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Design and Functional Testing of a Novel Blood Pulse Wave Velocity Sensor

The multiphotodiode array (MPA) is a novel transmission photoplethysmography (PPG) sensor to measure pulse wave velocity (PWV) in the finger. To validate the MPA, a setup was built to generate a red laser dot traveling over the MPA with known and constant scanning velocities. These scanning velocities were chosen to include speeds at least twice as high as those found in the normal range of PWV in healthy populations and were set at 12.9, 25.8, 36, or 46.7 m/s. The aim of this study was to verify the functionality of the MPA: performing local noninvasive PWV measurements. To illustrate the applicability of the MPA in clinical practice, an in vivo pilot study was conducted using the flow-mediated dilation (FMD) technique. The in vitro accuracy of the MPA was ±0.2%, 0.3%, 0.5%, and 0.6% at the applied scanning velocities. The MPA can measure PWVs with a maximum deviation of 3.0%. The in vivo pilot study showed a PWV before the FMD of 1.1±0.2 m/s. These results suggest that this novel MPA can reliably and accurately measure PWV within clinically relevant ranges and even well beyond.
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Keywords: arterial stiffness, photoplethysmography (PPG), pulse wave velocity (PWV)

Introduction

Globally, cardiovascular diseases (CVDs) are the number one cause of death. Smoking, unhealthy diet, physical inactivity, and excessive use of alcohol are the most important behavioral risk factors for CVDs. As an effect, individuals may develop hypertension, diabetes, heart failure, or atherosclerosis, most of which are related to a change in arterial stiffness. Arterial stiffness is most commonly used to express the viscoelastic property of the arterial wall, which is expressed in the relationship between change in pressure and change in volume [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]. The effect of increased arterial stiffness is a decreased propagation time of pressure pulse waves (PWs) through the vessels and thus an increase of the pulse wave velocity (PWV) [5,6]. The arterial stiffness of a blood vessel is important because the elastic walls of the arteries attenuate the systolic pressure wave of each heartbeat. The potential energy stored in the vessel walls is used to continue to propel the blood during the diastole between successive heartbeats [1].

To determine arterial stiffness, the gold standard is to measure the PWV, because the speed with which the PWs travel through the blood is directly related to the incremental elastic modulus $E_{\text{inc,vessel}}$, vessel wall thickness h_{vessel}, and vessel radius r_{vessel} by the Moens–Korteweg equation (with ρ_{blood} the density of blood) [7]

$$\text{PWV} = \sqrt{\frac{E_{\text{inc,vessel}} \cdot h_{\text{vessel}}}{2r_{\text{vessel}} \cdot \rho_{\text{blood}}}} \tag{1}$$

The PWV is measured as an average speed of a PW between two locations on the body. Note that the PWV is not the speed of blood, but the speed of the pressure pulse traveling through the moving blood (comparable to a sound wave). The PWV can be measured both invasively and noninvasively and is highly reproducible [8]. In clinical practice, the PWV is generally determined as an average velocity over the carotid-femoral trajectory or the brachial-ankle trajectory. Depending on age, in healthy subjects the PWV is about 6–10 m/s over the carotid-femoral trajectory. In cardiovascular risk patients, the PWV can be as high as 20 m/s over the same trajectory [6,9,10], so two to three times as high as in healthy subjects.

Several noninvasive techniques to measure PWV are clinically available, e.g., Doppler ultrasound [11], tonometric (SphygmoCor), oscillometric (Arteriograph), and piezoelectronic (Complior) techniques [12]. To the best of our knowledge, only one group has reported on relatively peripheral PWV, providing the average PWV over the trajectory between the wrist and finger [13], using the Hall effect and photoplethysmography (PPG). The drawback of these methods is that they require two separate devices. Limitations of these techniques include the difficulty of accurately placing the sensors, and the discrepancy between the distance between the sensors and the actual path length traveled by the PW. Moreover, these methods are not always comfortable for the patient; for example, the use of the blood-pressure cuff arteriography technique is inconvenient. Furthermore, Doppler ultrasound requires an experienced operator to conduct the measurements. Clinical practice would benefit from a device that can reliably measure the PWV over a short, accurately known

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distance, using a simple technique that is already familiar to clinicians. The measurement preferably should not require an experienced operator, should allow continuous monitoring, should not cause the patient discomfort, and should potentially be easily added to available clinical monitoring systems.

We designed a device, further called the multiphotodiode array (MPA), that enables peripheral, noninvasive PWV measurements along a trajectory of 12.0 mm, without having the drawbacks of the currently available alternatives. The MPA will guide to enable comfortable measurements with a single, simple device without requiring highly trained operators. The working principle of the MPA is based on PPG—a widely used noninvasive optical technique, to measure volumetric expansion and contraction of vessels (Fig. 1) [14]. The maximum volumetric expansion at any point along a vessel occurs when the peak of a PW passes that point. Thus, the peripheral 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. It is not yet known to what extent this peripheral PWV measured in, for example, a finger correlates with PWVs elsewhere in the vascular system. However, to investigate this, it should first be validated whether the MPA can be used to properly measure peripheral PWV. If this proves to be feasible and if there is good correlation with conventional measuring techniques, using the MPA for determining the PWV would open the road to fast and simple PWV-based diagnostics that do not put any burden on patients. Furthermore, with some small alterations of the design, the MPA could also be used for reflective measurements, making it suitable for noninvasive measurement of PWVs for, e.g., the carotid arteries. The aim of this study was to verify the functionality of the MPA, more specifically, to determine whether the MPA accurately measures the velocity of light pulses traveling over it.

Method and Materials

Multiphotodiode Array (MPA). The MPA is a transmission PPG sensor for measuring the PWV, for example, in the finger by measuring light transmission at multiple points along a short trajectory. The PPG-sensor element is a Si PIN S8558 photodiode array (Hamamatsu Photonics, Hamamatsu, Japan) with 16 high-sensitivity photodiodes, with a peak sensitivity wavelength of 960 nm, positioned in a single row. Each photodiode has an active area of 0.7×2.0 mm. An array with more than two photodiodes was chosen because this enabled assessing which combination of the number of photodiodes and the distances between them would provide the most accurate PWV measurements. The array of 16 photodiodes was chosen rather arbitrarily because of its availability and because it enabled achieving the study goals. The light source of the MPA consists of two red (620 nm) and two infrared light emitting diodes (880 nm). These two wavelengths are known to provide very good signal transmission through the finger and to the photodiode array [15]. All 16 analog signals from the photodiode array are converted to digital signals through a NI-USB 6229 Multifunction Data Acquisition system and LabVIEW 2010 software (both: National Instruments, Austin, TX). The data acquisition system has a 250 kHz sampling rate and 32 analog, 16-bit input channels.

Validation Setup and Protocol. To functionally validate the MPA, a setup (Fig. 2) was built in which a laser dot periodically scanned over the MPA with a known and constant scanning velocity. A linearly polarized laboratory Helium Neon Laser with a power of 0.5 mW (25-LHP-213, Melles Griot, Carlsbad, CA) provided a continuous 632.8 nm wavelength red laser light dot with a 0.46 mm beam diameter ($1/e^2$). This laser was chosen for its wavelength, as it resembles the spectrum transmission through the finger when using commercial PPG sensors. The laser dot was made to scan over the MPA using a rotating mirror, which was actuated using a stepper motor to deliver various velocities of the light dot scanning over the MPA.

Four different scanning velocities were used with 24 scans (24 full mirror rotations) for each scanning velocity. These scanning velocities were chosen to include speeds over twice as high as the normal range of PWVs found in healthy populations over the carotid-femoral trajectory to ensure including values that can be expected when measuring locally on the carotid artery and to explore the full potential of the MPA, and were chosen to be 12.9, 25.8, 36.0, or 46.7 m/s. These scanning velocities were preset by setting the motor actuating the mirror to a matching rotational speed Ω using the relation

$$\Omega = \frac{v_{set}}{2\pi \cdot r_{path}} \tag{2}$$

where v_{set} is the desired scanning velocity and r_{path} is the distance between the mirror center and the MPA (Fig. 3). In order to achieve a constant scanning velocity over the entire MPA, it was necessary to have a large r_{path} of 1390 mm (Fig. 3). To avoid requiring a very large space for the setup for increasing r_{path}, the laser beam was made to zigzag five times between two mirror strips before reaching the MPA (Fig. 2). As a result, the resulting laser dot speed variation across the MPA was only about 0.0001%.

The MPA was placed in a holder that allowed precise horizontal, vertical, and rotational positioning and orienting. A mask with a $(1.00 \pm 0.05$ mm) high slot was placed over the entire width of the MPA to limit the amount of light exciting the photodiodes. As a result of the laser dot scanning over the MPA, the photodiodes

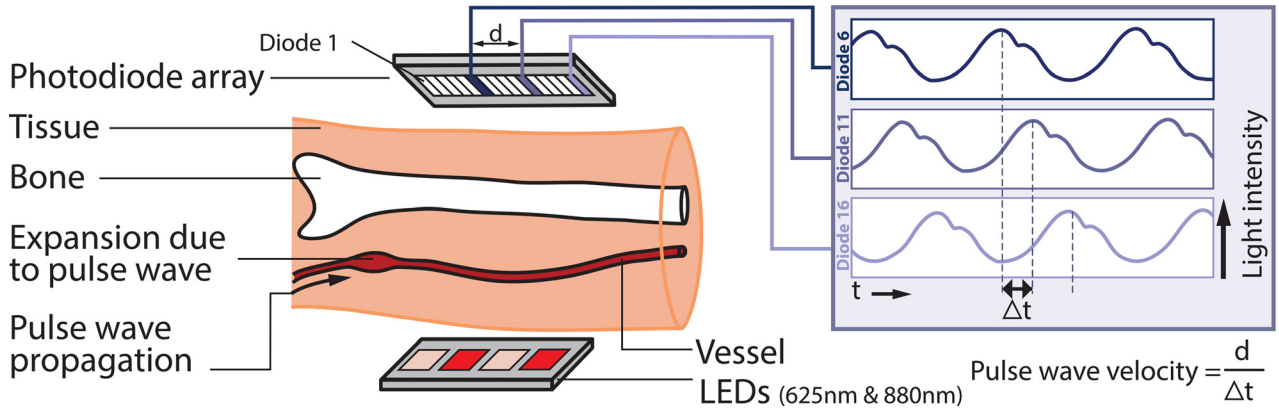

Fig. 1 Schematic overview of the MPA and calculation of the PWV

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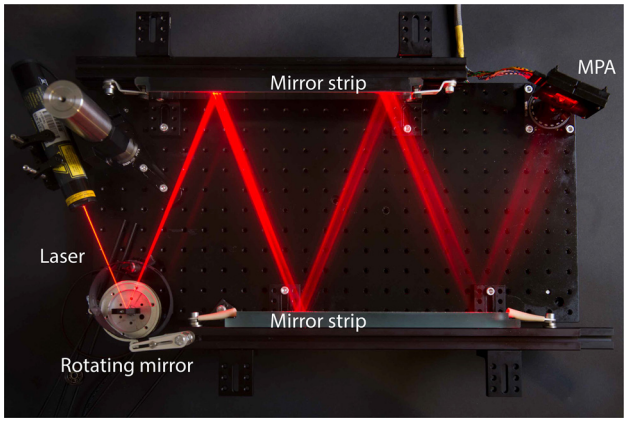

Fig. 2 Overview of the validation setup

consecutively received a light pulse of sinusoidally varying intensity with a clearly defined peak.

The actually delivered scanning velocity (v_{scan} (m/s)) at the MPA depends on the accuracy of the set Ω and r_{path}. Therefore, v_{scan} was continuously verified for each mirror rotation by measuring the time period T between the successive peaks received in the signal measured at photodiode 1 in the MPA

$$v_{scan} = \frac{2\pi * r_{path}}{T} \tag{3}$$

The peaks of the photodiode 1 signals were detected using an off-the-shelf MATLAB (The MathWorks, Inc., Natick, MA) function called "Peakdet" [16].

In order not to overestimate the accuracy of the MPA, the four most relevant tolerances (T1–T4) in the validation setup and the MPA were determined and taken into account. First, the scanning velocity tolerance of the validation setup was determined by

- T1—the accuracy of the distance between the rotating mirror and the MPA
- T2— the accuracy of the speed of the rotating mirror

Second, the accuracy of the measured pulse velocity by the MPA was determined by

- T3—the tolerance of the distances between the successive photodiodes
- T4—the accuracy of the detection of the peaks of the light pulses received by the photodiodes, which is mainly determined by the data acquisition sampling frequency (SF)

These tolerances were determined using manufacturers' specifications of the components and the of measurement equipment used.

Because of the multiplexing in the data acquisition system, the actual sampling frequencies with which the MPA data were gathered depended on the number of photodiodes that were read out. To verify the functioning of the MPA at different SFs and interdiode distances, all scanning velocities were applied 24 times with each of the three protocols:

- Protocol 1: using two photodiodes (no. 1 and 16) at a SF of 125 kHz
- Protocol 2: using four photodiodes (no. 1, 6, 11 and 16) at SF of 62.5 kHz
- Protocol 3: using all 16 photodiodes at a SF of 15.6 kHz

Figure 4 shows an example of the signals measured when the laser dot makes a single scan over the MPA and protocol 2 is used.

Data Analysis. After obtaining the MPA data, MATLAB R2010a was used for the data analysis and to calculate the velocity of the

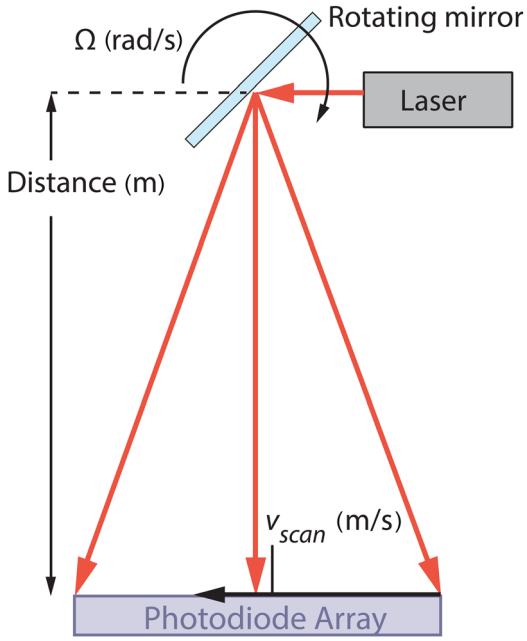

Fig. 3 Schematic overview of the validation setup

laser dot ("measured pulse velocity") from the signals received by the MPA. The measured pulse velocity was calculated as the distance between a pair of photodiodes divided by the time difference between the peaks detected on the signals measured by these photodiodes. The peaks were detected using an off-the-shelf MATLAB function called Peakdet [16]. For each protocol, this was done for each combination of any two of the photodiodes used. That way, any eventual misalignments of the MPA with respect to the laser dot travel path potentially causing slight laser dot speed variations over the MPA, and any influences of the geometrical tolerance on the distance between the sensor's photodiodes (2%) were averaged out. Finally, the average measured pulse velocity was calculated by averaging all the measured pulse velocities from all combinations of two photodiodes for all 24 scans.

The data obtained with protocol 2 showed that the SF of 62.5 kHz was too low to accurately measure the highest simulated PWV of 45.0 m/s. Therefore, these data were interpolated over time using the MATLAB function "v5cubic interpolation." The v5cubic interpolation function determines the interpolated value at a point based on a shape-preserving piecewise cubic interpolation of the values at neighboring points. This results in a more accurate approximation of the wave peaks because it takes the shape of the wave into account.

For protocol 3, the SF of 15.6 kHz was too low to fit any proper curve through the data samples for any of the applied scanning velocities. Therefore, the datasets for protocol 3 were excluded from further analysis. For protocols 1 and 2, it was verified whether the measured pulse velocities matched the applied scanning velocities.

In Vivo Pilot Study. To illustrate the applicability of the MPA in practice, an in vivo pilot measurement was conducted on the right finger of the first author (Marit H. N. van Velzen) as a healthy volunteer, using the flow-mediated dilation (FMD) technique [17] which provokes the release of nitric oxide, resulting in vasodilation, causing the pulse wave amplitude (PWA) to increase after release of the blood-pressure cuff and causing the PWV to decrease. The Medical Ethics Committee Erasmus MC of Rotterdam, the Netherlands, confirmed that the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO) do not apply for this in vivo pilot study. Therefore, the study was allowed without further review by

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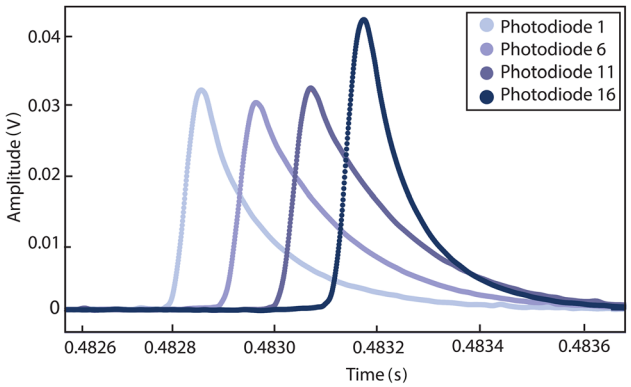

Fig. 4 Example of light pulse detection with the MPA using four photodiodes

the MEC board. The MPA was placed on the right finger and set to use protocol 1. The healthy volunteer was sitting on a chair with both hands resting on a table, in a quiet room under tranquil conditions and without talking or moving during the measurement. First, the PWV was measured for 1 min to obtain a baseline. Next, the blood-pressure cuff, placed around the upper arm, was inflated to 150 mmHg pressure to block the blood flow to the lower arm. After 5 min, the blood-pressure cuff was instantly released. During this entire process, the PWV was measured. After releasing the blood-pressure cuff, the PWV and PWA were measured for 5 min and averaged over each 30 s.

Results

Functional Validation. The validation setup has a scanning velocity tolerance which was determined by

- T1—the accuracy of the distance between the rotating mirror and the MPA
- T2—the accuracy of the speed of the rotating mirror

The tolerance of the distance between the rotating mirror and the MPA was determined to be 1% (using a solid aluminum breadboard with a tolerance of 0.25 mm between the mounting holes). For the peak detection, the accuracy was ±1 sample for the two lowest scanning velocities and ±2 samples for the two highest scanning velocities. T1 and T2 together lead to uncertainties in the scanning velocities of ±0.5 m/s for two lowest scanning velocities and ±1.1 m/s for two highest scanning velocities. Table 1 shows the mean±SD of the scanning velocities.

The measured pulse velocity tolerance by the MPA was determined by:

- T3—the tolerance of the distances between the successive photodiodes
- T4—the accuracy of the detection of the peaks of the light pulses received by the photodiodes

The tolerance specified by the manufacturer for the distance between photodiodes 1 and 16 was ±0.25 mm over the full distance of 12.0 mm. Therefore, the uncertainties in the measured pulse velocities caused by T3 and T4 are ±0.2%, 0.3%, 0.5%, and 0.6% for the successive measured pulse velocities. Table 1 shows the mean±SD of the measured pulse velocities using protocols 1 and 2.

Figure 5 shows the relative difference between the scanning velocity and the measured pulse velocity and their variation. The maximum differences was 3.0% when using the four photodiodes by the highest scanning velocity. For using two photodiodes, protocol 1, the maximum differences was 1.7%. Both reported accuracies are including the additional potential deviations caused by the system tolerances.

In Vivo Pilot Study. Figure 6 shows the PWV and the PWA averaged over each 30 s as measured for each heartbeat before and after the FMD test. After release of the blood-pressure cuff, the PWA increased, which agrees with the guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery [17]. The PWV measured between photodiodes 1 and 16 before inflating the blood-pressure cuff was 1.1±0.2 m/s during this 1 min baseline. The PWV was higher after releasing the blood-pressure cuff and then decreased over time.

Discussion

To the best of our knowledge, this study is the first to demonstrate measuring the PWV based on photoplethysmography with a single photodiode array. The validation setup used enabled assessing the maximum technical accuracy for measuring pulse speeds in the range of naturally occurring pressure pulse wave velocities and beyond.

Scanning Velocity. The scanning velocities used to validate the functionality of the MPA were relatively high compared to commonly reported average PWVs in healthy subjects or patients. However, these velocities were chosen in order to assure that proper PWV measurements can also be obtained in patients—who often have exceptionally high PWVs—and to explore the full potential of the designed sensor, for application both in the primarily intended transmission measurements on the extremities and in future reflective measurements on, e.g., the carotid artery. Furthermore, the measurement inaccuracies increase with increasing PWV, which is why the chosen velocities provide a very strong worst-case validation. Despite the tolerances causing uncertainties in the applied scanning velocities, the validation setup proved to be sufficiently accurate for our purposes.

Measured Pulse Velocity. At all scanning velocities, the MPA accuracy proved to be more than adequate to provide reliable results. In the MPA, any inaccuracies in the measured pulse velocity could in principle be caused by the following:

(a) the tolerance on the distances between the photodiodes, which is a systematic error because the interdiode distances never change;
(b) the response time of the MPA photodiodes, which was unlikely to be a source of inaccuracy because the amplitudes were comparable for all measured velocities;
(c) and the sampling frequency, of which the relative effect size depends on the pulse velocity to be measured.

Table 1 Scanning velocities and measured pulse velocity (m/s) (averaged over 24 scans for each velocity)

Scanning velocity Mean±SD	Protocol 1 measured pulse velocity Mean±SD	Protocol 2 measured pulse velocity Mean±SD
12.9±0.02	13.1±0.16	13.2±0.28
25.8±0.06	25.9±0.14	26.0±0.52
36.0±0.04	36.0±0.11	36.8±0.78
46.7±0.09	46.7±0.19	48.1±1.23

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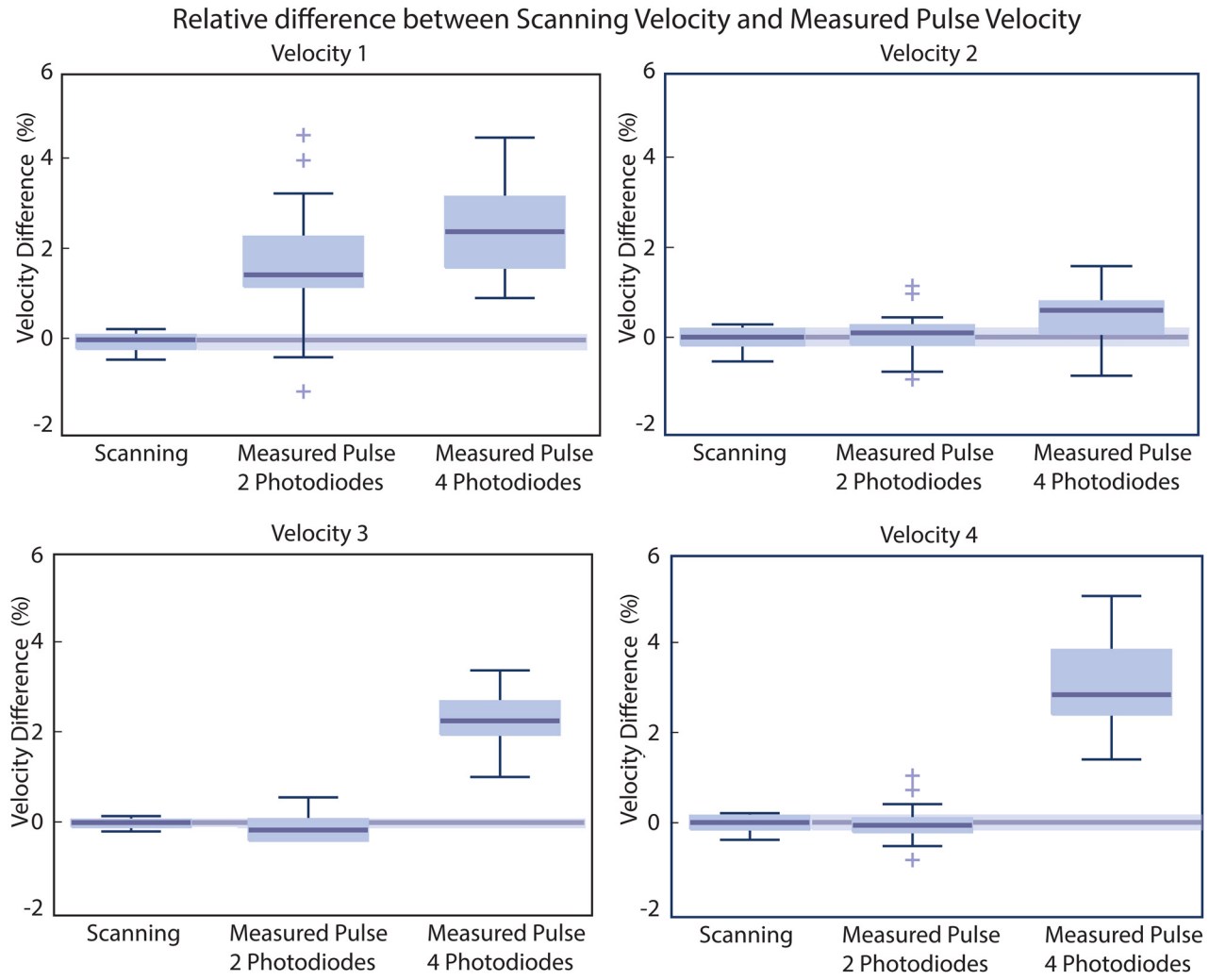

Fig. 5 Boxplot showing the relative difference between the applied scanning velocities and the pulse velocities measured with the MPA (for two and four photodiodes)

One may notice in Fig. 4 that the amplitude of the response of photodiode 16 was higher than that of the other photodiodes. No explanation for this systematic deviation could be found, but it could have been induced by a small irregularity in the laser-cut mask in front of the MPA, which might have caused reflections or slightly more light to pass the mask. However, irrespective of the cause of the amplitude variation, such systematic response amplitude variations between the different diodes do not affect the speed calculations, as these do not change the location of the amplitude peaks on the time axis.

The MPA showed to enable accurate measurement of PWVs up to 45.0 m/s when using two photodiodes (spaced 12.0 mm apart) at 125 kHz. When using four photodiodes (spaced 4 mm apart) at 62.5 kHz, the MPA can accurately measure PWVs up to 25.0 m/s without the need for interpolation and up to 45.0 m/s with interpolation. In clinical practice, the PWV is unlikely to exceed 20.0 m/s [6,9,10]. Therefore, the MPA is sufficiently accurate for clinical use when using four photodiodes. Having four or more photodiodes instead of two can be of potential value when local artifacts disturb the PW shapes and inhibit proper detection of the PW peaks, something often observed in clinical practice. In such cases, the velocity measurements can be made more robust by ignoring any diodes that return disturbed PW signals and averaging the velocities measured over several sections of the array. Furthermore, using more than two photodiodes allows to investigate whether there is a change in PWV over a short trajectory; this could potentially be useful to determine the presence of arthrosclerosis in a specific area.

When sampling all 16 photodiodes, the MPA could not accurately measure the PWV for any of the applied scanning velocities. The sampling frequency (which is multiplexed over all channels) was too low to accurately provide the true peak location, even after interpolation. The 16 photodiodes array was selected because of its availability, but having two photodiodes suffices for measuring the PWV and with four photodiodes the robustness of the PWV measurements can be increased. However, having a plurality of photodiodes could potentially maximize the robustness of the velocity measurements in patients demonstrating high rates of disturbed PWs. Obviously, the MPA performance with 16 photodiodes could be improved by using higher sampling frequencies, but that would require costlier equipment. A way to improve the measurements while using low sampling frequencies could be to determine the time differences of the pulse waves arriving at the different diodes using cross-correlation instead of peak detection. However, the current study focused on the use of peak detection because this is a simple approach that can be applied easily in many software packages and analysis tools. Additionally, peak detection requires little computational power compared to using cross-correlation methods, making it more suitable for fast, real-time measurements.

The pulse velocities measured using two or four photodiodes had deviations of at most 3.0% compared to the corresponding

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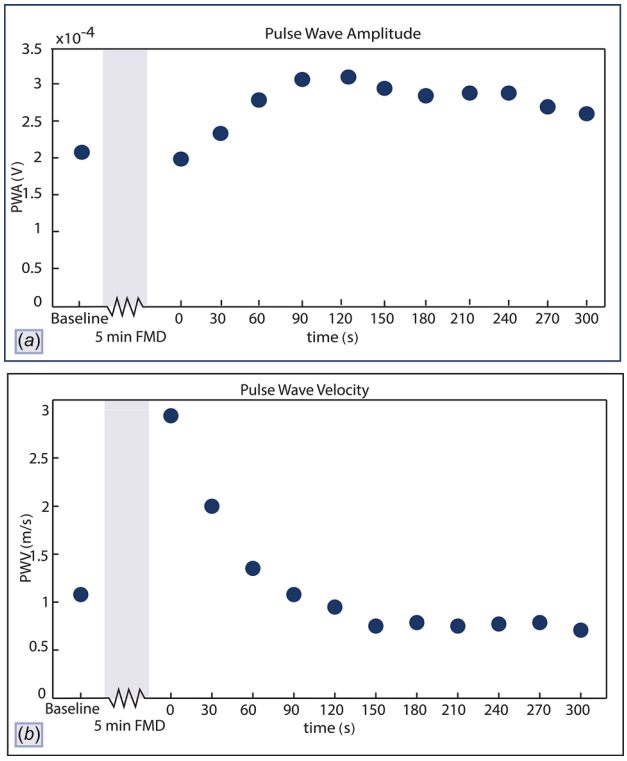

Fig. 6 Pulse wave amplitude and PWV before and after FMD

scanning velocities. In an in vivo study, Boutouyrie and Vermeersch measured PWVs to differ between healthy volunteers (optimal) and patients with CVD (grade II/III HT) by more than 25% (for ages $\leq$30 years a mean PWV of 6.0 m/s versus 7.6 m/s) [6], implying once more that, when using two or four diodes, the MPA can reliably measure clinically realistic PWV values with sufficiently high accuracy to detect clinically relevant PWV variations. The applicability of the MPA could be even further increased by adapting it to enable reflective PPG measurements. This would allow measuring PWVs on locations that can be approached from a single side only, such as the carotid artery.

In Vivo Pilot. To further test the clinical applicability of the MPA, an in vivo pilot study was conducted on author Marit H. N. van Velzen. These results were similar to those reported by Nam et al. [13], i.e., around 0.8 m/s. Furthermore, the response of the PWA to the FMD agrees with that described in the guidelines for FMD measurement [17]. It is known that the PWA increases during FMD. Assuming other parameters (e.g., cardiac output, heart rate) to be constant throughout the experiment, the PWV should decrease after FMD; our pilot results were in line with this expectation.

It is not yet known to what extent the peripheral PWV measured in a finger correlates with conventional techniques of measuring the PWV in the aortic. To investigate this, the functionality of the MPA first had to be verified, as was done in this research. The correlation between conventional PWV measurements and peripheral PWV is currently being investigated. If there is good correlation, this novel way of measuring the PWV will open the road to fast and simple PWV-based diagnostics with minimal burden on patients.

Conclusion

The results of this study indicate that the novel photoplethysmography-based MPA can accurately and reliably measure PWV within clinically relevant ranges, and even well beyond. Some important advantages of the MPA as compared to other PWV measuring systems are that the MPA is easy-to-use, noninvasive and objective. Using the MPA will not require trained staff or costly equipment, and allows continuous monitoring. In addition, the MPA eliminates the need for any other measurement systems, such as electrocardiography, for measuring PWVs.

Further research is required to investigate whether the PWVs measured with the MPA on the fingers can be used as an index for evaluation of aortic stiffness as a factor of cardiovascular risk [9]. A subsequent step is to examine the reproducibility and variance of the PWV in healthy volunteers and cardiovascular risk patients when applying measurements over short trajectories, instead of the currently used measurements over larger distances.

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