive to disturbances and displacements would greatly simplify measuring PWVs and would be essential for application in clinical practice.

5. Conclusion

The results of this study demonstrated that the PWV values were consistently lower when measured with the MPA system than when measured with the Biopac-system, which fits the fact that they were measured over a more peripheral vascular trajectory. Furthermore, the measurements were shown to be in good agreement. This suggests that as long as one is aware of the relation between PWV and the vascular trajectory over which the PWV is measured, either system could be used to reliably measure PWV. When basing diagnoses or research outcomes on absolute PWV values, one should be very much aware of how the PWV was measured, with what system, and over which trajectory. Further research will have to be carried out to develop a better sensor to enable simple and consistent placement of the MPA on the finger. Next, a follow-up study should investigate whether the PWVs measured with the MPA on the finger can be used as an index for evaluation of aortic stiffness as a factor of cardiovascular risk.

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Disclosures

All authors state that there are no conflicts of interest to disclose.

ORCID iDs

Marit H N van Velzen https://orcid.org/0000-0003-4196-4407

References

[1] Quinn U, Tomlinson L A and Cockcroft J R 2012 Arterial stiffness *JRSM Cardiovasc Dis.* **1** 1 18
[2] Blacher J, Guerin A P, Pannier B, Marchais S J, Safar M E and London G M 1999 Impact of aortic stiffness on survival in end-stage renal disease *Circulation.* **99** 2434–9
[3] Laurent S *et al* 2001 Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients *Hypertension.* **37** 1236–41
[4] Cruickshank K, Riste L, Anderson S G, Wright J S, Dunn G and Gosling R G 2002 Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation.* **106** 2085–90
[5] Laurent S *et al* 2006 Expert consensus document on arterial stiffness: methodological issues and clinical applications *Eur. Heart J.* **27** 2588–605
[6] Boutouyrie P and Vermeersch S J 2010 Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: establishing normal and reference values *Eur. Heart J.* **31** 2338–50
[7] Van Bortel L M, De Backer T and Segers P 2016 Standardization of arterial stiffness measurements make them ready for use in clinical practice *American Journal of Hypertension* **29** 1234–6
[8] Cavalcante J L, Lima J A C, Redheuil A and Al-Mallah M H 2011 Aortic stiffness: current understanding and future directions *J. Am. Coll. Cardiol.* **57** 1511–22
[9] McDonald D A 1968 Regional pulse-wave velocity in the arterial tree *J. Appl. Physiol.* **24** 73–8
[10] Asmar R *et al* 1995 Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies *Hypertension.* **26** 485–90
[11] Bramwell J C and Hill A V 1922 The velocity of the pulse wave in man *Proceedings of the Royal Society of London Series B, Containing Papers of a Biological Character* **93** 298–306
[12] Wilkinson I B *et al* 1998 Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis *J. Hypertens.* **16** 2079–84
[13] Van Velzen M H N, Loeve A J, Mik E G and Niehof S P 2017 Design and functional testing of a novel blood pulse wave velocity sensor *J. Med. Devices* **12** 7

[14] Jatoi N A, Mahmud A, Bennett K and Feely J 2009 Assessment of arterial stiffness in hypertension: comparison of oscillometric (Arteriograph), piezoelectronic (Complior) and tonometric (SphygmoCor) techniques *J. Hypertens.* **27** 2186–91
[15] Baulmann J *et al* 2008 A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods *J. Hypertens.* **26** 523–8
[16] Calabia J *et al* 2011 Doppler ultrasound in the measurement of pulse wave velocity: agreement with the complior method *Cardiovasc Ultrasound.* **9** 13
[17] Allen J 2007 Photoplethysmography and its application in clinical physiological measurement *Physiol. Meas.* **28** R1–39
[18] Ellins E A *et al* 2016 Validation of a new method for non-invasive assessment of vasomotor function *European Journal of Preventive Cardiology* **23** 577–83
[19] Naka K K, Tweddel A C, Doshi S N, Goodfellow J and Henderson A H 2006 Flow-mediated changes in pulse wave velocity: a new clinical measure of endothelial function *Eur. Heart J.* **27** 302–9
[20] Corretti M C *et al* 2002 Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the international brachial artery reactivity task force *J. Am. Coll. Cardiol.* **39** 257–65
[21] Green D J, Jones H, Thijssen D, Cable N T and Atkinson G 2011 Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? *Hypertension* **57** 363–9
[22] Flammer A J *et al* 2012 The assessment of endothelial function: from research into clinical practice *Circulation.* **126** 753–67
[23] Mordi I, Mordi N, Delles C and Tzemos N 2016 Endothelial dysfunction in human essential hypertension *J. Hypertens.* **34** 1464–72
[24] Thijssen D H *et al* 2011 Assessment of flow-mediated dilation in humans: a methodological and physiological guideline *Am. J. Physiol. Heart. Circ. Physiol.* **300** H2–12
[25] Weissler A M, Harris W S and Schoenfeld C D 1968 Systolic time intervals in heart failure in man *Circulation.* **37** 149–59
[26] Kortekaas M C, van Velzen M H N, Grüne F, Niehof S P, Stolker R J and Huygen F J P M 2018 Small intra-individual variability of the pre-ejection period justifies the use of pulse transit time as approximation of the vascular transit *PLoS One* **13** e0204105
[27] Newlin D B and Levenson R W 1979 Pre-ejection period: measuring beta-adrenergic influences upon the heart *Psychophysiology.* **16** 546–53
[28] Kortekaas M C, Niehof S P, Van Velzen M H N, Galvin E M, Huygen F J P M and Stolker R J 2012 Pulse transit time as a quick predictor of a successful axillary brachial plexus block *Acta Anaesthesiologica Scandinavica.* **56** 1228–33
[29] Kortekaas M C, Niehof S P, Van Velzen M H N, Galvin E M, Stolker R J and Huygen F J P M 2012 Comparison of bilateral pulse arrival time before and after induced vasodilation by axillary block *Physiol. Meas.* **33** 1993–2002
[30] Teng X F and Zhang Y T 2006 The effect of applied sensor contact force on pulse transit time *Physiol. Meas.* **27** 675–84
[31] Chiu Y C, Arand P W, Shroff S G, Feldman T and Carroll J D 1991 Determination of pulse wave velocities with computerized algorithms *Am. Heart J.* **121** 1460–70
[32] van Velzen M H, Loeve A J, Kortekaas M C, Niehof S P, Mik E G and Stolker R J 2016 Effect of heat-induced pain stimuli on pulse transit time and pulse wave amplitude in healthy volunteers *Physiol. Meas.* **37** 52–66
[33] Clifford G D 2008 Rpeakdetect function (ECG toolbox) [Massachusetts Institute of Technology] (http://www.mit.edu/~gari/CODE/)
[34] van Velzen M H N, Loeve A J, Niehof S P and Mik E G 2017 Increasing accuracy of pulse transit time measurements by automated elimination of distorted photoplethysmography waves *Med. Biol. Eng. Comput.* **1** 1–12
[35] van Velzen M H N, Stolker R J, Loeve A J, Niehof S P and Mik E G 2018 Comparison between pulse wave velocities measured using Complior and measured using Biopac *J. Clin. Monit. Comput.* 1–7
[36] Van Velzen M H N, Loeve A J, Mik E G and Niehof S P 2017 Design and functional testing of a novel blood pulse wave velocity sensor *J. Med. Devices* **12** 1–7
[37] Cauwenberghs N *et al* 2018 Flow-mediated slowing of brachial-radial pulse wave velocity: methodological aspects and clinical determinants *Artery Research.* **21** 29–37