Characterization of an Acoustic Based Device for Local Arterial Stiffness Assessment

H.C. Pereira[1,2(✉)], J. Maldonado[3], T. Pereira[4], M. Contente[1], V. Almeida[1], T. Pereira[1], J.B. Simões[1,2], J. Cardoso[1], and C. Correia[1]

[1] Physics Department, Instrumentation Centre (CI-GEI), University of Coimbra, Coimbra, Portugal
{cpereira, vaniagalmeida, taniapereira, cardoso, correia}@lei.fis.uc.pt, m_ines_c@hotmail.com

[2] ISA - Intelligent Sensing Anywhere, Coimbra, Portugal
jbasilio@isa.pt

[3] Instituto de Investigação e Formação Cardiovascular, Aveleira, Penacova, Portugal
instituto@iifc.pt

[4] Escola Superior de Tecnologia da Saúde de Coimbra, S.Martinho do Bispo, Coimbra, Portugal
telmo@estescoimbra.pt

Abstract. Arterial stiffness, recognized as an independent predictor of cardiovascular events, can be assessed non-invasively by regional and local methods. The present work proposes and describes a novel and low-cost device, based on a double-headed acoustic probe (AP), to assess local arterial stiffness, by means of pulse wave velocity (PWV) measurements. Local PWV is measured over the carotid artery and relies on the determination of the time delay between the signals acquired simultaneously by both acoustic sensors, placed at a fixed distance. The AP was characterized with dedicated test setups, in order to evaluate its performance concerning waveform analysis, repeatability, crosstalk effect and time resolution. Results show that AP signals are repeatable and crosstalk effect do not interfere with its time resolution, when the cross-correlation algorithm for time delay estimation is used. The AP's effectiveness in measuring higher PWV (14 m/s), with a relative error less than 5 %, when using two uncoupled APs, was also demonstrated. Finally, its clinical feasibility was investigated, in a set of 17 healthy subjects, in which local PWV and other hemodynamic parameters were measured. Carotid PWV yielded a mean value of 2.96 ± 1.08 m/s that is in agreement with the values obtained in other reference studies.

Keywords: Local pulse wave velocity · Double headed probe · Microphones · Test bench systems · in-Vivo measurements

1 Introduction

Arterial stiffness, which results from the progressive degeneration of the wall's elastic fibres, is a marker of cardiovascular risk that in the last few years has gained great relevance in the medical community due to its predictive value for cardiovascular

M. Fernández-Chimeno et al. (Eds.): BIOSTEC 2013, CCIS 452, pp. 98–114, 2014.
DOI: 10.1007/978-3-662-44485-6_8

mortality and morbidity, target organ damage, coronary events and fatal strokes in patients with different levels of risk [1–4]. The most direct, simple and robust method of assessing arterial stiffness is pulse wave velocity (PWV), i.e. the velocity at which the pressure wave propagates along an artery. Carotid-femoral PWV is considered the 'gold standard' measurement of arterial stiffness, being supported by several clinical studies that highlight the relevant contribution of this parameter to the diagnosis, prognosis and follow-up of the general population/patient [5, 6].

The most prominent commercial devices require moderate technical expertise; however they have several drawbacks in PWV assessment. The practical solution used by these systems relies on the acquisition of pulse waves at the carotid and femoral arteries to determine the time delay measured between pressure upstroke at each site (t). The distance between the two acquisition locations (d) is usually assessed using a measuring tape and then PWV is automatically determined using the linear ratio between d and t [7, 8]. One source of error is related to time delay estimation and the lack of standardization on its determination. There are severable feasible methods to estimate it, however they can't be used interchangeably [9]. On the other hand, this solution not only negligence opposite wave propagation but also presents errors in estimating the distance between the recording locations (for example, the curvature of the arteries cannot be taken into account) [10–12]. Finally, it introduces a rough estimate of local properties of the artery, since it integrates different segments of arterial stiffness (carotid, aorta, iliac, femoral), being unable to differentiate between the muscular and elastic parts.

The possibility of assessing the local hemodynamics is in fact very useful, particularly in the carotid artery due to its predisposition to atherosclerotic plaques formation and its significance in the development of coronary and cerebrovascular diseases [13–16]. Several methods have already been investigated with the intention of evaluating indices of local arterial stiffness, such as distensibility, compliance, elastic modulus and local PWV. Most of them are based on the simultaneous assessment of diameter and pressure waveforms via ultrasound systems, however they present important limitations in what concerns the local pressure assessment that is often taken in a vessel distant (braquial) or at a time distant from where and when diameter waveform is acquired (carotid) [17–20]. To avoid inaccuracies related to local blood pressure measurement, two different approaches were further suggested. The first one proposed by Giannattasio et al. combines ecographic data with the pressure waveform captured using arterial tonometry in the contralateral artery, taking the ECG as reference point [21]. With this approach it is possible to perform a synchronized acquisition of diameter and pressure at similar regions. On the other hand, Hermeling et al. investigated an alternative method to assess local PWV that does not require the measurement of local blood pressure. This technique is based on the calculation of time delay between the several diameter waveforms acquired using piezoelectric elements of an ultrasound probe [22, 23].

In spite of the methodological advances that have been observed in local hemodynamic assessment, the devices available for the measurement of these variables require high technical expertise and also burdensome and specialized imaging technologies (i.e.: ultrasound and echo tracking techniques) limiting their generalized use in clinical practice [16]. These limitations show that the introduction of low-cost, non-invasive and easy accessible devices that identify local changes in arterial wall dynamics and also other hemodynamic parameters would be of great interest, mainly in CVDs surveillance and monitoring.

The present work intends to contribute to the achievement of the previous scenario, presenting and characterizing an efficient and low-priced tool based on a non-invasive device that is placed over the carotid artery and can be easily handled in diagnostic trials by an operator. Based on a previous work, where a double headed piezoelectric probe was designed and characterized in laboratory [24, 25], we developed a simpler and novel system that assesses local arterial stiffness by means of non-invasive PWV measurements and also other hemodynamic parameters, such as left ventricular ejection time (LVET), in a short length of an artery (less than 15 mm). The device is based on a double configuration of two acoustic sensors that are placed at a fixed distance, d, allowing simultaneous acquisition of two (sound) pulse waves. The measurement of time delay between the waves, Δt, allows local PWV to be determined, simply, as:

$$PWV(ms^{-1}) = \frac{d}{\Delta t} \tag{1}$$

2 Materials

2.1 The Double Headed Probe

The developed probe, presented in Fig. 1, consists of two acoustic transducers (Pro-Signal, ABM-712-RC, microphone-solder pad) that are placed approximately 11 mm apart and fixed at the top of a plastic box (Multicomp, 77 mm × 49 mm × 26.6 mm). The transducers, based on 9.7 mm diameter electret condenser microphones with an operating frequency of 100 Hz–10 kHz and noise cancelling directivity, are placed at the minimum separating distance, while avoiding mechanical contact. These elements form an ergonomic configuration that allows a safe and effective way of collecting the pulse wave on the carotid artery for both the patient and the operator.

Fig. 1. Representation of the double headed acoustic probe. M_1 – Microphone 1; M_2 – Microphone 2; c1 - distance between transducers centres: ≈11 mm; d1: microphones diameter: 9.7 mm; h1: sensors external height: 2 mm.

The probe does not include any type of signal conditioning circuit, so the acoustic signals are acquired directly by a Personal Computer (PC) Sound Card. The AP uses parallel audio cable to convey the information obtained directly from the transducers, to the microphone input of the PC Sound Card. In circumstances in which the PC Sound Card does not have stereo input, the probe connects first to an external Sound Card (7.1 Sweex® USB Sound Card, 16-bit, 48 kHz Maximum Sampling Rate, 90 dB Signal to Noise Ratio) that then delivers the collected signals to the PC, via USB. The data acquisitions are displayed in real time, through a dedicated Matlab® Based Graphical User Interface (Cardiocheck GUI) and automatically stored in a non-commercial Microsoft Access® based database (Cardiocheck DB). The data is subsequently processed using different algorithms (detailed in Sect. 3.3) that aim the extraction of several hemodynamic parameters, namely the PWV and the LVET (Fig. 2).

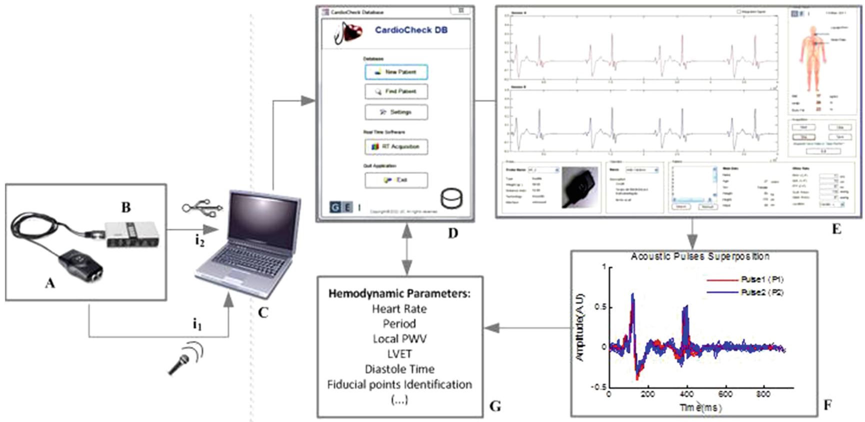

Fig. 2. Schematic representation of the overall system used in in-vivo measurements. A - Acoustic Probe; B - External USB Sound Card; C - PC; D - Cardiocheck Database; E - Cardiocheck Graphical User Interface; F - Data Pre-processing; G - Hemodynamic Parameters Extraction.

2.2 Test Setups

For characterizing the AP, as well as the various parameters extraction algorithms, it was developed two special purpose sets of test bench systems. The test setup I was designed to evaluate the ability of the probe in reproducing repeatedly different types of waveforms but also to evaluate the existence of crosstalk between both transducers. The setup uses a 700 μm stroke actuator, ACT, driven by a high voltage linear amplifier, HVA (Physik Intrumente GmbH P-287 and E-508, respectively) to generate a pressure wave that is fed to the acoustic probe by means of a “mushroom” shaped PVC interface (Fig. 3). This PVC interface (10 mm diameter), coupled to the ACT, is in mechanical contact with the transducer, without affecting the output voltage since the sensors does not respond to DC excitation. With this mechanical adapter it is possible to transmit the ACT’s motion associated to the pressure wave, in such a way that the longitudinal forces are responsible for the transducer electric response. The waveforms are programmed and downloaded into an arbitrary waveform generator, AWG, Agilent 33220A that delivers the signal that is generated by the ACT and also the synchronism that triggers the data acquisition system, DAS (National Instruments®, USB6210). Although the AP is a prototype suitable for clinical tests, designed to be combined with a PC Sound Card, it was necessary to use a different DAS in test bench experiments, in order to acquire additional reference signals.

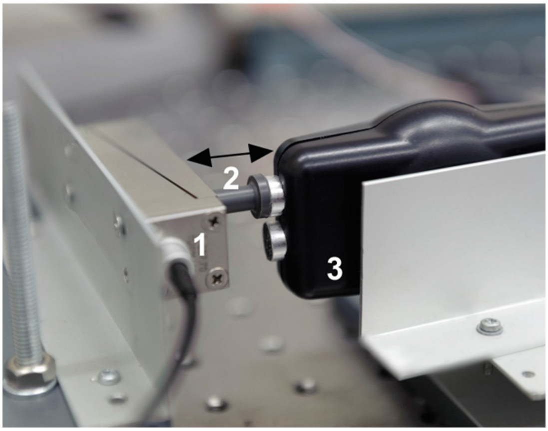

Fig. 3. Representation of the mechanical structure of the test setup I. 1 - ACT. 2 - PVC interface. 3 - AP. The arrow represents the movement of the ACT and PVC interface.

The test bench system II, schematically presented in Fig. 4, was developed aiming the assessment of the temporal resolution of the AP. This test bench emulates the main arterial pressure wave propagation features of the cardiovascular system, presenting an upgrade in relation to the experimental setup developed previously by Pereira et al. [26]. The main difference is based on the use of a natural rubber latex tube, considered to be a reliable material to simulate the compliance of a human artery and providing a higher distensibility than the silicon tube originally used. As in the test bench I, the pressure waveform is firstly generated using the AWG and then delivered to the ACT/HVA, that through a piston ("mushroom" shaped PVC, 15 mm diameter) - rubber membrane mechanism launches the wave into a 200 cm long latex tube (Primeline Industries, 7.9 mm inner diameter, 0.8 mm wall thickness), filled with water. The tube's sealing is made using a T-shaped scheme, guaranteeing geometric homogeneity. The wave is captured by the AP placed along the tube and by two pressure sensors PS1 and PS2 (Honeywell, 40PC015G1A), placed transversely and longitudinally to the tube. These sensors are used as the main reference for time delay/pulse wave velocity assessment but also monitor the DC pressure level of the tube, imposed by a piston P and a mass m at one of the tube's extremities. The range of DC pressure levels in the tube varies, approximately, from 30 mmHg to 400 mmHg, including (and exceeding) the pressure variations registered in a healthy and non-healthy human system. Although the variation in the DC pressure level interferes with the wave propagation velocity, the AP was tested at a constant DC pressure (≈66 mmHg), since it was not crucial for the present work having several wave propagation velocities.

To record simultaneously the different sensors response it was used the aforementioned DAS, triggered by the AWG.

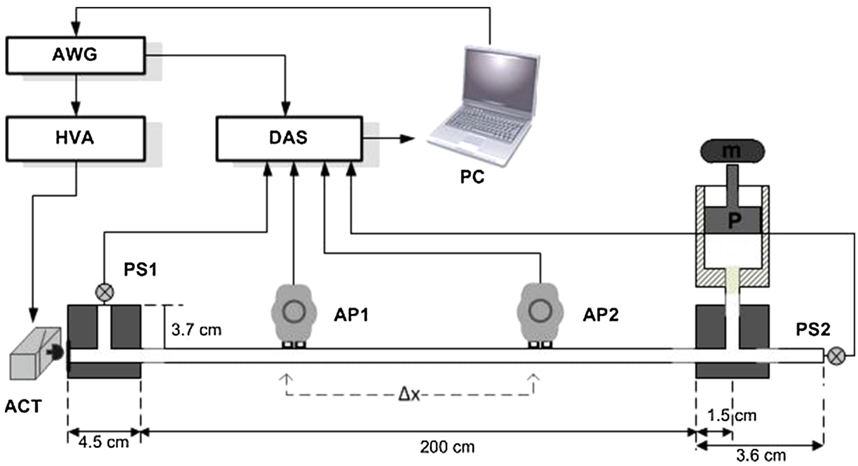

Fig. 4. Schematic representation of the test setup II.

3 Methods

3.1 Experimental Characterization

The experimental characterization of the AP consisted in the evaluation of its performance regarding three main aspects: repeatability in assessing pressure waveform, occurrence of crosstalk phenomenon and estimation of time resolution. Several pressure waveforms were programmed and used as inputs in these studies, including Gaussian-like and Cardiac-like pulses. The last ones, synthesized using a weighted combination of exponentially shaped sub-pulses [27], reproduce different states of arterial wall elasticity: type A and type B, correspond respectively to cases of pronounced and slight arterial stiffness (non-healthy subjects) and type C, commonly seen in healthy individuals, characterize elastic arteries [28].

In all the experiments, the data acquisition was performed through a dedicated acquisition module of National Instruments (NI© USB6210) and data logging was accomplished by NI LabView™ 2010 SignalExpress. All the signals were sampled at 5 kHz and stored for offline analysis using Matlab®. Data processing was undertaken in Matlab® 2009a and statistical analysis was performed using Microsoft Excel® 2010.

Waveform Analysis/Repeatability. The first part of this study aimed to examine the probe's response for different types of waveforms generated by the Agilent 33220A and exerted by the ACT. To obtain the best response of the transducer it was selected for each input signal, the best amplitude (3.5 V) and frequency (1 Hz). All the sensors signals were submitted to a 300 Hz low pass filter and to a band cut filter of 49 Hz–51 Hz, in order to avoid, respectively, the presence of the resonant frequency of the actuator ($\sim$380 Hz ± 20 %) and the 50 Hz power line interference. It was also performed an integration of the transducer signals using the Matlab® function *cumsum* to compare them with the original input signals.

In the second part, it was intended to measure the same waveform repeatedly and under the same conditions by the AP. For this study, each sensor was excited with fifty independent impulses (with the same amplitude and width (Gaussian, 1 s width, 1 Hz frequency). With those signals, it was determined the average signal which was used as reference to determine the root mean square error (RMSE), for each one. The RMSE was then computed to each signal.

Crosstalk Analysis. Since the two transducers composing the AP were incorporated in the same case with a very small separating distance, it was important to analyse whether some kind of interaction between them existed. The first part of this study was done simultaneously with the repeatability test, where one of the acoustic transducers was being actuated (microphone 1) and the other one was left free (microphone 2), that is to say without any contact with the PVC adapter/ACT (Fig. 3). The responses of both transducers for fifty independent impulses (Gaussian, 1 s width, 1 Hz frequency) were recorded and the average signals were estimated. This procedure was then applied to the other sensing element, such that the actuated transducer was microphone 2 and the free transducer was microphone 1.

The actuated transducers generated a typical differential signal with a good signal-to-noise ratio, while the free transducers generated a much lower amplitude signal, with a profile substantially opposite to that obtained for the actuated transducers (see results Sect. 4.1). Due to the characteristics of the signal obtained for the free transducers, it was necessary to perform an additional experiment to determine whether this transmission might interfere with one of the most important aspects of the probe: its time delay assessment. Thus, the second test consisted in the direct and simultaneous actuation of both transducers, with the purpose of time delay assessment. Both sensors were excited with three independent impulses (Gaussian, 1 s width, 1 Hz frequency) and for each acquisition it was determined the time delay between both transducers, using different algorithms yet to be described on Subsect. 3.3. In this particular experiment, the signals were sampled at 12.5 kHz, the same sampling frequency used in in vivo tests.

Time Resolution Evaluation. One of the main goals of the AP characterization was the evaluation of its ability of precisely assessing the time delay between two distinct points, separated from a very small distance.

In order to evaluate its time resolution, it was used two different APs (AP1 and AP2) that were placed on the tube of the test bench II, with the help of two external clamps (Fig. 4). One of the probes was kept fixed at the 50 cm position, while the other one was moving from 100 cm position to 54 cm position by 2 cm intervals. For each position, a Gaussian waveform (100 ms width, 10 Hz frequency) was delivered to the system, and then time delay and PWV were estimated between the first microphones of both probes and also between the pressure sensors (PS1 and PS2), attached at the extremities of the tube.

The relative errors between the reference PWV and the PWV obtained with the uncoupled transducers for each separating distance (Δx) were calculated, using the algorithms of Sect. 3.3. The test was repeated for more two times, for a constant DC pressure of ≈66 mmHg.

3.2 in-Vivo Measurements

Participants and Study Protocol. Seventeen young volunteers aged 22.12 ± 1.96 years were recruited and gave written informed consent prior to recording. Each participant was properly weighed and measured and after 5 m of rest of supine position, a blood pressure measurement was obtained from his right brachial artery, using an automatic clinically validated sphygmomanometer (MAM Colson BP 3AA1-2 ®; Colson, Paris). Next, a straight arterial segment of the right common carotid artery was identified by a skilled operator and a record of approximately 20 s–30 s was obtained with the probe longitudinally aligned to the artery. Data acquisition was performed with the dedicated real-time software Cardiocheck GUI and automatically stored in the Cardiocheck DB. Age, sex, weight, height, waist, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also stored in the same database.

All the signals were acquired at a sample rate of 12.5 kHz and were processed offline in Matlab® 2009a, aiming the extraction of carotid PWV and other hemodynamic parameters.

3.3 Signal Processing

In the first part of this work (experimental characterization), a set of dedicated algorithms have been developed aiming the estimation of time delay in two main situations: between the signals of the AP transducers and between the signals of pressure sensors (test setup II). After a common pre-processing, based on a low-pass filter with a cut-off frequency of 100 Hz to reduce high frequency noise, four different methods were used for time delay estimation: (a) maximum of cross-correlation function, (b) maximum and (c) minimum amplitude identification and (d) zero-crossing detection. The cross correlation method uses the xcorr function of Matlab's Signal Processing Toolbox to determine the peak of cross-correlogram that allows delay estimation by subtracting the peak time position from the pulse length. The other methods ensure an accurate detection of some fiducial points of the signal, such as the maximum, the minimum and the zero. As so, the methods of maximum and minimum amplitude identification use a 6th polynomial fit in the maximum and the minimum region of the signals, while the zero-crossing method applies a linear fit to the region where the signal crosses the zero. For all the methods, time delay is estimated between the maxima, minima and zero points detected in each set of signals.

In the last part of this work, the AP was used to assess PWV and other hemodynamic parameters in human carotid arteries. Since the acquisitions were constituted by several cardiac cycles, it was necessary to apply a dedicated segmentation routine, based on a minima detection approach to divide the data stream into single periods. Before applying the segmentation algorithm, the signals were filtered with the aforementioned 100 Hz low pass-filter and then heart rate was determined. For each cardiac cycle, the maximum of cross-correlation was used for carotid PWV estimation and an average value was obtained. Besides PWV, it was also possible to determine hemodynamic parameters, such as: LVET, defined as the period of time from the start of the pulse (aortic valve open) to the dicrotic notch (closure of the aortic valve) and diastole phase (DP), defined as the period of time from the dicrotic notch to the end of the pulse. These parameters were extracted based on the conviction that the onsets of the first and second carotid sounds (S1 and S2) coincide respectively with the onset and with the dicrotic notch of the carotid pulse waveform [29]. The onsets of carotid sounds S1 and S2 were identified as the maxima of the second time derivative of the acoustic signal. LVET and DP were calculated for each cardiac cycle. Data were expressed as mean ± SD.

4 Results and Discussion

4.1 Experimental Characterization

The first part of probe's experimental characterization consisted in the evaluation of the AP output to different waveforms and its repeatability. The response obtained by the AP for each one of the waveforms is presented in Fig. 5. The AP profiles are similar to those expected by a differentiator circuit; however it is not possible to precisely recover the original pressure waveform. When the acoustic signals are integrated there are noticeable similarities with the input signals, however the RMSE between both signals is quite high (approximately 13 % for each case). This performance was predictable, since the sensitivity of the acoustic sensors must be reduced for low frequencies that are below the microphone's 3 dB bandwidth (100 Hz–10 kHz). Since low frequencies are determinant for the precise reconstruction of arterial pressure waveform, the use of these acoustic sensors limits the possibility of the AP for waveform estimation purposes. Nevertheless, this fact does not disqualify the use of this probe this probe for its main purpose: local PWV estimation, once the method does not depend on the waveform accuracy.

The results regarding the repeatability test are shown in Table 1 and Fig. 6.

Although the microphone 2 (0.6198 ± 0.0298) exhibits a better performance than the microphone 1 (1.1781 ± 0.0345), the RMSE variance values obtained for both probes are identically low, evidencing the reliability of the system.

The second part of the AP's characterization intended to study the presence or absence of crosstalk effect in both transducers. The first results achieved in this study are illustrated in Fig. 7. The actuated sensors present a good signal-to-noise ratio and a typical profile when compared with the one obtained previously in the waveform analysis test (Fig. 5(a)).

The free transducers also present a slight profile but of much lower amplitude. Although the results suggest the existence of crosstalk effect, this phenomenon was seen as a mass inertial effect (transducer resistance to conserve its idle state), since the

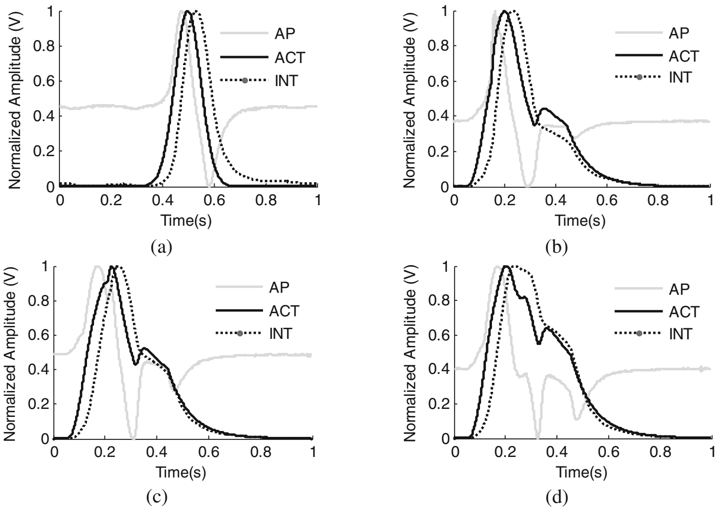

Fig. 5. Acoustic sensor responses to different excitation pressure waveforms. (a) Gaussian-like Pulse. (b) Type A Cardiac-like Pulse. (c) Type B Cardiac-like Pulse. (d) Type C Cardiac-like Pulse. AP - Acoustic Sensor Signal. ACT - Input Signal. INT - Integrated Sensor Signal.

Table 1. Statistics of the measurements obtained in the repeatability test.

Transducer	Mic 1	Mic 2
Nº acquisitions	50	50
Mean (%)	1.1781	0.6198
Std. deviation (%)	0.0345	0.0298
Maximum (%)	1.2849	0.7379
Minimum (%)	1.1174	0.5890

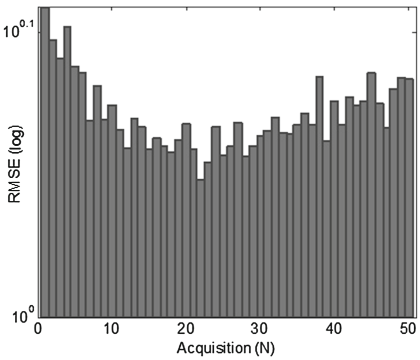

Fig. 6. Graphic representation of the RMSE distribution between the reference signal and the microphone 2 output, obtained in the repeatability test.

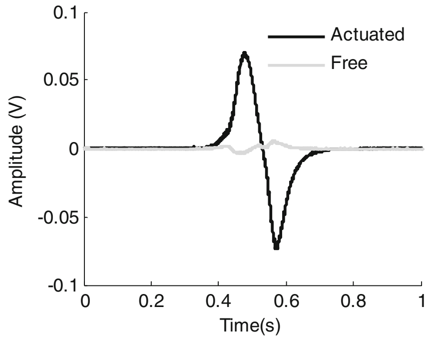

Fig. 7. Crosstalk phenomenon study: average response of both AP's transducers to fifty independent pulses. The actuated transducer is microphone 2 and the free transducer is microphone 1.

profile of the free transducer had an inversed shape relatively to the actuated one. This assumption could not be proven in the present work but it will be aim of futures studies. Nevertheless, and since the main purpose of this probe is the assessment of local PWV, it was employed a different approach, in order to determine if this "transmission" might interfere with the AP's time delay. For this purpose, both transducers were simultaneously actuated with three independent Gaussian waves and time delay was calculated using different algorithms. The results regarding this experiment are presented in Table 2 and Fig. 8.

Table 2. Time delay values obtained for each algorithm when both transducers are simultaneously actuated with three independent Gaussian impulses.

N	Time delay estimation method			
	xcorr	max	min	zc
1	8e-5	0.0134	0.0136	0.0037
2	8e-5	0.0109	0.0142	0.0038
3	8e-5	0.0103	0.0140	0.0035

The time delay obtained for each one of the algorithms is very different and actually surprising. It was not expected to obtain such a variable and elevated time delay values for maximum, minimum and zero crossing algorithms. In contrast, the cross-correlation algorithm presented a great performance, where time delay always matched the minimum detectable time, limited by the system, i.e.:, the sampling time (1/12500 Hz). In order to understand the achieved results, the AP's response was also analysed (Fig. 8). It is visible that the profiles obtained for each one of the transducers are identical; however, they present important differences in terms of amplitude and peaks correspondence. It was expected that the maxima and the minima of both signals were in agreement, but actually that didn't happen. These slight profiles difference can be justified with the experiment level of difficulty. It is extremely important that the simultaneous actuation of both transducers is made rigorously under the same

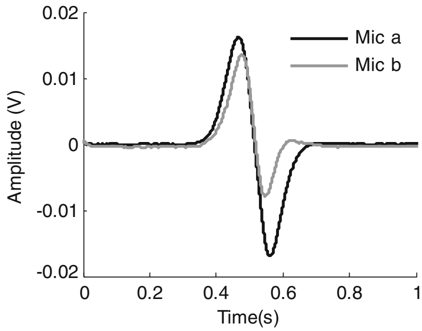

Fig. 8. Crosstalk phenomenon study: typical response of both AP's transducers to a Gauss ian pulse, simultaneously delivered to them.

conditions; otherwise the waveforms of each transducer can be affected. This also suggests that time delay algorithms that depend only on a fiducial point are more susceptible to error, especially if the waveforms don't have exactly the same profile. Finally and in what concerns to crosstalk effect, it can be concluded that the existence of a possible transmission between sensors does not affect the time delay, when the cross-correlation algorithm is used. In order to prove the effectiveness of the other algorithms, it will be necessary to proceed to additional experiments.

The last test concerning AP's experimental characterization intended to evaluate its time resolution. In this test, it was determined the PWV for two uncoupled AP's in successively smaller separation distances and the PWV reference obtained using the pressure sensors PS1 and PS2. The PWV results obtained for each algorithm and the relative errors between the reference PWV and the PWV obtained with the uncoupled transducers, for each separating distance and method are presented, respectively, in Figs. 9 and 10. The statistics of the measurements are synthesized in Table 3.

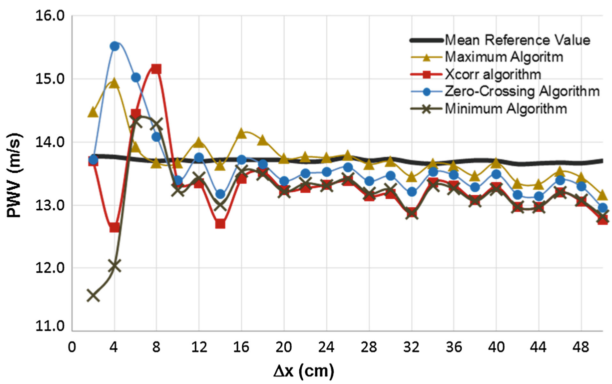

Fig. 9. Time resolution study: PWV values of uncoupled acoustic sensors and pressure sensors, yielded by the four algorithms. Each point is an average of three trials.

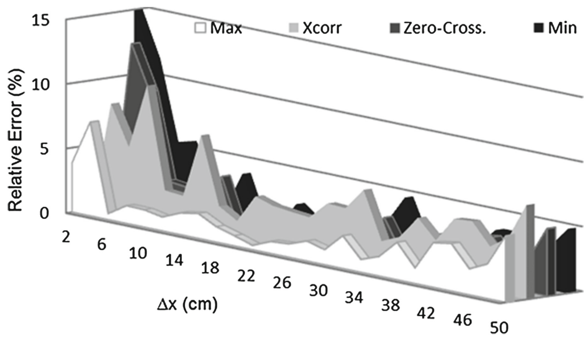

Fig. 10. Time resolution study: relative errors for each distance and method.

Table 3. Statistics of the measurements obtained in the time resolution test.

Algorithm	PWV(m/s)		Relative error mean (%)
	Pressure sensors (reference)	Acoustic sensors	
Maximum	13.856 ± 0.037	13.742 ± 0.372	2.083
Xcorr	13.716 ± 0.037	13.308 ± 0.524	4.246
ZC	13.702 ± 0.034	13.592 ± 0.560	2.863
Min	13.540 ± 0.039	13.176 ± 0.547	3.550

The algorithms with the best and worst general performance are the maximum and the cross-correlation with an average error less than 3 % and 5 %, respectively. However, and for the minimum distance achieved (2 cm) the magnitude of the errors is less than 1 %, when considering cross-correlation and zero-crossing algorithms.

The results obtained for AP time resolution for each algorithm, exhibit a very good performance suggesting that the AP have enough accuracy to be considered an interesting stand-alone instrument for local PWV/arterial stiffness assessment.

4.2 in-Vivo Measurements

Following the preliminary tests of the probe in the test benches, it was performed a set of measurements in human carotid arteries, in order to test the AP in in vivo conditions (Fig. 11). The characteristics of the patients, as also the results of the parameters assessed by the AP, (heart rate, local PWV, LVET and DP) are given in Table 4.

In order to assess pulse wave velocity, it was only used the cross-correlation algorithm, since it has presented the best performance both on crosstalk and on time resolution studies. The range of obtained values for carotid PWV are slightly lower than the values obtained by other reference studies that also assess the carotid PWV (≈4 m/s) [22, 30]. However, the number of analysed subjects not only is small as also include very young people (22.12 ± 1.96 years), which can justify a lower PWV mean (≈3 m/s), due to the high elasticity of young and healthier arteries. Although the

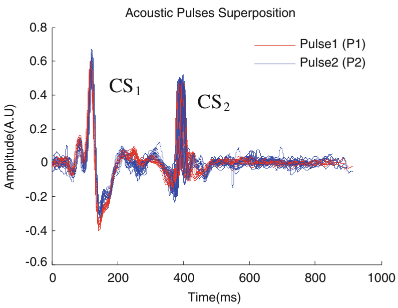

Fig. 11. Preliminary results of the AP acquiring data in a healthy young subject. CS_1 - First Carotid Sound. CS_2 - Second Carotid Sound.

Table 4. Main characteristics of the volunteers and AP parameters assessment.

Variable	Mean ± SD
Age, years	22.12 ± 1.96
N(Male/Female)	17(6/11)
Height, cm	166.82 ± 11.73
Weight, Kg	66.18 ± 18.87
BMI, Kg/m^2	23.50 ± 4.94
Waist, cm	75.35 ± 14.85
Brachial SBP, mmHg	114.35 ± 12.62
Brachial DBP, mmHg	70.94 ± 7.11
Heart Rate, bpm	67 ± 12.09
Local PWV(m/s)	2.96 ± 1.08
LVET (ms)	288.59 ± 21.42
DP (ms)	611.07 ± 148.84

obtained PWV variance is high (N = 17, ≈1 m/s), it is concordant with the PWV variance obtained in a recent study for a significant number of healthier subjects (N = 1774, ≈1.64 m/s) [30].

Nevertheless and in order to address more accurate results, it will be necessary to assess to a higher number of subjects, not only with a broader range of ages but also with pathologies, such as hypertension or atherosclerosis, where is expected to observe an increase of local PWV. The use of a reference method is also indispensable to validate the developed algorithms for AP hemodynamic parameters extraction. Currently, the probe presented a good performance in acquiring signals with a good bandwidth and signal-to-noise ratio in human carotid arteries, allowing the application of various algorithms that extract clinically relevant information.

Regarding the LVET values, we believe that is actually possible to determine this parameter as the time delay between the main onsets of each carotid sounds, since the estimated values are generally close to the expected for healthy subjects [31]. This parameter will be the subject of a further study, to evaluate the robustness of the algorithm.

5 Conclusions

A novel and low-cost doubled headed probe specifically designed to assess local stiffness, by means of non–invasive PWV measurements in a short segment of carotid artery, has been developed and characterized in dedicated test bench systems.

The probe demonstrated good performance on the dedicated test setups and results showed that its signals are repeatable and crosstalk effect do not interfere with its time resolution when the cross-correlation algorithm for time delay estimation is used.

It is also possible to conclude favorably towards the effectiveness of the AP in the measurement of local PWV. The maximum amplitude and the cross correlation algorithms exhibited the capability of measuring higher PWV ($\approx$14 m/s) with an error less than 10 %, for the several separating distances (50 cm–2 cm).

The natural follow-up to this work will be the continuation of the assessment of local PWV and other hemodynamic parameters in a significant numbers of patients (healthy and with various pathologies), under medical control. One of these studies would evaluate the agreement between the PWV values obtained with the AP and the ones obtained with the current 'gold-standard' system (Complior®). In general, lower values are expected for PWV measured over the carotid artery (local stiffness) than PWV measured over the carotid-femoral path (regional stiffness), nevertheless a correlation with aging and (cardiovascular) disease must be investigated. Another study will be designed to compare the experimental and in vivo performance of the AP probe with an improved version of the double headed piezoelectric probe [24], also developed in this research group, with the same purpose of local hemodynamics assessment.

Although studies to validate the clinical use of AP are still required, this device seems to be a valid alternative system, to local PWV stand-alone devices.

Acknowledgements. The authors acknowledge Fundação para a Ciência e Tecnologia for funding SFRH/BDE/15669/2007 and PTDC/SAU-BEB/100650/2008, project developed under the initiative of QREN, funding by UE/FEDER, through COMPETE - Programa Operacional Factores de Competitividade. The authors also thank to the company ISA-Intelligent Sensing Anywhere and the medical collaboration of Instituto de Investigação e Formação Cardiovascular, Clínica da Aveleira and Escola Superior de Tecnologia da Saúde de Coimbra.

References

1. Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., et al.: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension **37**, 1236–1241 (2001)
2. Mattace-Raso, F., van der Cammen, T., Hofman, A., van Popele, N., Bos, M., Schalekamp, M., et al.: Arterial stiffness and risk of coronary heart disease and stroke the Rotterdam study. Circulation **113**, 657–663 (2006)
3. Mancia, G., De Backer, G., Dominiczak, A., Cifkova, R., Fagard, R., Germano, G., et al.: 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC). J. Hypertens. **25**, 1105–1187 (2007)

4. Laurent, S., Katsahian, S., Fassot, C., Tropeano, A.I., Gautier, I., Laloux, B., et al.: Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke **34**, 1203–1206 (2003)
5. Maldonado, J., Pereira, T., Polonia, J., Silva, J.A., Morais, J., Marques, M., et al.: Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de DIstensibilidade VAscular) project. J. Hypertens. **29**, 669–675 (2011)
6. Ben-Shlomo, Y., Spears, M., Boustred, C., May, M., Anderson, S., Boutouyrie, P., et al.: Prognostic value of carotid-femoral pulse wave velocity for cardiovascular events: an IPD meta-analysis of prospective observational data from 14 studies including 16,358 subjects. Artery Res. **5**, 138–139 (2011)
7. Asmar, R., Benetos, A., Topouchian, J., Laurent, P., Pannier, B., Brisac, A.M., et al.: Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation Clin. Appl. Stud. Hypertens. **26**, 485–490 (1995)
8. Boutouyrie, P., Briet, M., Collin, C., Vermeersch, S., Pannier, B.: Assessment of pulse wave velocity. Artery Res. **3**, 3–8 (2009)
9. Millasseau, S.C., Stewart, A.D., Patel, S.J., Redwood, S.R., Chowienczyk, P.J.: Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. Hypertension **45**, 222–226 (2005)
10. Rajzer, M.W., Wojciechowska, W., Klocek, M., Palka, I., Brzozowska-Kiszka, M., Kawecka-Jaszcz, K.: Comparison of aortic pulse wave velocity measured by three techniques: Complior. SphygmoCor Arteriograph. J. Hypertens. **26**, 2001–2007 (2008)
11. Weber, T., Rammer, M., Eber, B., O'Rourke, M.F.: Determination of travel distance for noninvasive measurement of pulse wave velocity: case closed? Hypertension **54**, e137 (2009)
12. Segers, P., Kips, J., Trachet, B., Swillens, A., Vermeersch, S., Mahieu, D., et al.: Limitations and pitfalls of non-invasive measurement of arterial pressure wave reflections and pulse wave velocity. Artery Res. **3**, 79–88 (2009)
13. Agabiti-Rosei, E., Mancia, G., O'Rourke, M.F., Roman, M.J., Safar, M.E., Smulyan, H., et al.: Central blood pressure measurements and antihypertensive therapy a consensus document. Hypertension **50**, 154–160 (2007)
14. Tu, S.T., Wang, I.W., Lin, H.F., Liao, Y.C., Lin, R.T., Liu, C.S., et al.: Carotid intima-media thickness and stiffness are independent risk factors for atherosclerotic diseases. J. Investig. Med. **58**, 786–790 (2010)
15. Gaszner, B., Lenkey, Z., Illyes, M., Sarszegi, Z., Horvath, I.G., Magyari, B., et al.: Comparison of aortic and carotid arterial stiffness parameters in patients with verified coronary artery disease. Clin. Cardiol. **35**, 26–31 (2012)
16. Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., et al.: Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur. Heart J. **27**, 2588–2605 (2006)
17. Brands, P.J., Willigers, J.M., Ledoux, L.A.F., Reneman, R.S., Hoeks, A.P.G.: A noninvasive method to estimate pulse wave velocity in arteries locally by means of ultrasound. Ultrasound Med. Biol. **24**, 1325–1335 (1998)
18. Meinders, J.M., Hoeks, A.P.: Simultaneous assessment of diameter and pressure waveforms in the carotid artery. Ultrasound Med. Biol. **30**, 147–154 (2004)
19. Segers, P., Swillens, A., De Schryver, T., Vermeersch, S., Rietzschel, E., De Buyzere, M.: Assessing arterial distensibility using ultrasound wall-tracking diameter distension. In: 2009 IEEE International Ultrasonics Symposium (IUS), Rome, Italy, pp. 2460–2463 (2009)

20. Giannarelli, C., Bianchini, E., Bruno, R.M., Magagna, A., Landini, L., Faita, F., et al.: Local carotid stiffness and intima-media thickness assessment by a novel ultrasound-based system in essential hypertension. Atherosclerosis **223**, 372–377 (2012)
21. Giannattasio, C., Salvi, P., Valbusa, F.O., Kearney-Schwartz, A., Capra, A., Amigoni, M., et al.: Simultaneous measurement of beat-to-beat carotid diameter and pressure changes to assess arterial mechanical properties. Hypertension **52**, 896–902 (2008)
22. Hermeling, E., Reesink, K.D., Reneman, R.S., Hoeks, A.P.: Measurement of local pulse wave velocity: effects of signal processing on precision. Ultrasound Med. Biol. **33**, 774–781 (2007)
23. Hermeling, E., Reesink, K.D., Kornmann, L.M., Reneman, R.S., Hoeks, A.P.: The dicrotic notch as alternative time-reference point to measure local pulse wave velocity in the carotid artery by means of ultrasonography. J. Hypertens. **27**, 2028–2035 (2009)
24. Pereira, H.C., Pereira, T., Almeida, V., Borges, E., Figueiras, E., Simoes, J.B., et al.: Characterization of a double probe for local pulse wave velocity assessment. Physiol. Meas. **31**, 1449–1465 (2010)
25. Pereira, H.C., Simões, J.B., Malaquias, J.L., Pereira, T., Almeida, V., Borges, E., et al.: Double headed probe for local pulse wave velocity estimation - a new device for hemodynamic parameters assessment. In: BIODEVICES, pp. 444–447. SciTePress, Rome (2011)
26. Pereira, H.C., Cardoso, J.M., Almeida, V.G., Pereira, T., Borges, E., Figueiras, E., et al.: Programmable test bench for hemodynamic studies. In: Dössel, O., Schlegel, W. (eds.) World Congress on Medical Physics and Biomedical Engineering, Munich, Germany, September 7–12, 2009. IFMBE Proceedings, vol. 25/4, pp. 1460–1463. Springer, Heidelberg (2010)
27. Almeida, V., Pereira, T., Borges, E., Figueiras, E., Cardoso, J., Correia, C., et al.: Synthesized cardiac waveform in the evaluation of augmentation index algorithms - case study for a new wavelet based algorithm. In: BIOSIGNALS, pp. 385–388. INSTICC Press, Valencia (2010)
28. Murgo, J.P., Westerhof, N., Giolma, J.P., Altobelli, S.A.: Aortic input impedance in normal man: relationship to pressure wave forms. Circulation **62**, 105–116 (1980)
29. Hasegawa, M., Rodbard, D., Kinoshita, Y.: Timing of the carotid arterial sounds in normal adult men: measurement of left ventricular ejection, pre-ejection period and pulse transmission time. Cardiology **78**, 138–149 (1991)
30. Borlotti, A., Khir, A.W., Rietzschel, E.R., De Buyzere, M.L., Vermeersch, S., Segers, P.: Noninvasive determination of local pulse wave velocity and wave intensity: changes with age and gender in the carotid and femoral arteries of healthy human. J. Appl. Physiol. **113**, 727–735 (2012)
31. Willems, J.L., Roelandt, J.O.S., De Geest, H., Kesteloot, H., Joossens, J.V.: The left ventricular ejection time in elderly subjects. Circulation **42**, 37–42 (1970)