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# Ultrasonically assisted evaluation of the impact of atherosclerotic plaque on the pulse pressure wave propagation: A clinical feasibility study

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ABSTRACT

The purpose of this work was to evaluate ultrasound modality as a non-invasive tool for determination of impact of the degree of the atherosclerotic plaque located in human internal carotid arteries on the values of the parameters of the pulse wave. Specifically, the applicability of the method to such arteries as brachial, common, and internal carotid was examined. The method developed is based on analysis of two characteristic parameters: the value of the mean reflection coefficient modulus $|\Gamma|_a$ of the blood pressure wave and time delay $\Delta t$ between the forward (travelling) and backward (reflected) blood pressure waves. The blood pressure wave was determined from ultrasound measurements of the artery's inner (internal) diameter, using the custom made wall tracking system (WTS) operating at 6.75 MHz. Clinical data were obtained from the carotid arteries measurements of 70 human subjects. These included the control group of 30 healthy individuals along with the patients diagnosed with the stenosis of the internal carotid artery (ICA) ranging from 20% to 99% or with the ICA occlusion. The results indicate that with increasing level of stenosis of the ICA the value of the mean reflection coefficient measured in the common carotid artery, significantly increases from $|\Gamma|_a = 0.45$ for healthy individuals to $|\Gamma|_a = 0.61$ for patients with stenosis level of 90–99%, or ICA occlusion. Similarly, the time delay $\Delta t$ decreases from 52 ms to 25 ms for the respective groups. The method described holds promise that it might be clinically useful as a non-invasive tool for localization of distal severe artery narrowing, which can assist in identifying early stages of atherosclerosis especially in regions, which are inaccessible for the ultrasound probe (e.g. carotid sinus or middle cerebral artery).



## 1. Introduction

The purpose of this work was to evaluate ultrasound modality as a non-invasive tool for determination of impact of the degree of the atherosclerosis located in human internal carotid arteries on the values of the parameters of the pulse waves. Specifically the applicability of the method to such arteries as brachial-, common- and internal carotid was examined. The diagnosis method developed involves determination of the value of the mean reflection coefficient modulus $|\Gamma|_a$ and identification of the pulse waves components with their subsequent decomposition into the forward (travelling) and backward (reflected) blood pressure waves. Below, a brief review of the literature relevant to this work is given and with this background the organization of the paper is presented.

The decomposition of pulse waves into travelling and reflected components was proposed by several research teams [1–10], however, the analysis adopted here was based on the approach developed in [1,2] and later extended as described in [11,12]. Capitalizing on the earlier results published in [2], where it was pointed out that the decomposition requires the local blood pressure, blood flow and characteristic impedance of the artery considered to be known, the authors of [1] developed a model using electro-mechanical analogies. More specifically, the model described the artery as a transmission line, where the blood pressure and blood flow were represented by the electric potential (or voltage) and current, respectively. Further, the model accounted for the frequency dependent attenuation of the propagating and reflected waves and allowed characteristic impedance of the artery to be determined. The aspect of novelty of the work presented here includes the fact that the approach presented uses the non-linear relationship between the blood pressure and the artery diameter. This is in contrast to the analysis proposed in [9], where the linear relationship alone was considered.

This paper is organized as follows. In Section 2 the basic parameters related to wave reflection and vascular characteristic impedance are introduced. These parameters are discussed as they were used in the development of the brachial artery experiment

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employed here to predict the separation of the wave components. In Section 3 the conceptually predicted results are compared with those obtained from *in vivo* measurements of five groups of patients with different levels of stenosis. The fundamental limitations of the approach proposed are examined in Section 4 and it is concluded that within certain limitations, the method developed has a potential to provide a quantitative information that could enhance the diagnostic power when determining the atherosclerotic lesions in human arteries.

## 2. Reflection model and methods

In this section, the analytical expressions for reflection coefficient, frequency dependent artery's impedance, pulse wave velocity, and the relationship between the vessel diameter and systolic and diastolic pressures are defined. These expressions are semi-empirical and were derived based on the results of the non-invasive *in vivo* experiments in human arteries.

To gain a better insight into the analysis presented it is useful to note that during each heart contraction a volume of blood is travelling from the left ventricle to the aorta and through the arterial tree to the small peripheral arterioles creating blood waves and introducing local changes in the blood pressure. As mentioned earlier the assumption that the electric transmission line can be used as an adequate artery model was originally proposed in [2], where it was observed that the arterial tree allows a number of points where from the pressure wave is partially reflected to be identified. Such points or sources of the wave reflection are due to the impedance mismatch at each bifurcation (see Eq. (2)) because each branch of an artery has its individual characteristic impedance. The sources are also formed by the atherosclerotic stenosis (plaques) deposited in the arteries. The vascular tree model was further examined in [13] where it was shown that the total blood pressure wave $P$ measured at any point of the tree consists of the forward (travelling) wave $P_f$ and the backward (reflected) wave $P_r$ and can be expressed as:

$$P = P_f + P_r = P_f(1 + \Gamma), \tag{1}$$

where $\Gamma$ is the complex reflection coefficient.

The coefficient $\Gamma$ describes the relation between the reflected and travelling wave at the specific location where the measurement is performed. The value of this coefficient is calculated from the vascular input impedance $Z$ and the vascular characteristic impedance $Z_o$ according to the formula [3]:

$$\Gamma = \frac{P_r}{P_f} = \frac{Z - Z_o}{Z + Z_o}. \tag{2}$$

The impedances $Z$ and $Z_o$ are measured in the frequency domain and defined [3] as:

$$Z = \frac{P}{Q}, \quad Z_o = \frac{P_f}{Q_f} = -\frac{P_r}{Q_r}, \tag{3}$$

where $Q$, $Q_f$, $Q_r$ describe the total, forward (travelling) and backward (reflected), blood flow waves, respectively.

As already noted, the aim of the present study was to examine whether the diagnosis of stenosis or occlusion can be refined or aided by using non-invasive ultrasound modality. This required an assessment of the dependence of the artery stenosis on the mean reflection coefficient (see, Eq. (4)) and the time delay $\Delta t$ between the backward (reflected) and forward (travelling) pulse waves. The time delay $\Delta t$ was determined here by the widely accepted "zero-crossing" method [14] after the systemic mean blood pressure value was eliminated. Mean pressure is calculated as an integral over the heart cycle of the total pressure time wave.

The mean reflection coefficient modulus $|\Gamma|_a$ was calculated from the values of the moduli $|P_f|$ and $|P_r|$, which were determined for the first 10 harmonics of the heartbeat according to following expression:

$$|\Gamma|_a = \sum_{n=1}^{10} |P_{rn}| \Big/ \sum_{n=1}^{10} |P_{fn}|. \tag{4}$$

The inclusion of 10 harmonics was considered adequate as they contain over 90% of the energy of the propagating pulse wave.

The relationship between the blood pressure $P$ and the square value of artery diameter $D$ was determined using the expression derived in [11] and later corroborated in [12,15–16]:

$$P(t) = P_d \exp\left[\frac{D^2(t) - D^2_{\min}(t)}{D^2_{\max} - D^2_{\min}} \ln\left(\frac{P_{\text{sys}}}{P_d}\right)\right], \tag{5}$$

where $D_{\min}$ and $D_{\max}$ are the minimum and maximum diameters for the diastolic $P_d$ and systolic $P_{\text{sys}}$ pressure, respectively.

According to Eqs. (3) and (5), the vascular input impedance $Z$ in arteries can be calculated from the simultaneous measurements of the blood flow and the vessel diameter and the measurements of maximum and minimum values of blood pressure.

As indicated is Eq. (3), in addition to vascular input impedance $Z$, the knowledge of characteristic impedance $Z_o$ is also of importance. Whereas this impedance can be determined in several ways, in this work the method proposed in [17] was selected:

$$Z_o = \frac{\rho\, c_o}{\pi R^2 \sqrt{1 - \sigma^2}\sqrt{M'_{10}}} e^{-i\frac{\varepsilon_{10}}{2}}, \tag{6}$$

where $\rho$ is the blood density, $R$ is the vessel radius, $\sigma$ is the Poisson constant, $i$ is an imaginary number, $M'_{10}$ and $\varepsilon_{10}$ are tabulated values [17], which are functions of the vessel radius, blood viscosity and harmonic frequencies of the pressure wave; $c_o$ is the propagation pressure pulse wave velocity (PWV) in the vessel.

Eq. (6) was chosen because it adequately describes the arterial conditions, both *in vitro* (using a freely suspended elastic tube) and *in vivo*. The procedure leading to the derivation of Eq. (6) employed linearized Navier–Stokes equations for calculation of the pulsatile viscous blood flow. For the typical hematocrit of 45% and for the values of blood pressure varying between 80 mm Hg and 120 mm Hg, in the artery such as CCA considered in this work, the value of the blood viscosity coefficient $\eta$ ranges from $4 \times 10^{-3}$ to $5 \times 10^{-3}$ Pa s [18]. The visco-elastic material of the arterial wall was described by Womersley [17] in terms of the complex Young's modulus $E' = E(1 + i\omega\Delta E)$, and complex Poisson's coefficient $\sigma' = \sigma(1 + i\omega\Delta\sigma)$; where $\omega$ is angular frequency of the heart bit. $E$ [Pa] and $\sigma$ are static values while $\Delta E$ [Pa] and $\Delta\sigma$ are dynamic values of the Young's modulus and Poison's coefficient, respectively. Values of $\Delta E$ and $\Delta\sigma$ are proportional to the viscosity of the material of the arterial wall (for the CCA typical values are: $\sigma = 0.5$ for $|\omega\Delta\sigma| = 0.053 \cdot \sigma$, and $E = 0.1$–$1 \times 10^6$ Pa for $|\omega\Delta E| = 0.005$–$0.1 \cdot |E|$). According to the Womersley's theory, $\Delta E$ and $\Delta\sigma$ decrease with heart bit frequency.

In Eq. (6) the $c_o$ that is the propagation pressure pulse wave velocity (PWV) in the vessel can also be determined in several ways [19–20]. Here, the Moens–Korteweg equation presented in [21] and modified by Bramwell and Hill in [22] was employed:

$$c_o \cong \sqrt{\frac{\Delta P D^2_{\min}}{\rho\,(D^2_{\max} - D^2_{\min})}}, \tag{7}$$

where $\Delta P$ is the blood pressure change corresponding to the change in the vessel diameter from $D_{\min}$ to $D_{\max}$. Eq. (7) is widely accepted because it provides the results very close to those obtained from

Moens–Korteweg's original formulation and allows the data to be determined in the non-invasive way.

### 2.1. In vivo studies

The method proposed here was tested on 70 patients, who were divided into five groups (referred in the following to as A–E – see Table 1). Each of the groups represented different gender and different levels of the ICA stenosis. The level of stenosis was measured following the method proposed in [23]. The measurement was performed using a noninvasive ultrasound scanner ECCOCEE (Toshiba Inc., Japan), operating in B-mode and using 7.5 MHz linear array probe. The penetration depth was close to 8 cm. The axial and lateral resolution were equal to 0.25 mm and 0.7 mm, respectively. The maximum percentage level of stenosis was computed by subtracting the values of residual lumen and the original diameter and dividing the difference by the original diameter. To minimize the overall error (see Section 4) this was performed by the same operator using the same ultrasound scanner at the site where the maximum stenosis was located.

In the next section the clinical data are presented.

## 3. Results of clinical examinations

All clinical studies were performed at the Department of the General and Thoracic Surgery of the Warsaw Medical University. All patients consented to the study according to the protocol approved by the University's Ethic Commission (Internal Review Board – IRB).

The studies were performed using two easily accessible vessels: the human brachial (BA) and common carotid arteries (CCAs). Prior to the clinical studies the preliminary testing of the concept of the proposed method was performed using the brachial artery of a healthy volunteer. As already noted the brachial artery was selected because it is easily accessible for ultrasound imaging and relatively long. It is also characterized by virtually stable (or laminar) blood flow without any turbulence. In addition, it allows unobstructed access to perform the blood pressure measurement using a sphygmomanometer and facilitates stenosis simulation. The simulation is readily implemented by the attending clinician by simply exerting digital force on the artery, in order to cause the flow occlusion or impede the flow. The carotid artery was selected because it is the one that is routinely examined during the pre-stroke diagnosis of the atherosclerotic stenosis.

The instantaneous value of the artery diameter (Eq. (5)) was measured non-invasively by laboratory designed pulse-echo, A-mode ultrasound digital wall tracking system (WTS) [12]. The system is an intrinsic part of the ultrasound Vascular Echo Doppler (VED) device comprising CW Doppler blood velocity meter with the two-channel 128 points FFT color spectrum density analyser [12]. The ultrasonic Doppler and pulse beam axes were fixed at the angle of 30°. The choice of the CW Doppler flow meter and its frequency 4.5 MHz and pulse-echo transducer frequency operation 6.75 MHz complied with the criteria and guidelines, developed in [24]. The precision of the WTS measurement of the vessel wall displacements was determined by the ½ cycle of the hardware clock operating at 54 MHz, and was better than 7 μm. The axial resolution of the vascular diameter measurements was tested on two thin (0.1 mm) parallel mounted transparent films immersed in the water tank, and determined to be less than 0.33 mm. The corresponding lateral resolution was approximately 0.8 mm. These resolutions were considered to be sufficient for the measurements described in the following.

The blood pressure diastolic $P_d$ and systolic $P_{sys}$ values were measured by the sphygmomanometer HPM-100-FIFO (TEMED Inc., Poland).

Fig. 1 shows the results obtained using the Vascular Echo Doppler device and displayed on its screen. Fig. 1a represents the echoes from the walls of the CCA measured by A-mode, 6.75 MHz ultrasound. Fig. 1b displays the internal diameter variations of the examined artery during heart cycles while the corresponding Doppler density spectrum of the blood velocity in the artery is depicted in Fig. 1c.

The total blood flow waves $Q$ (Eq. (3)) were calculated as a product of the measured blood velocity and the inner cross-section of the artery at the measurement instant. Further, it was assumed that the artery cross-section was circular as the pressure on the artery due to the application of the ultrasound probe during the examination was negligible.

It is commonly accepted that for a human in supine position the blood pressure in the CCA is virtually identical to the blood pressure in the brachial artery (BA). The possible differences between the arm and carotid pressures could be of concern only if the pulse pressure ratio were varying between 0.4 and 1.6 for individuals of age between 20 and 70 years [25].

To obtain the trace of the blood pressure in the CCA, the values of diastolic $P_d$ and systolic $P_{sys}$ blood pressure are needed (see Eq. (5)). These were taken from the blood pressure sphygmomanometer measurements during which a pressure cuff was positioned on the arm. The values of the forward (travelling) and backward (reflected) blood pressure waves in the CCA were determined using the characteristic impedance calculated from Eq. (6).

To demonstrate the influence of the arterial stenosis on the pulse wave parameters, the preliminary validation of the method proposed was experimentally performed on 22 years old healthy male volunteer. The test object was asked to rest for 15 min in supine position to ensure stabilization of both the respiratory process and of the heart rate.

The initial test included measurements of the blood pressure and pulse wave under two different conditions as described below

**Table 1**
Parameters determined in groups of healthy and ill individuals.

| Examined group | (A) Control | (B) ICA stenosis 20–49% | (C) ICA stenosis 50–69% | (D) ICA stenosis 70–89% | (E) ICA stenosis 90–99% or occlusion |
|---|---|---|---|---|---|
| Number of cases | 30 | 10 | 10 | 10 | 10 |
| Age (years) | 48 ± 14 | 68 ± 7 | 66 ± 5 | 65 ± 9 | 71 ± 10 |
| $P_{sys}$ (mm Hg) | 120 ± 11 | 138 ± 19 | 153 ± 21 | 141 + 15 | 156 ± 22 |
| $P_d$ (mm Hg) | 74 ± 9 | 80 ± 14 | 84 ± 13 | 80 ± 11 | 86 ± 9 |
| $D_{min}$ (mm) | 7.2 ± 1.1 | 7.8 ± 0.9 | 7.7 ± 1.1 | 7.8 ± 1.1 | 8.0 ± 1.3 |
| $Q_{med}$ (dm$^3$/min) | 0.61 ± 0.11 | 0.53 ± 0.16 | 0.47 ± 0.13 | 0.4 ± 0.13 | 0.32 ± 0.13 |
| $c_o$ (m/s) | 6.8 ± 1.5 | 8.5 ± 1.3 | 9.2 ± 2.0 | 9.4 ± 1.3 | 8.9 ± 2.9 |
| $\|\Gamma\|_a$ | 0.45 ± 0.05 | 0.5 ± 0.06 | 0.55 ± 0.06 | 0.56 ± 0.13 | 0.61 ± 0.14 |
| $\Delta t$ (ms) | 52.5 ± 13 | 45.2 ± 11 | 33.2–11 | 33.7 ± 14 | 25.3 ± 15 |

ICA – is the internal carotid artery, $P_{sys}$, $P_d$ – are the systolic and diastolic blood pressures in the brachial artery, respectively. $D_{min}$ – is the minimum diameter of the common carotid artery (CCA), $Q_{med}$ – is the mean value of blood flow rate in CCA, $c_o$ – is the pressure pulse wave velocity (Eq. (7)), $|\Gamma|_a$ – is the mean value of the reflection coefficient modulus, $\Delta t$ – is the time delay between backward and forward traveling pressure waves. Note that all patients in groups C–E suffer from hypertension (see Section 4).

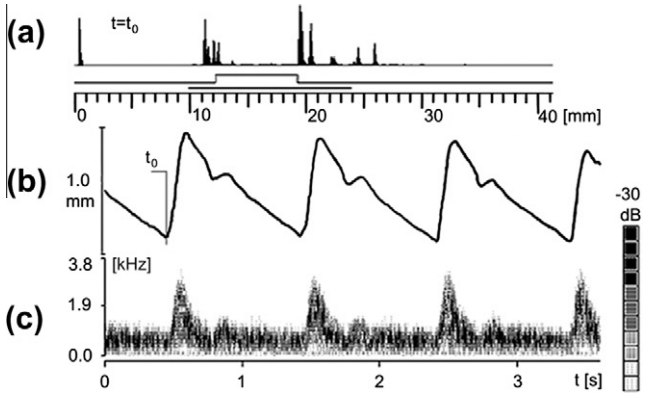


**Fig. 1.** An example of the data displayed on the Vascular Echo Doppler (VED) system during the measurements in the human common carotid artery (CCA): (a) echoes from the wall of the artery ($t_o$ – time of registering the echoes), (b) artery diameter variations, (c) blood velocity in the CCA (Doppler spectrum) (see text for more detailed description).

and carried out at the site located in the middle of the left arm at the distance of 56 cm from the fingertips (see Fig. 2). This location was chosen because there the diameter of the BA is relatively large (over 4 mm). At this very site the blood pressure was determined using the pressure cuff, the pulse wave was determined using the ultrasound VED system. Specifically, two measurements were carried out: one without exerting any external pressure on the BA, and the second one with the BA being slightly compressed with the help of the rubber band; The rubber band was applied on the forearm (slightly below the elbow joint) at the distance of approximately 12 cm below the first measurement site, i.e. below the VED's ultrasound measurements site.

Both sites were chosen for the easiness of mimicking stenosis via blood vessel narrowing using simple compression. As indicated above, the time delay $\Delta t$ between forward (travelling) and backward (reflected) pulse waves was determined by the zero-crossing method [14]. When the BA was compressed, the blood velocity spectrum density (visualized on the VED display) was decreased and the associated blood flow was reduced by about 60%. The corresponding time delay $\Delta t$ decreased from 132 ms to 35 ms, whereas the mean value of the reflection coefficient $|\Gamma|_a$ increased from 0.4398 to 0.7983 (see Fig. 2). In Fig. 3 all three traces of the pressure waves, namely the total one $P$, forward (travelling) $P_f$ and backward (reflected) $P_r$ as determined from the BA measurements are shown. Fig. 3a shows the trace measured in the unobstructed artery. In Fig. 3b the result corresponding to the artery depressed to mimic stenosis at a distance of 12 cm below the measurement point is shown; here, $P_s$ represents the mean pressure. It

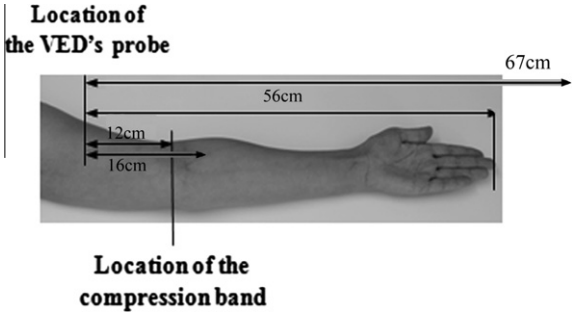


**Fig. 2.** Schematically shown positioning of the Vascular Echo Doppler probe and the compression band used during healthy volunteer verification of the method described here. The band was used to mimic stenosis of the brachial artery (see text for more detailed description).

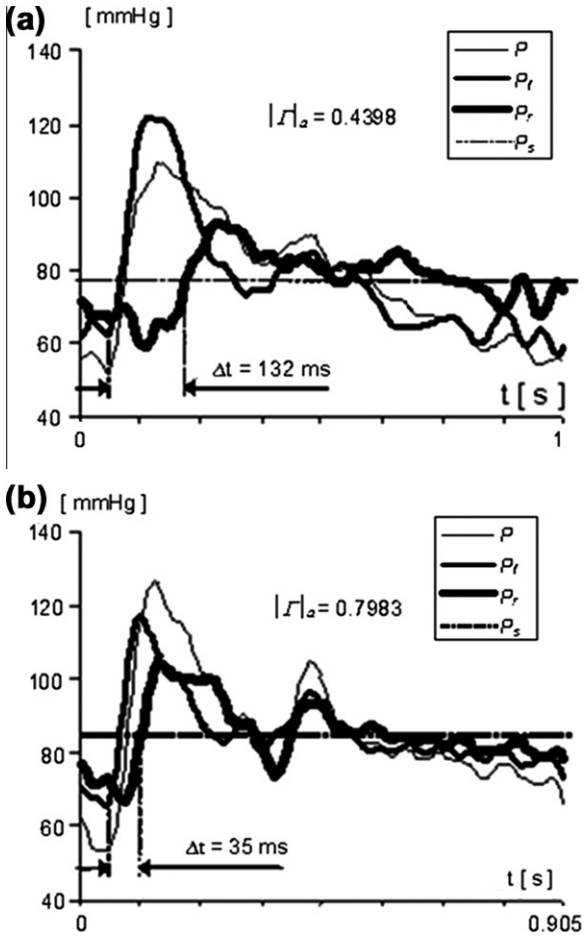


**Fig. 3.** An example of pulse waves obtained during the examination of 22 year old healthy male: total $P$, forward $P_f$ and reflected $P_r$ determined from brachial artery measurements: (a) measured in the unobstructed artery and (b) measured with the pressed artery at a distance of 12 cm below the measurement point; $P_s$ is the mean pressure (see text for more detailed description).

is worthwhile to note that after the BA was externally occluded the amplitude of the total pressure wave $P$ increased from 114 to 127 mm Hg, while the value of the mean pressure $P_s$ increased from 77 to 84 mm Hg. The exact location (see Fig. 2) of the hypothetical main reflection point (where the rubber band was applied, i.e. 12 cm below the 1st measurement site) was calculated on the base on the pulse wave velocity $c_o$ (Eq. (7)) as half value of the product of $c_o$ and $\Delta t$. This calculation revealed that the "effective" main reflection point distance was 67 cm instead 56 cm. Similarly, the calculated position of the rubber band induced stenosis was determined to be 16 cm that is 4 cm further down towards the palm. This indicates that Eq. (2) used to calculate pulse wave velocity $c_o$ (10.2 m/s for not clamped artery and 9.5 m/s for rubber band compressed artery) does not account for the complexity of the distal blood vessel tree architecture.

The above discussed significant changes of the reflection coefficient $|\Gamma|_a$, the time delay $\Delta t$ between forward (travelling) and backward (reflected) pulse waves, and the artificially induced (using the rubber band) stenosis location, suggested that an appropriate correlation of these parameters will allow to evaluate the true distance from measurement point to the stenosis and the degree of the stenosis of the examined artery. This result encouraged the subsequent clinical trial performed on 70 patients (see Table 1). All seventy patients were examined in the supine position after resting for 15 min. The systolic and diastolic blood pressures were measured just before and just after the ultrasound examinations

using the VED system were carried out. The mean values of the measured blood pressures were taken into account to perform the required – Eqs. (5) and (7)'s – calculations. The VED ultrasound probe was placed on the common carotid artery (CCA) at a distance of 3 cm below the bifurcation and at this specific location in none of the patients examined any stenotic plaques were detected, i.e. no changes in the arteries were observed. The distance of 3 cm was chosen for two reasons. Firstly, it allowed the values of the time delay $\Delta t$ associated with the possible sources of stenosis existing in the ICA in the immediate vicinity of the CCA bifurcation to be determined. Secondly, it permitted to ensure virtually turbulence free flow conditions. The free flow condition exists because this distance is located about 10 (or more) cm from an arch of the aorta from which the CCA branches.

The A group (the control cohort of 30, see Table 1) did not show any pathological changes in the arteries. The groups B, C, D and E (each representing 10 individuals) included patients with atherosclerotic changes found unilaterally that is in one branch of the internal carotid artery (ICA). It is here appropriate to note that each human has two – left and right – carotid arteries and the term unilaterally indicates here that the stenosis was located only at either left or right internal carotid artery (ICA) and ranged from 20% stenosis level to the total occlusion located just behind the CCA bifurcation (Table 1).

In Fig. 4 the results for 68 year old healthy male and 78 year old female patient with 60% stenosis in the ICA are summarized.

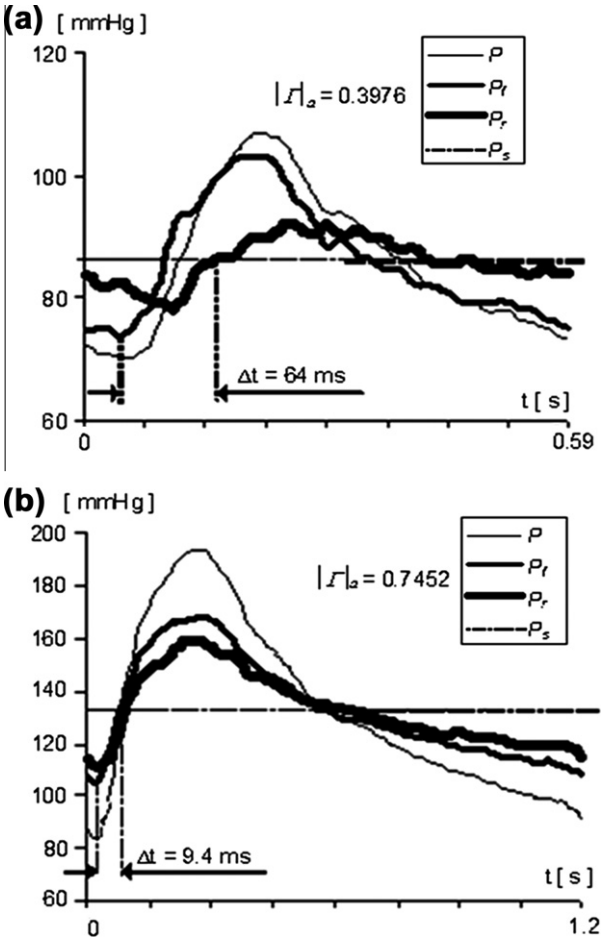


**Fig. 4.** Pulse waves recorded during the examination of the CCA: (a) measured in 68 year old healthy male without atherosclerotic lesions in carotid arteries and (b) measured in 78 year old female patient with 60% stenosis in the ICA; total wave $P$, forward $P_f$ and reflected $P_r$, $P_s$ is the mean pressure (see text for more detailed description).

Similarly to the plots depicted in Fig. 3 the three traces of pressure waves are shown: the total one, the forward one, the reflected one and the mean one, denoted as $P$, $P_f$, $P_r$ and $P_s$, respectively.

As shown in Fig. 4, the mean reflection coefficient $|\Gamma|_a$ of Eq. (4) was 87% higher and the time delay $\Delta t$ between forward $P_f$ and backward $P_r$ pressure waves was 6.8 times shorter for the stenosis diagnosed individual than for a healthy one.

The clinical results of ultrasonic evaluation of $|\Gamma|_a$ – the mean reflection coefficient modulus of the pulse pressure waves and the time delay $\Delta t$ – between forward (travelling) $P_f$ and backward (reflected) $P_r$ pressure waves for A, B, C, D and E groups are also presented in Fig. 5, where $p$ is the statistically significant level in the non-parametric Mann–Whitney U test.

The results corresponding to each group are presented as mean ± standard deviation; the value of $p < 0.05$ was considered to be statistically significant. The statistical analysis using non-parametric Mann–Whitney U test – *Statistica* program ver. 8 (StatSoft Inc., USA) was selected because the random variables considered did not exhibit normal distribution.

Table 1 lists additional data recorded for each of the five groups of the examined patients. The control group A consisted of patients aged between 26 and 79. The age of the patients groups B, C, D, and E was between 52 and 86. The mean values of the systolic and diastolic pressures were ranging from 120/74 mm Hg for control group A to 156/86 mm Hg for patients of group E. The minimum inside diameter $D_{min}$ of the CCA was 7.2 mm for the control group A and ranged from 7.7 to 8 mm for B–E groups. This slight growth of the diameter of the CCA was found to correlate with the mean age of particular groups of patients and similar result was reported in [16]. The mean values of the blood flow $Q_{med}$ decreased with the arterial stenosis from 0.61 for the control group A to 0.32 dm$^3$/min for patients with the critical stenosis level of the ICA, (group E). The

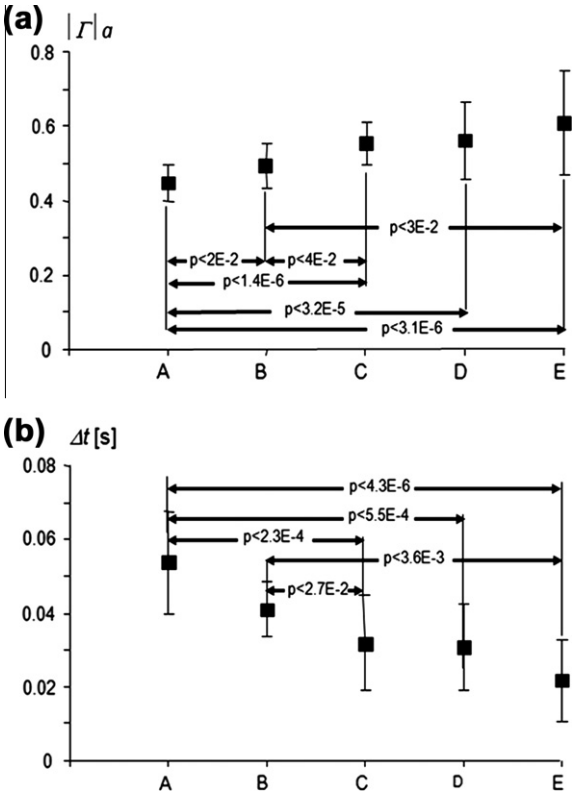


**Fig. 5.** The clinical results of A–E groups (see Table 1): (a) $|\Gamma|_a$ – is the mean reflection coefficient modulus of the pulse pressure waves and (b) $\Delta t$ – is the time delay of the reflected wave, $p$ – is the statistical significant level in the non-parametric Mann–Whitney U test (see text for more detailed description).

mean pulse wave velocity PWV (Eq. (7)) was determined to be equal to 6.8 m/s for the control group A and was found to be considerably lower in comparison with the range of 8.5–9.4 m/s observed in groups B–E.

## 4. Discussion and conclusion

As indicated earlier, for this study the brachial artery was selected initially as it is easily accessible and allows stenosis to be simulated or mimicked by applying external pressure. In the experiments described such artificially induced stenosis reduced the blood flow by about 60% and also reduced the time delay, between forward (travelling) and backward (reflected) pulse waves, from 132 ms to 35 ms. Such behavior is in agreement with the one reported in [26], where transmission line analogy was also used in order to predict the influence of the characteristic impedance of an artery for the backward component of the pulse wave. It should be noted, however, that the measurements described in [26] were obtained in the canine's CCA and were measured in invasive way. In contrast, in the present work all clinical data pertain to human subjects and were acquired noninvasively. It is well known [8], that in the arterial tree there exist many mismatch points (e.g. each bifurcation, stenosis or peripheral resistances) from which the travelling pressure wave can be partially reflected. In the present work the individual reflections were considered as one reflected wave representing the additive combination of all individual waves.

As discussed in the previous section, the results presented in Table 1 and Figs. 4 and 5 indicate, that a vessel stenosis causes a considerable increase in the value of the mean reflection coefficient modulus $|\Gamma|_a$ (from 0.45 to 0.61) and a substantial decrease in time delay $\Delta t$ between the reflected and forward pressure waves (from 52 ms to 25 ms) measured at the point proximal to the locations of the stenosis. It was not possible to discriminate the control group A from the B group (with relatively low – 25–50% – stenosis level of the ICA) unequivocally using the time delay $\Delta t$ only (see Fig. 5).

However, the use of the $|\Gamma|_a$ as a discriminator of the ICA stenosis level aided in classification of the patients in the groups A–C (which exhibited a medium – 50–69% – stenosis level in the ICA). Further, the $|\Gamma|_a$ also allowed discrimination of groups B–E from the control group (A). Based on these outcomes it would appear that, overall, the method is not yet clinically optimized because – as shown in Table 1 – the distinction or differentiation between the patients in groups C–E was not successful.

A comparison of the two statistically significant parameters examined here, i.e. the mean reflection coefficient modulus $|\Gamma|_a$ and the time delay $\Delta t$ suggests that the usefulness of the $|\Gamma|_a$ may be more promising because this parameter was also capable of differentiating the group A from B.

The overall uncertainty of the method described is primarily dependent on the ultrasound measurement errors $E_1$ and $E_2$ and with error $E_3$ which are associated with the two ultrasound techniques – B-mode imaging and wall tracking system (WTS) – used here, and provided by the blood pressure measurement technique, respectively. The error in the level of stenosis determination when using B-mode imaging system was estimated to be $E_1 = \pm 5\%$ [23]. The similar value of $E_2 = \pm 5\%$ error was introduced by the wall tracking system used (see Section 3 and [15]). The error $E_3$ associated with the pressure blood gauge was also ±5% according to the manufacturer's specifications. From these values the standard error *SE* of the method described above was calculated as $SE = \sqrt{E_1^2 + E_2^2 + E_3^2} = 8.66\%$ and, finally, the root mean square error *RMSE* was determined as $RMSE = \frac{SE}{\sqrt{n}} = 5\%$, where $n$ is the total number of contributing error sources (here, 3). Both the *SE* and *RSME* values are acceptable in the clinical practice.

All in all, the results of the ultrasound examinations in the human brachial and the common carotid arteries indicate that the vessel stenosis causes a substantial increase in the mean reflection coefficient and a considerable decrease of the time delay between the forward and reflected pulse waves at the measurement point located in the proximity of the stenosis. This outcome suggests that the statistically significant mean reflection coefficient modulus $|\Gamma|_a$ can be used as a quantitative measure of degree of the atherosclerosis in the ICA. However, as the change in $|\Gamma|_a$ was not sufficient to diagnose the level of atherosclerosis in groups C–E it seems to suggest an existence of an (yet) unidentified masking agent that prevented the correct diagnosis of atherosclerosis in all three of these groups (C–E). It is plausible that this masking agent is hypertension, which was indeed, the case for all patients in groups C–E (see Table 1).

In view of the above discussion, the method described holds promise that it might be clinically useful as a non-invasive tool for localization of distal severe artery narrowing, which can assist in identifying early stages of atherosclerosis, especially in regions, which are inaccessible for the conventional ultrasound probe testing site (e.g. stenosis developing distally from the carotid bifurcation such as stenosis in carotid sinus or middle cerebral artery).

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