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Determination of Pulse Wave Velocity in Arteries using High-Frequency and Single-Channel Focused Ultrasound

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Abstract: Pulse wave velocity (PWV) is a key indicator of our vascular age, a risk predictor of cardiovascular disease. The gold-standard method to measure PWV relies on the measurement of the carotid-femoral arterial distance, and it is not very reliable, due to the changes in the arterial tree. We present in this paper a method to measure local PWV based on high-frequency ultrasound, with a mono channel transducer at 20 MHz, at the arterial site of measurements. We performed in-vitro measurements in a phantom with tubes of 1.5 mm of diameter. Four ultrasound methods to extract PWV based on difference velocity estimation are compared. PWV was validated with pressure sensors and gave a mean error of only 1.1 m/s.

Keywords: High-frequency ultrasound, pulse wave velocity, cardiovascular disease, loop-based methods, medical phantom, blood flow, diameter waveform.

Background, Motivation and Objective

In healthy conditions, our heart pumps 5 litres of blood per minutes through our arteries and veins at rest. Simultaneously, the arteries adapt their diameter to the cardiac output to maintain constant blood pressure. If we measure the movement of the blood in our arterial tree from the aorta to the periphery, we will see a travelling pulse wave. The pulse wave velocity (PWV) depends on the stiffness of our arteries, being increased with our biological age [1] or the hardening of our artery walls, and it is a key indicator of vascular age and a predictor of cardiovascular disease.

The standard PWV measurement is performed at large arteries and over large distances such as the carotid-to-femoral (cfPWV), and it is defined as regional PWV [2]. The gold-standard medical device to measure PWV is the tonometer, which uses two measurement points (at the carotid and femoral artery) to determine the shift in time of the waveforms. The cfPWV is then calculated as the ratio of the distance between those measurement points (ΔD) and the time displacement of the pulse waves (pulse transient time, PTT), as indicated in Eq. (1).

$$cfPWV = \frac{\Delta D}{PTT} \tag{1}$$

cfPWV is given in (m/s), and the mean typicall values for healthy subjects is around 5.8-7.5 m/s for young adults (less than 50 years-old) and of 8.0-8.5 m/s for older adults (more than 50 years-old). Moreover, cfPWV is bigger in males than females. [1]

The main challenge with the cfPWV measurement is the vague estimation of the carotid-femoral distance (ΔD), which is usually done with a ruler externally. Moreover the arterial stiffness is not uniform in all the vessels (change in vessel diameters, wall-thickness and viscoelastic properties), and the global PWV increases distal to the heart and further down to the vascular tree. To solve this problem, local PWV (applied at a single arterial segment and short distances) can be used. Local PWV can assess the arterial heterogeneity and identify early cardiovascular risk at single arterial segments with more precision than global PWV [3].

To measure the PWV at pre-clinical studies in animals, and for microcirculation, high-frequency and high-frame rate ultrasound is required, ensuring accuracy in the detection of the arterial wall movement, and in the measurement of the fast movement of the PWV. Local PWV with ultrasound can be monitored by using dual or multiple ultrasound arrays [4], and applying Eq. (1) as for the global PWV. However, this approach requires synchronization between sensors and also the post-processing of numerous signals.

In this work, we apply the diameter-velocity loop method to determine the local PWV in a customed-made phantom. Velocity and diameter are physiological signals that can be monitored directly with ultrasound using a mono channel-probe, requiring low

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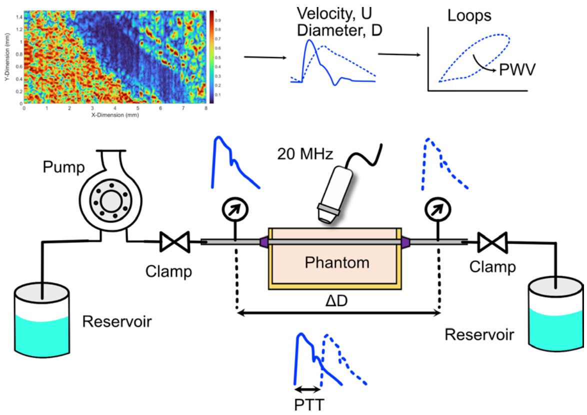

Fig. 1: In-vitro setup for the measurement of the local PWV in the phantom. The PWV is extracted with U and D from the ultrasound acquisition. The measurements are validated with two pressure sensors, after applying Eq. (1)

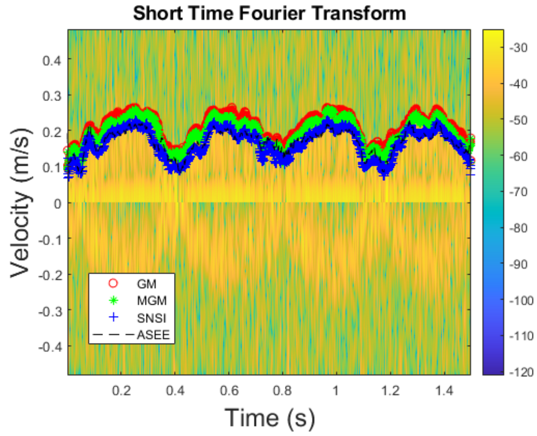

Fig. 2: Velocity curves calculated for the spectrogram of the flow speed in the phantom. The spectral envelope is compared using the geometrical method (GM), modified geometrical method (MGM), signal noise slope intersection (SNSI), and the adaptive spectral envelope estimation (ASEE).

power consumption and also low thermal exposure to the tissue for long-time measurements. The ultrasound device is custom-made, and is mounted in a 3-axis system with motors to obtain B-Mode images. B-mode images provide information of the angle between the liquid flow and the transducer. However, to measure velocity, the probe was operated in a static position, with repeated acquisitions at high pulse repetition frequency (M-mode).

Each line of the M-Mode image is afterwards post-processed. Four different algorithms are applied to extract the ultrasound velocities and the time-of-flight is applied for diameter-wall distension. Validation of the PWV measurements is performed by using commercial pulse pressure sensors.

Ultrasound phantom and in-vitro setup

The measurements and derivation of PWV were performed in an in-vitro setup, as illustrated in Figure 1. The setup consisted on a peristaltic pump (Watson-Marlow) that emulates the heart, silicone tubes, a customized phantom, clamps to change the resistance at the input and ouput of the phantom, and pressure sensors as reference devices for the PWV. The pump delivers the mimicked fluid (that includes *Saccharomyces cerevisiae* yeasts of approximately 7 μm in size to emulate blood cells) from the pump through the phantom.

The phantom is fabricated with polyvinyl alcohol (PVA) at a concentration of 10% by weight (Sigma Mw130000, 99%+ hydrolyzed). Aluminum particles at a concentration of 0.5% by weight and chlorhexidine digluconate as an antiseptic at a concentration of 0.05% by weight (Desinclor, antiseptic solution, chlorhexidine digluconate 1%) are added to PVA. Freeze-thaw cycles are applied to the phantom, which makes the PVA-based mixture form an hydrogel suitable to be used for ultrasound imaging applications. Inside the phantom, a silicone tube with diameter of 1.5 mm, and wall thickness of 0.2 mm is included. The clamps at the inlet and outlet of the phantom help to change the resistance of the setup and maintain a constant pressure inside the phantom.

Two simultaneous measurements were performed: M-Mode ultrasound measurements at one single point, and two pressure measurements with pressure sensors (ABPMANN004BGAA5, Honeywell) for comparison. The probe has a focalized wide-band piezoelectric transducer (Imasonic), with 14 mm curvature radius, 7 mm surface diameter and 20 MHz central frequency. A Difrascope (Dasel Technologies) pulse-echo electronics was used to send and acquire the electric pulses. Pulse repetition rates in the range of 3-20 kHz were applied in this study.

Velocity-Diameter Loop Determination

After monitoring the movement of the particles with the 20 MHz ultrasound probe in the XYZ direction, M-Mode images with the customized setup were acquired. The images at various pump speeds (from 30 RPM till 100 RPM, with steps of 10 RPM) are obtained and save for post-processing. From the M-Mode images, diameter distension and velocity waveforms are derived using MATLAB.

The diameter waveforms are obtained through the application of a band-pass filter, peak detection of the arterial wall for each signal of the M-Mode image (a total of 30.000), and finally the application of the time-

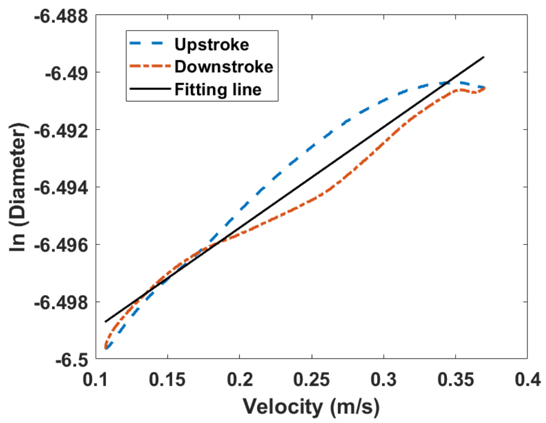

Fig. 3: ln DU-loops measured with ultrasound in the PVA Phantom (for a pump speed of 60 RPM). The upstroke is represented with a discontinued line. The straight line represents the fitting of the loop and provides the value of the slope.

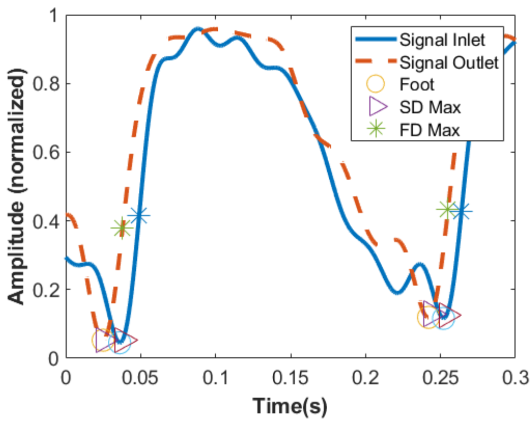

Fig. 4: Waveforms measured with the commercial pressure sensors at the inlet and outlet of the phantom for a pump velocity of 70 RPM. The fiducial points (Foot, FD Max and SD Max) used for the PTT calculation are indicated in the plot with symbols.

of-flight equation. For the velocity, the short-time-fourier-transform provided us with the spectrogram of the ultrasound images. The four algorithms described in [5] are applied into the obtained spectrogram to automatically determine the mean particle velocity in the fluid. An example of the application of the four algorithms to obtain the velocity waveforms is shown in Figure 2.

Velocity-Diameter Loop

Once that the velocity and diameter waveforms for each pump speed are obtained, it is possible to plot the diameter-velocity loops (DU-loops). According to [6], the local wave speed can be determined from the linear relationship between diameter and velocity (when only unidirectional waves are present). That means, if we construct ln DU-loops, the forward wave corresponds to a straight line in the early part of the cycle. After determining the straight line, the wave speed can be estimated as the inverse of the slope of that straight line, following Eq. (2).

$$PWV(US) = \frac{1dU}{2d(lnD)} = \frac{1}{2slope} \qquad (2)$$

The ln DU-loops have been calculated with MATLAB for each of the pump speeds. An example is illustrated in Figure 3. Afterwards linear fitting is applied (in the form of $y = x * slope + b$) to determine the slope of the linear region of the curves. For each Pump speed, the PWV is calculated four times (one for each of the velocity algorithms applied for the velocity spectral estimation).

Validation with two pressure sensors

The PWV obtained with high-frequency ultrasound can be validated by placing two pressure sensors at the inlet and outlet of the phantom. For the determination of the time difference between the two pressure waveforms (PTT), various fiducial points can be used. The most typical one is to use the foot of the waveform. However that point shows non-linear behaviour and reflected waves in some of our measurements. Therefore, apart from the foot, also the peak or maximum of the first derivative (FD Max) and of the maximum of the second derivative (SD Max) are applied as fiducial points for the determination of the PTT.

Figure 4 shows two measured waveforms (at the inlet and the outlet) with the corresponding fiducial points. The PWV is determined dividing the distance between the pressure sensors by the PTT at those fiducial points.

Results

The mean and standard deviation values of the PWV measurements at the different pump speeds (between 30 RPM and 100 RPM) for the pressure sensors is shown in Tab. 1. The PWV determined at the peak of the first derivative provides the highest value, with 12.23 m/s and a standard deviation of 0.61 m/s. When using the foot as the fiducial point the PWV is reduced to 9.23 m/s. However the peak of the second derivative provides a slightly higher PWV (10.06 m/s) with the minimum variation between values (0.39 m/s of standard deviation).

The PWV measured by the ln DU-loops with ultrasound are compared to the PWV measured by the

Tab. 1: Local PWV measurements with the pressure sensors

Fiducial point (Pressure sensors)	PWV average m/s	PWV std m/s
Foot	9.23	1.01
FD Max	12.23	0.61
SD Max	10.06	0.39

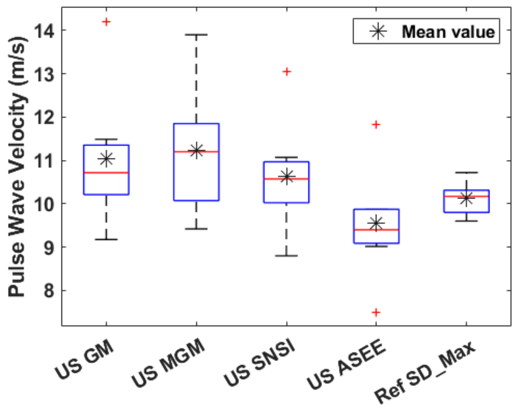

Fig. 5: Box-plots of the PWV measured by ultrasound (In DU-loops) obtained by four ultrasound velocity derivation methods: GM, MGM, SNSI, ASEE. The reference value of PWV measured by the commercial sensors and calculated at the fiducial point SD Max is included for comparison.

pressure sensors in the box-plots of Figure 5. We include only the PWV determined with the SD Max for simplicity in the comparison. The SNSI method in ultrasound provides the lowest PWV error in comparison to the commercial pressure sensors. SNSI achieved a mean PWV of 10.63 m/s and a median PWV of 10.57 m/s. That means, a mean difference with the SD Max of 0.51 m/s (error of 5 %) and a median difference of 0.4 m/s (error of 5.04 %). The ultrasound method with the highest error is the MGM, with a mean error of 1.1 m/s, and a median difference of 1.03 m/s.

Thus, we demonstrate that the custom made high-frequency mono-channel ultrasound can be used to determine the PWV as a potential predictor of atherosclerosis and cardiovascular risks.

Conclusion

In this paper we show and validate a proof-of-concept of a high-frequency monochannel transducer working at 20 MHz for cardiovascular applications. The ultrasound device requires low power, it is non-invasive and low-cost and provides very accurate measurements of PWV in-vitro at single segments of the artery. Through this method the mistakes due to the inhomogeneity of the arterial-tree and the change of PWV through the periphery can be avoided. Thus, high-frequency ultrasound may provide a more patient-specific and more accurate prediction of the vascular age of our microvascular system.

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