Estimation of radial artery reactive response using high frequency ultrasound

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Background: There is a growing interest in the application of non-invasive clinical tools allowing one to assess the endothelial function, preceding atherosclerosis. The precision in estimating of the artery Flow Mediated Vasodilation (FMD) using standard 10-12 MHz linear array probes does not exceed 0.2 mm, far beyond that required.
Methods: We have introduced a wide-band, high frequency 25-30 MHz, Golay encoded wobbling type imaging to measure dilation of the radial artery instead of the brachial one. 18 young volunteers, and 4 volunteers with cardiac events history, were examined. In the second approach 20 MHz linear scanning combined with 20 MHz pulsed Doppler attached to the linear array was used. The radial artery FMD was normalized using shear rate at the radial artery wall. Results and Conclusions: For the "healthy" group, the FMD resulting from reactive hyperemia response was over 20%; while in the "atherosclerotic" group, the FMD was at least twice as small, not exceeding 10%. The shear rate (SR) normalized FMD_{SR} was in the range from 7.8 to 9.9 in arbitrary units, while in patients with minor cardiac history FMD_{SR} was clearly lower, 6.8 to 7.6. The normalized FMD_{SR} of radial artery RARR can be an alternative to the brachial FMD where the precision of measurements is lower and the diameter dilation does not exceed 7-10%.

Keywords: *thick film transducers; atherosclerosis; flow mediated vasodilation*

1. Introduction

Endothelial dysfunction is one of the earliest vascular changes that occur in the pathogenesis of many cardiovascular diseases, including the development of atherosclerosis.

Current medical interventions and lifestyle changes that reduce cardiovascular risk are associated with an improved vascular function. Therefore, the assessment of microvascular endothelial function can be utilized as a tool to detect early vascular changes: changes that may occur due to medical conditions and diseases, or to monitor the response to pharmacological interventions.

In 1992, Celermajer et al. [2] developed a Flow Mediated Dilation (FMD) measurement technique using ultrasound as a noninvasive method for assessing endothelial function. Since that time, ultrasonic evaluation of FMD in response to a few minutes of ischemia, induced by occlusion of the artery pressure cuff placed on the forearm, and then the reactive hyperemia after release of the pressure cuff, has been extensively documented in the literature.

It is believed that endothelial function, enhanced by the FMD, correlates well with the secretion of nitric oxide NO. A few minutes of ischemia and subsequent reactive hyperemia increases the shear stress along the lines of the blood streams in laminar flow. The next step is to smooth muscle relaxation and vasodilation. The percentage change of FMD [%] is determined by comparing the diameter of the vasodilated vessel after reactive hyperemia, with the baseline diameter before vessel occlusion.

In 2002 Corretti et al [3] have published preliminary guidelines for assessing FMD of the brachial artery, using ultrasound, adjusting the original methodology introduced by Celermajer [2] to clinical measurement conditions.

The precise measurement of the artery diameter, after releasing the occlusion, is especially important for a proper assessment of FMD. Peak blood flow velocity usually occurs within the first 20 seconds; however, the maximum extension of the artery occurs some 40 to 80 seconds after the cuff was released [1].

It was demonstrated that a change of FMD reflects not only the state of endothelial cells, but also the value of the endothelium stimulator acting as a shear stress increased by reactive hyperemia after releasing the cuff, [3,7,10,11].

Harris et al [4,5] showed that normalization of FMD by the shear rate (SR) helps in obtaining more robust results. Typically, the accumulated shear rate, and area under the curve (AUC), of shear rate – calculated for the time between releasing the cuff and maximum vessel extension, is used. SR is calculated from the blood velocity recordings by an external Doppler device, or Duplex scan. The normalization of FMD to shear is done by dividing peak FMD by the accumulated value of shear rate area under the curve $SR_{AUC,}$ calculated for the time span between releasing the cuff and peak dilation.

The paper is organized as follows: in Section 2 the influence of the transducer bandwidth on encoded imaging is addressed. In Section 3 the description of high frequency thick film transducers used for Golay encoded imaging is given. Section 4 describes the method and the preliminary results of measurements of the radial artery diameter and the shear rate normalized artery dilation $FMD_{SR,}$ and the Conclusions are given in Section 5.

2. Influence of the transducer bandwidth on Golay coded imaging

The issue of maximizing penetration depth, with concurrent retaining or enhancement of image resolution, constitutes one of the time invariant challenges in ultrasound imaging. Concerns about potential and undesirable side-effects set limits on the possibility of overcoming the frequency dependent attenuation effects by increasing peak acoustic amplitudes of the waves probing the tissue. To overcome this limitation, a pulse compression technique employing 16-bit Complementary Golay Code (CGS) was implemented at 35 MHz. In comparison with other, earlier proposed, coded excitation schemes, such as chirp, pseudo-random chirp and Barker codes, the CGS allowed virtually side-lobe-free operation, [9].

The bandwidth of a Golay coded sequence often exceeds the fractional bandwidth of the available imaging transducer. This section investigates the effect of an ultrasound imaging transducer's fractional bandwidth, on the gain of the compressed echo signal for different spectral widths of the complementary Golay sequences.

Computer simulated 16-bit length Golay sequences at the nominal frequency of 35 MHz, and their corresponding spectrum are shown in Fig.1.

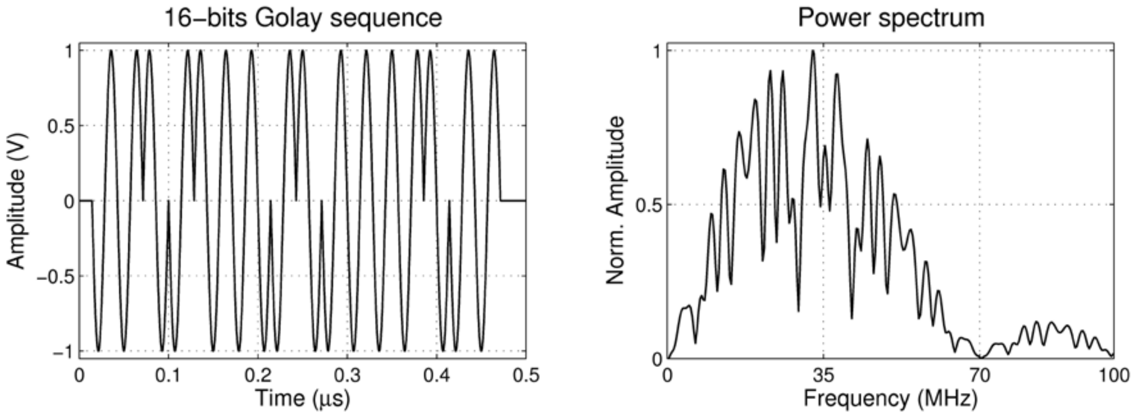

Fig. 1. One of the two 16-bit complementary Golay sequences (left) and the corresponding power spectrum (right) at the nominal frequency of 35 MHz.

As already mentioned, the effective or overall bandwidth that is the one determined by the overall imaging chain, of an ultrasonic transducer, may have influence on transmitted signal distortion and efficiency of the compression. Therefore, the influence of the overall bandwidth on the amplitude of the compressed signal was computer simulated for different filter bandwidths at the center frequency of 35 MHz. Fig.2 shows the simulation results obtained for the compressed Golay complementary coded pairs of length 16-bits, with one-cycle bit length for transducer bandwidths ranging from 50 to 100%.

The simulations were performed using Matlab® software, and the following algorithm: first, the 16-bit Golay sequences were numerically synthesized; next, their Fourier transforms were computed. The band-pass filtering was performed using a second order Chebyshev filter. To return to the time domain, the results were inverse Fourier transformed and plotted.

In Fig.2 (top left) the compressed signal is shown for the case of 100% fractional transducer bandwidth, i.e. the full coded signal spectrum is transmitted. The time duration T of each coded sequence is equal to 457 ns. After filtering, the time duration of the obtained compressed signal is equal to $2T$, here 914 ns. The amplitude of the compressed signals is equal to $2n$, where n is the number of cycles in sequences. In our simulation, n was equal to 16. To facilitate the comparison with the results of the experiments described in the next section, obtained under pulse-echo conditions, the simulation was performed twice using Matlab®. The first simulation procedure determined the transmitted signal waveform, the second one determined the received echoes. The set of experimentally recorded echo signals was used to obtain a power spectrum, which was subsequently inverse Fourier transformed into the time domain, and correlated with the original signal. The results of Fig.2 illustrate that the amplitude of the compressed pulse decreases with narrowing of the fractional transducer bandwidth. For example, in the case of 80% fractional transducer bandwidth, the peak-to-peak amplitude in the compressed signal decreases by 90%, and is equal to 43 V (Fig.2 top right). A similar simulation obtained with 60% fractional bandwidth, resulted in the amplitude decreasing by 57% (Fig.2 bottom left). Finally, for a 50% fractional transducer bandwidth, the amplitude of the compressed signal decreased by 50% (Fig.2 bottom right).

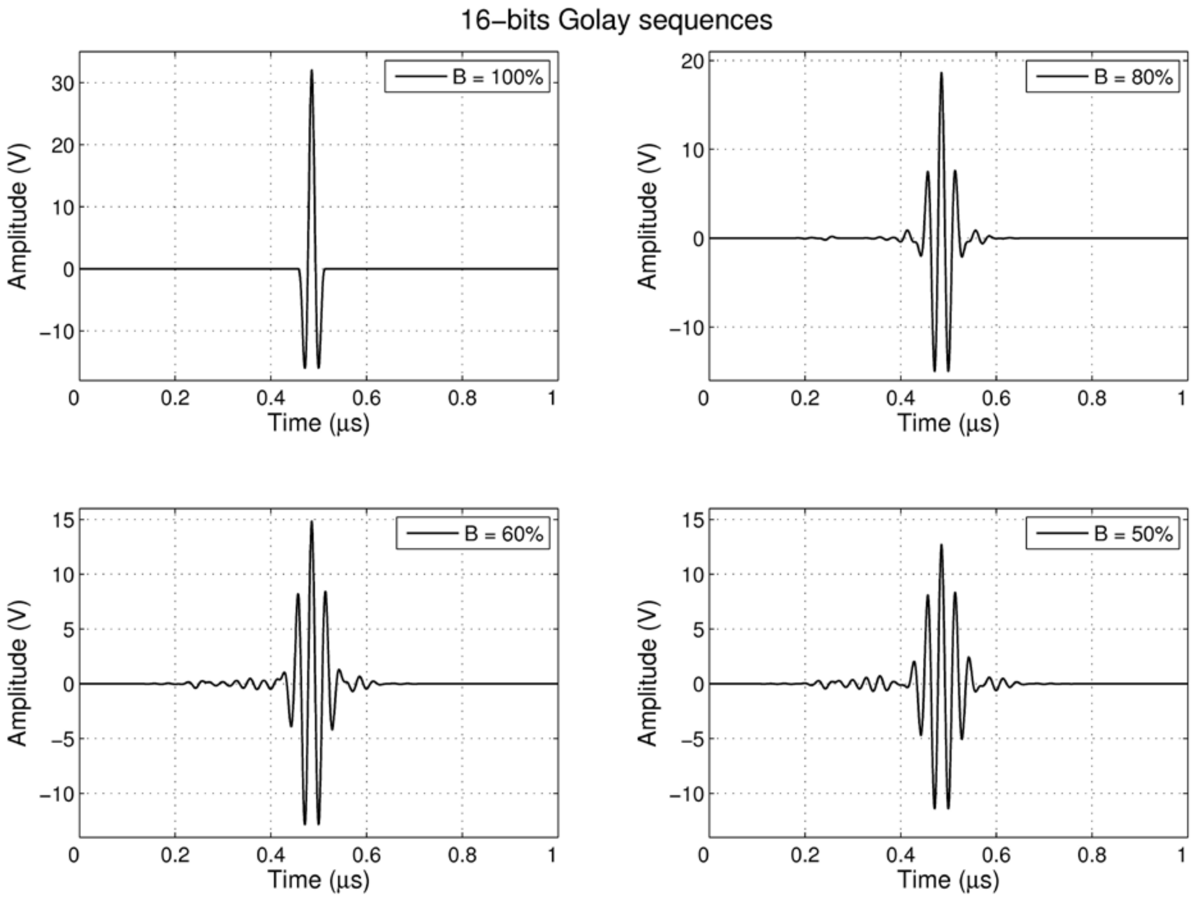

Fig. 2. The compressed coded sequences for different transducer bandwidth (100%, 80% 60% and 50%) at the center frequency of 35 MHz.

Also, with the narrowing transducer bandwidth, the pulse width elongates. In the case of an 80% fractional transducer bandwidth, the full width at half maximum (FWHM) in the compressed signal is equal to 37ns. Following transducer bandwidth decreases, there is FWHM widening, and for the 60% and 50% fractional transducer bandwidth, the FWHM in the compressed signal is equal to 61.4 ns and 63.5 ns, respectively. Assuming the speed of sound in tissue equal to 1540 m/s, the corresponding spatial FWHM would be equal to 43 μm, 57.3 μm, 94.5 μm and 97.8 μm respectively.

3. Wideband thick-film transducer technology

The new technology of piezoelectric transducers, based on PZT thick film devices, has already been successfully commercialized by InSensor A/S. Since the PZT thick film transducers are relatively new devices existing on the market, special attention must be put into the characterization methods that take into account some specific features of these transducers. The backing material (InSensor SU37) is based on a Ferroperm composition Pz37, a porous engineered structure version of PZT [8]. The backing is also used as substrate for the thick film, and will therefore be referred to as the substrate. The pores in the substrate give rise to a significant surface roughness. Since the surface roughness is comparable to the thickness of the thick film, a smoothing layer is printed before deposition of the bottom electrode layers. In order to deposit thick film layers on a curved surface, the technology of pad printing has been implemented. For this purpose, paste prepared for traditional screen-printing, with some modification of the rheological properties, is used. The printing setup consists of a silicone rubber pad, a steel cliché, a doctor blade and a substrate. The paste is flooded onto the etched pattern in the cliché, and the doctor blade removes excess paste. Hereafter, the paste is transferred to the substrate by a silicon pad.

After printing, the organic vehicle is dried off in a ventilated oven at about100°C. Several layers of PZT are printed in order to obtain the desired thickness of the film. For a fired thickness of about 20 µm 15 layers of PZT are printed in this manner. After printing of all the layers, the film is sintered at 850°C for one hour. For bottom and top electrodes, commercial gold and silver pastes are used, respectively. Since the pad is flexible, the thick film can be deposited onto substrates with complex topography. However, the flexibility of the pad can also cause a distortion of the pattern. For simple structures such as circles, this distortion is not a problem, but for more complicated structures, and structures where different patterns have to be aligned to each other; this must be taken into consideration. The samples are poled (polarized) in air at 150°C with an applied field of 10 kV/mm for 10 minutes. The paste prepared for the traditional screen-printing can be used for pad printing as well; however, after some modification of the rheological properties.

The proper material for wide-band, thick film, flat and concave transducers, was developed by Insensor® - Meggitt (Copenhagen, Denmark). The technology based on screen or pad printing process offers not only the flexibility of defining the thickness (i.e., resonant frequency) of the transducers through printing the specified number of film layers; but also the option of readily selecting the shape of the transducer, and semi-assembling of the final device, since the film can be deposited on the appropriate substrate, e.g., of porous ceramic with well defined acoustic properties acting as backing for the transducer. Last, but not least, the printing process offers the possibility to deposit the piezoceramic film on a focusing substrate. The piezoceramic film will follow the curvature of the backing, forming an active layer of well-defined, and uniform, thickness. The top and bottom electrodes are deposited as a part of the printing process, and provided with leads for electrical connections. The typical pulse shape and frequency spectrum of a high frequency thick film transducer is shown in Fig.3.

Piezoceramic thick films have a relatively low acoustic impedance of approx. 18 MRayls, and the acoustic properties of the substrate/backing material have been optimized to match it.

4. Methods and results

Eighteen healthy young volunteers (25-37 years), gave their written informed consent to participate, and underwent simultaneous testing with radial artery ultrasound imaging. The study protocol was approved by the Human Investigation Review Committee at the Military Medical Institute. Subjects were instructed to fast, starting the night before testing, and to refrain from ingesting alcohol or caffeine, and taking any vasoactive medications on the day, and the day before, of testing. Each patient was placed in a supine position for 10 min of rest in a quiet setting before the measurement. The transducer was placed in parallel to the radial artery, and the end-diastolic internal diameter was measured. The transducer location was marked, and all subsequent images were obtained at the same location.

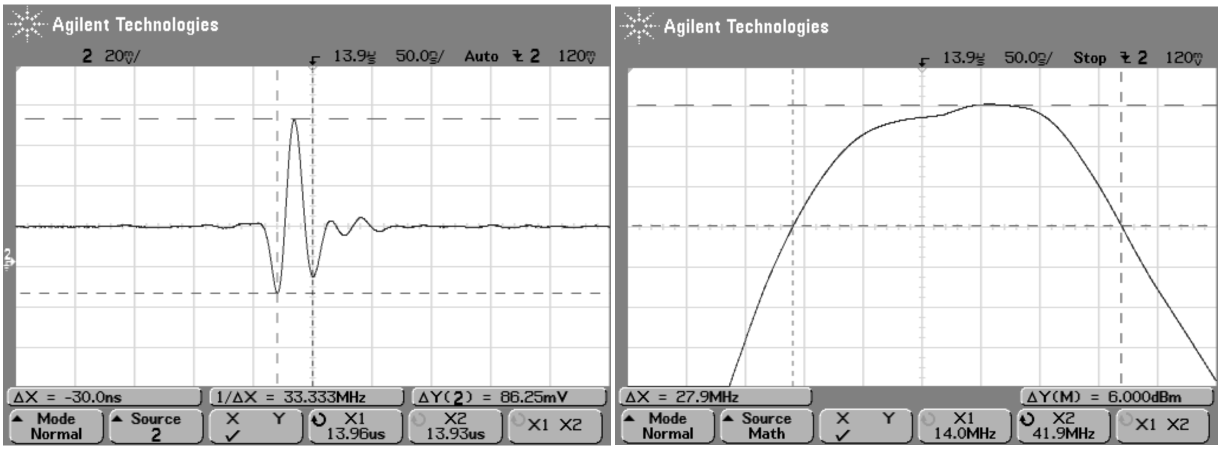

Fig. 3. FFT spectrum of the ultrasonic echoes for the thick film transducer; central frequency close to 27 MHz, bandwidth= 27.5 MHz.

The longitudinal scan of the radial artery of a 36-year-old volunteer is shown in Fig.4. In vivo and in vitro examinations were performed using a high frequency ultrasound scanner uScan developed at IPPT PAN [6]. The device operates with a single element mechanically wobbling thick film transducer at the frequency 25-35 MHz. The hyperemic stimulus was induced, placing the sphygmomanometer cuff at the level of the right midforearm arm, and the cuff inflated to about 50 mmHg above the maximal systolic blood pressure, for five minutes, and then was suddenly deflated. The diameter of the maximal radial artery was determined from ten recordings taken every minute after the cuff release. Restoration of blood flow in the artery strongly promoted the release of nitric oxide NO.

Radial artery reactivity was determined by recording diameter changes in the radial artery in response to increased blood flow generated during reactive hyperemia. The baseline and peak value diameters acquired during ischemia-induced hyperemia were used for the evaluation of the percentage FMD using the formula:

$$FMD\,[\%] = \frac{peak\ diameter - the\ baseline\ diameter}{baseline\ diameter} \tag{1}$$

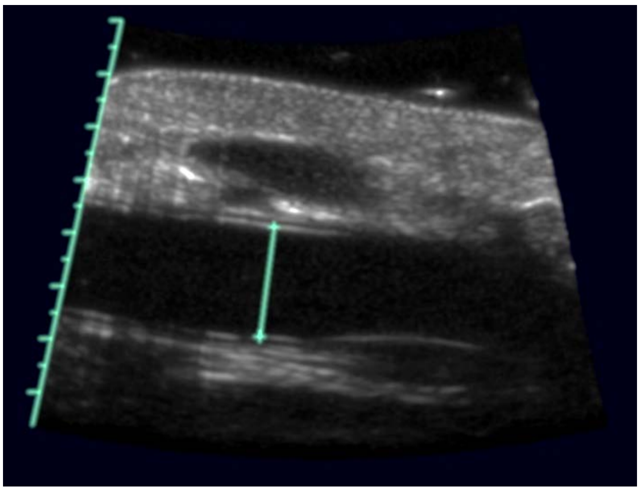

Fig. 4. Longitudinal scan of the radial artery, systolic diameter= 2 mm.

The measured initial internal radial artery diameter was in the range of 1.59-2.25 mm; the maximum diameter 2.01-2.60 mm was observed 40-75 seconds after tourniquet deflation. The results of FMD estimation are shown in Fig.5.

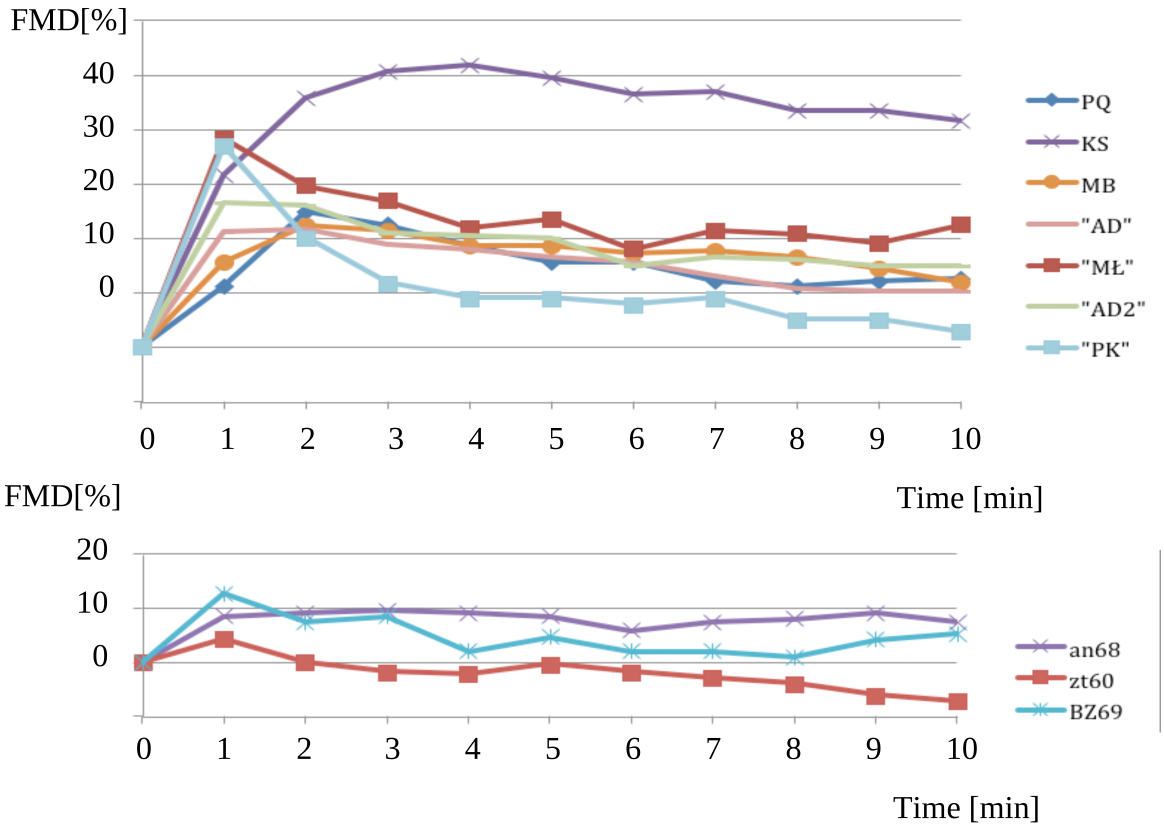

Fig. 5. FMD in healthy volunteers (upper plot), and with minor cardiac incidents (lower plot).

In the second part of the experiment, the preliminary examinations of the radial artery FMD were done in the experimental setup consisting of a 20MHz Ultrasonix scanner combined with a 20MHz pulse wave (PW) Doppler.

After fixing the probe over the radial artery in the wrist, both the clear longitudinal artery scan, and the Doppler signal from the sample volume (SV) position in the center of the artery, were recorded. The systolic vessel diameter, and blood flow velocity, were recorded for 3 to 10 cardiac cycles before cuff inflation. Next, the temporary, 5 min occlusion was introduced, creating the ischemic process distal to the cuff. During this time, the arm was immobilized, and sometimes a slight correction of the robe was done for imaging and insonation angle. 5 sec before releasing the cuff the Doppler recording and storing of the vessel scans, with FR=25 or 50, was turned on for about 2 min. Both recordings were post-processed in order to find the peek systolic vessel diameter (usually between 40 and 55 sec after cuff release).

The shear rate SR is calculated according to the formula,

$$SR = \frac{2V_{avg}\left(n+2\right)}{D} = \frac{V_{\max}\left(n+2\right)}{D} \tag{2}$$

where V_{avg} and V_{max} are average and maximum blood flow velocities, respectively. D is an average artery diameter, and n depends on the velocity profile (n=2 for parabolic profile, and increases when the velocity profile is flattening).

The shear rate is calculated as follows. First, the velocity profile across the vessel is measured, and in PW Doppler the following rule should be used: if the Doppler gate (sample volume) is small, and positioned along the center of the vessel, then rather the maximum velocity V_{max} is measured. For a wide Doppler gate, spanning from anterior to posterior intima covering the entire lumen of the vessel, then the V_{avg} should be used. For a parabolic profile, n=2 and $SR = 8V_{avg}/D = 4V_{max}/D$.

Next, the area under the shear rate SR (from the moment of the cuff release, up to the time of maximum vessel dilation was determined) and the normalized FMD_{SR} was calculated.

The normalization of FMD to shear rate was done by dividing the FMD by the accumulated shear rate SR_{AUC}.

$$FMD_{SR} = \frac{FMD}{SR_{AUC}} \tag{3}$$

In a limited number (18), of the examined young healthy patients, the FMD_{SR} were in the range from 7.77 to 9.89 in arbitrary units.

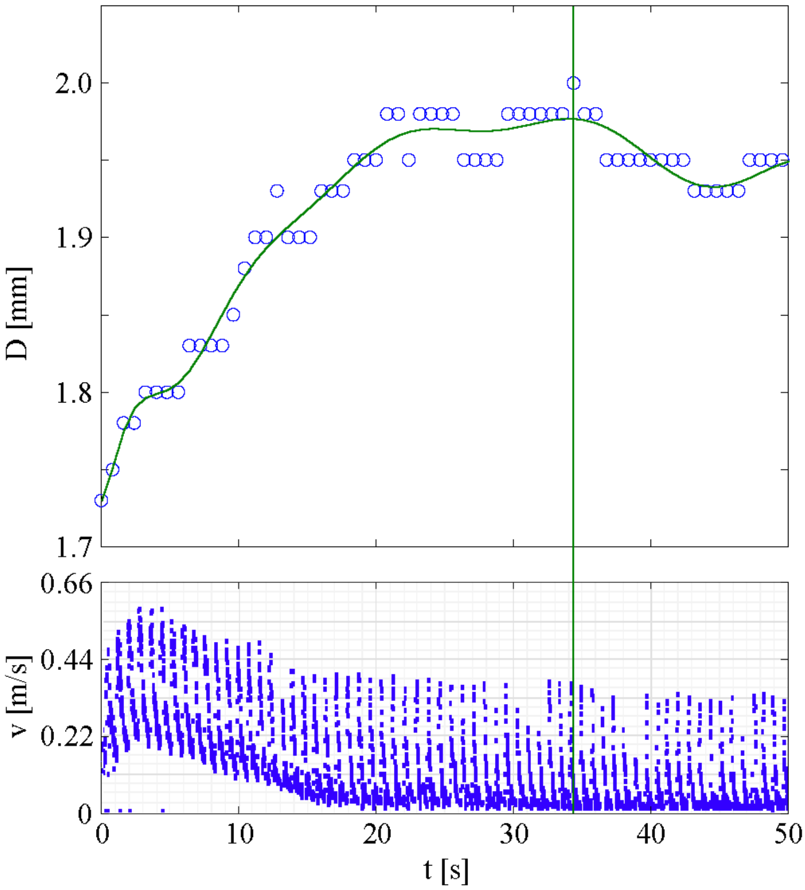

Fig. 6. 50 sec of Doppler flow/shear rate recording. SR_{AUC} calculated from cuff release time till peak dilation.

5. Conclusions

In the pilot study of the FMD of the radial artery, we have demonstrated that using high frequency (>20 MHz) scanning and Doppler ultrasound allowed us to precisely register both; the blood flow, and the dilation of the radial artery. Two instrumentation setups were used in this pilot study: a 30 MHz Golay encoded mechanical wobbling μScan, and a 20MHz linear array US combined with a 20MHz pulsed Doppler. The FMD results obtained using μScan revealed that the FMD in healthy volunteers was changing from 20 to 40 %, while in four volunteers after cardiac incidents, these changes did not exceed 10 %. In the second part of this study, the normalization of FMD by dividing the percentage of FMD by the accumulated shear rate SR was performed. The FMD alone showed similar results to those recorded with μScan. The Doppler recording was done according to the guidelines proposed by Harris et al. [4,5]. The high frequency Doppler probe allowed tracking the flow after cuff release with (by far) better sensitivity then the Doppler flow recorded using a linear array transducer.

Only 18 healthy subjects, and 3 patients with minor cardiac diseases, were examined; and drawing a conclusion from limited material is rather delicate. Our experience is, however, encouraging. The measuring method seems to be robust. Measurements repeated four times on several volunteers gave results that did not differ by more than 11%.

Normalized FMD of radial artery reactive hyperemia response can be an alternative to the brachial FMD, where the precision of measurements is lower, and the diameter dilation does not exceed 7-10%. The shear rate normalized FMD_{SR} was in the range from 7.77 to 9.89 in arbitrary units.

The normalized FMD_{SR} of the radial artery can be an alternative to the brachial FMD, where the precision of measurements is lower, and the diameter dilation does not exceed 7-10%.

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