Indices and Repeatability Tests of Cardiovascular Function Performed on the Arterial Distension Waveform

Case Study: Angiography Intervention

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Abstract: The arterial distension waveform (ADW) analysis is a reliable technique for cardiovascular function assessment. The purpose of this study was to perform the pre-clinical validation of a non-invasive prototype focusing the repeatability tests and cross-relationships between different subject groups. The evaluation focused parameters retrieved from ADW: systolic peak (SP), dicrotic notch (DN), RP (reflection point) and Augmentation index (AI). One hundred and fifty one subjects (61 men and 90 women, aged between 18 and 80 years) were assigned into four groups based on their clinical characteristics. Database is constituted by healthy, hypertensive and subjects that suffer from stenosis. The cross-correlations analysis between groups allows establishing time parameterizations for each one. Furthermore, the differences between the left and right carotid artery suggest intrinsically variability for each one of the subjects. The coefficient of variation (CV) mean value obtained for all measurements was 18.58%, maximum rate of 33.7% and minimum 8.9%. The stenosis case study demonstrate the potentialities of the use of this prototype in the detection of cardiac anomalies by the monitoring of state alterations through RP, SP and DN time parameterizations with visible changes in RP and SP values (after carotid intervention RP appears later than SP, in opposition with values before intervention), while DN associated time changes little. The tests performed on the ADW showed that is possible the reliable measurement of morphological patterns changes.

1 INTRODUCTION

The prevention and treatment guidelines of cardiovascular disease (CVD) have focused on the modification of risk factors, such as hypertension, smoking or hyperglycaemia, among others that could potentially reduce cardiac events. Furthermore, the early non-invasive identification of hemodynamic alterations that result from pathological situations can facilitate much more precise risk stratification.

Arterial walls are the primary site of disease in arteriosclerotic vascular disease, and their properties and function are commonly affected by the risk factors above referred. So, the assessment of wall integrity can provide an accurate prediction of cardiovascular (CV) risk (Hamilton et al., 2007). CV risk assessment can be performed using several risk tools based upon multi-variable equations. In spite of the difficulty in absolute risk prediction, they are extremely useful in assessing or estimating risk, as well as in prioritising treatments. The most used are the Framingham (Bitton and Gaziano, 2010) and the SCORE (Conroy, 2003).

Some factors have been focused by scientific community due to their relationship with risk occurrences. The INTERHEART study established the smoking status, history of hypertension or diabetes, waist hip ratio, dietary pattern, physical activity, alcohol consumption, blood apolipoproteins and psychosocial factors collectively accounting for more than 90% of the risk in the acute myocardial infarction (Yusuf et al., 2004). Serum total, high density (HDL) cholesterol and serum triglyceride are used in the most of risk scores. However, HDL is frequently ignored by some authors that emphasize its poor sensitivity for the identification of individuals at high risk (Jones et al., 2001). Hypertension is also reported as one of the most important factors, and should not be ignored. Arterial stiffness is one of the early detectable symptoms of adverse structural and functional changes

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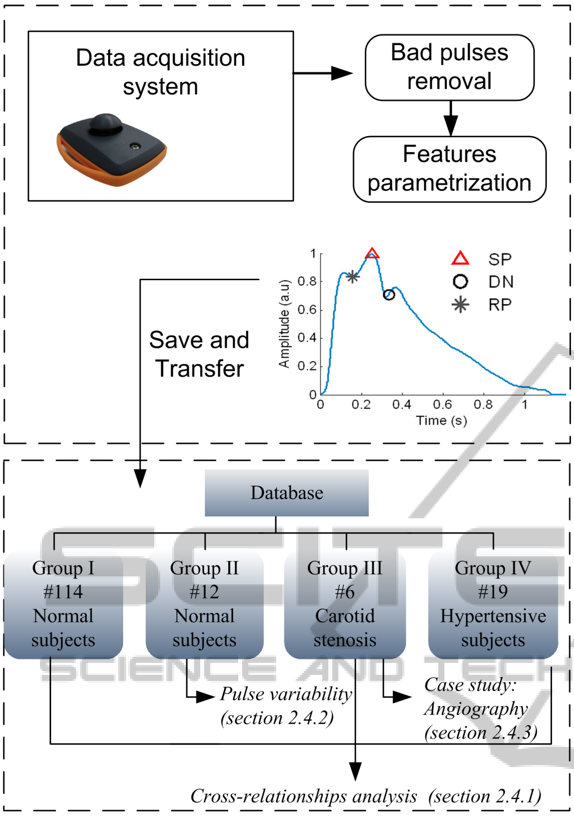

Figure 1: Database groups and signal processing tasks performed for each one.

within the vessel wall (Laurent, 2006). A wide variety of non-invasive techniques are employed to assess its development (Cavalcante et al., 2011; Mackenzie et al., 2002).

The arterial distension waveform (ADW) is an interesting signal that can be used in the analysis of relevant morphological features (Avolio et al., 2010). The major determinants are systolic peak (SP), reflected wave (RP) and dicrotic notch (DN) that results from the aortic valve closure at end of systole. The presence of branches and tapers in the arterial tree leads to occurrence of reflection waves that are influenced by the arterial wall stiffening. The increase of arterial stiffness leads to early occurrence of RP rather than SP leading to the augmentation phenomenon. The augmentation index (AI) is used to quantify this fact, and is calculated as a percentage of the increment of pressure to the pulse pressure (Hamilton et al., 2007).

Little is known about the cross-relationships of these indices in different risk groups. The available studies compare within the same subject (Huck et al., 2007) several techniques such as, tonometry, ultrasound, Doppler and brachial flow-mediated dilation (Liang et al., 1998). Furthermore, the analysis of ADW from different anatomical origins, such as left and right carotid artery could be interesting in the analysis of anatomical differences (Luo et al., 2011).

The non-invasive prototype to be tested was developed in a previous work for distension wave estimation based on piezoelectric (PZ) sensors. A set of preliminary tests were done in flexible tubes and in volunteers to physiological monitoring (Almeida et al., 2011a; Almeida et al., 2011b). The main focus of this work is performing a set of clinical tests, as follow:

- Exploration of the cross-correlations between subjects;
- Perform a set of repeatability tests in successive measurements and distinguish the differences between left and right carotid ADW;
- Evaluate the capability of probe in detect modifications in clinical states by the monitoring of ADW after and before angiography procedure, using an invasive method as reference.

The selection and description of primary variables and groups are issued in section 2. Results are presented in section 3. Finally, discussion and conclusions are stated in sections 4 and 5, respectively.

2 METHODS

This section describes the dataset and protocol used during data acquisition. The database details are depicted in Figure 1 (below row).

2.1 Subjects

One hundred and fifty one volunteers, 61 male and 90 female, aged between 18 and 80 years were included in this study. Subjects were recruited from Coimbra University Hospital Centre (*C.H.U.C.*) and advertisements placed in public platforms calling for healthy volunteers. Informal consent was obtained after full explanation of the purpose, nature and risk of all procedures used. The research was approved by the Committees of the Coimbra University Hospital Centre. The database is composed by four independent groups, whose demographic data are listed in Table 1.

- Group I is composed by 114 normal subjects (between 18 and 30 years).
- Group II is composed by 12 normal subjects between 21 and 29 years.
- Group III is composed by 6 subjects that suffer from severe stenosis.
- Group IV comprises 19 hypertensive subjects.

Table 1: Demographic data comparison for each one of groups analysed.

Variable	Group I	Group II	Group III	Group IV
Age	21.90 ± 3.32	23.50 ± 2.43	72.5 ± 5.44	58.63 ± 12.51
Sex (M/F)	45/69	4/8	4/2	8/11
Smoker (Y/N)	10/104	0/12	M.D.*	2/17
Diabetes (Y/N)	0/114	0/12	M.D.*	2/17
Weight (Kg)	62.46 ± 10.24	59.66 ± 10.96	M.D.*	74.42 ± 10.77
Height(m)	1.69 ± 0.09	1.66 ± 0.06	M.D.*	1.64 ± 0.10
BMI(Kg/m)	21.80 ± 2.59	21.45 ± 2.71	M.D.*	27.81 ± 5.28
SBP(mmHg)	108.78 ± 11.59	105.25 ± 5.86	144.33 ± 40.08	155.42 ± 27.32
DBP(mmHg)	69.52 ± 7.84	65.67 ± 6.71	81 ± 18.34	90.95 ± 17.45
HR(beats/min)	70.11 ± 10.83	71.17 ± 10.64	72.5 ± 3.53	63.79 ± 6.08

Note: Data were expressed in mean±standard deviation (SD)
*M. D. -Missing data

2.2 Protocol

ADWs were recorded at the sampling rate of 1kHz using a non-invasive PZ probe previously developed (Almeida et al., 2011b). The probe is placed over the carotid artery, and is held by a collar to avoid noise interference and artefacts that may arise from the interaction between the probe and the operators hand. Age, sex, weight, height, smoking habits and diabetes history were registered for each subject. The Body Mass Index (BMI) was later calculated. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) values were measured in the left arm with an automated digital oscillometric sphygmomanometer (Omron M6 Comfort, Kyoto, Japan). The following requirements were performed for each one of groups:

- Group I- One measurement (three trials) was taken for each subject during 30-40 seconds. The subjects remained quiet and seated on a comfortable chair;
- Group II- For each subjects two successive sessions were monitored. In each session, 3 trials of 30-40 seconds were performed for each carotid site (right and left). All measurements were made in a similar time of the day and at the same temperature controlled room (22-23°Celsius), to minimize the climatic variation. The subjects remained quiet and seated on a comfortable chair;
- Group III- These subjects were monitored under carotid intervention (due to a stenosis that partly blocks the artery blood flow). The angiography is the imaging method of choice to visualize it. After local anesthesia, a surgical cut is executed next to the groin, and after a filter device is opened above the lesion, the stent is implanted. The balloon is then inflated at the stenosis plaque level, decreasing the stenosis after deflation, and the filter device is kept open as prevention for an eventual embolic trapping. With this surgical technique, the blood flow was restored to the normal values since the diameter of the vessel enlarged to the same imposed by the stent. The ADW was sequentially collected by our probe and invasive equipment, Axiom Sensis (Siemens). Only a small segment of 3-4 seconds was analyzed.
- Group IV- The data from group IV were acquired during hospitalization. One measurement (three trials) was taken for each subject during 30-40 seconds. The subjects were monitored prior to taking any medication and subjects remained quiet and seated on a comfortable chair.

2.3 Signal Acquisition and Discrete Time Signal Processing

Data processing was undertaken in MATLAB 2011b and statistical analysis was performed using Microsoft Excel 2010 and SPSS18.0 statistical software. The collected data consisted in demographic and pulse waveform parameters. The overall list of demographic parameters (expressed as mean±S.D.) is described in Table 1.

The methodology adopted in the pulse wave analysis consists in the removal of bad pulses that may results from voluntary or involuntary movements, such as respiration. The criteria used to remove these pulses consisted in the analysis of amplitude and width abnormal pulse variations. Then, the pulse-by-pulse analysis was performed, consisting in the identification of the systolic peak (SP), diastolic notch (DN) and reflection point (RP) in the ADW, such represented in Figure 1 (upper row). An algorithm for prominent points identification was previously developed (Almeida et al., 2011a) for this task. This algorithm action is based on the analysis a number of features of the arterial distension waveform and its first derivative. After acquisition, the pulses are subject to a segmentation process and amplitude normalization to the diastolic-systolic pressure interval in a manner to allow a reliable comparison among subjects.

2.4 Data Analysis

2.4.1 Cross-relationships

SP, DN and RP associated time and amplitude was computed for all of the groups, as well as AI values. Group I and II are both composed by healthy subjects. To avoid similar patterns, only Group I was used in the analysis of cross-relationships. The arrival time histogram distributions were computed for the Groups I, III and IV, shown in Figure 2.

2.4.2 Pulse Variability

Group II was used to study of the data repeatability. The SP, DN and RP associated time and amplitude information was used for this purpose by the analysis of successive sessions and comparison of mean values and standard deviations. Furthermore the coefficient of variation (CV) within each subject in the same session was also computed. The left and right carotid differences were analysed. The time and amplitude parameterizations were also studied between left and right carotid side, as well as the AI values.

2.4.3 Physiological Changes During Angiography

The waveforms, before and after the procedure were collected through the invasive and non-invasive devices. However the comparison is only possible through visual inspection due to the limitations in data availability of invasive device.

3 RESULTS

3.1 Inter-groups Relationships

Figure 2 shows the arrival time histogram distributions, between all groups for the SP, DN and RP. SP occurs later in hypertensive subjects (Group IV) contrasting with RP that occurs early in group IV and later in group I. DN arrival time is similar in groups I and IV (hypertensive and normal subjects). However, DN presents a peculiar behaviour characterized by early time parameterizations in group III. When the algorithm is not able to identify the prominent

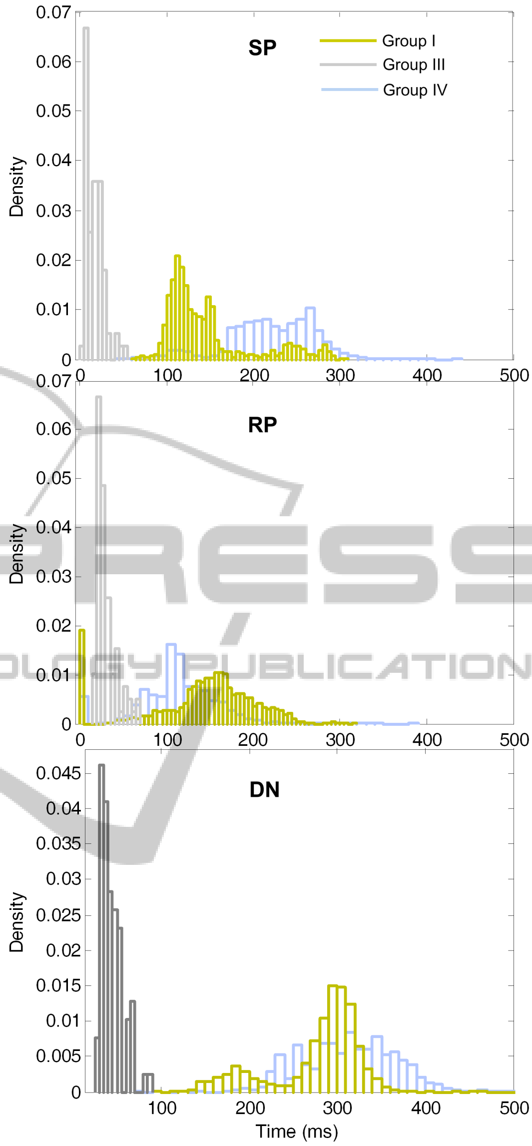

Figure 2: SP, DN, RP cross-relationships between groups I, II and IV.

points due to morphological artefacts or algorithm errors, a null timing is assumed, that is visible in the first bin of each histogram.

3.2 Pulse Variability

The pulse variability between sessions was studied for group II. The results are shown in Table 2, where for each one of the parameters was computed the *mean* $\pm$ *SD*.

Results demonstrate good repeatability obtained from RP analysis, 168.90 ± 40.12 ms and in amplitude 0.86 ± 0.09 (a.u.) in session I and 166.41 ± 34.10 ms and 0.87 ± 0.07 (a.u.) in session II. DN also

Table 2: Comparison of hemodynamic parameters obtained between sessions and bilateral common carotid acquisitions.

Parameter	Session 1	Session 2	Left	Right
SP (time(s))	155.69 ± 58.81	177.74 ± 64.26	163.70 ± 60.51	169.27 ± 64.51
SP (amp(a.u))	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01
DN (time(s))	285.98 ± 61.72	293.23 ± 39.31	286.96 ± 52.40	292.39 ± 51.98
DN (amp(a.u))	0.70 ± 0.15	0.72 ± 0.13	$0.72 \pm \pm 0.15$	0.71 ± 0.14
RP (time(s))	168.90 ± 40.12	166.41 ± 34.10	169.18 ± 39.48	165.98 ± 34.66
RP (amp(a.u))	0.86 ± 0.09	0.87 ± 0.07	0.88 ± 0.07	0.86 ± 0.08
AI (%)	-2.67 ± 15.94	0.48 ± 13.84	-1.55 ± 14.26	-0.70 ± 15.91

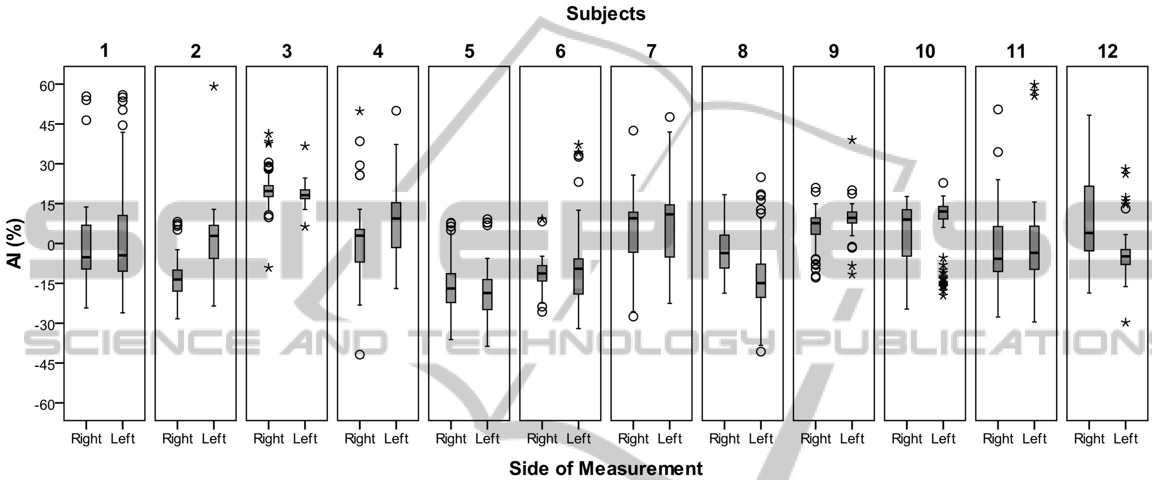

Figure 3: A: AI distribution in function of carotid side of measurement for each one of the subjects.

presents good agreement between time and amplitude information 285.98 ± 61.72 ms and 0.70 ± 0.15 (a.u.) in opposition with 293.23 ± 39.31 and 0.72 ± 0.13 (a.u.). SP presents more dispersion in time measurements. Since SP amplitude was previously normalized, during pre-processing, its relevance in the analysis is negligible.

The CV for each one of the subjects within the same measurement, independent of the visit and carotid side were computed. These values suggest intrinsically variability that needs to be taking in consideration for each one of the subjects. The CV mean obtained for all measurements was 18.58%, maximum rate of 33.7% and minimum 8.9%. All of the CV values are displayed in Table 3. The left-right carotid differences were also studied. The analysis of time parameterizations (mean ± SD) is satisfactory, without significant differences, as is presented in Table 2. Furthermore, for each one of the subjects were plotted the AI values depending of carotid side of measurement. It is evident AI dispersion for some of the subjects. The less marked differences in AI distribution are achieved for subjects 3 and 9, which are according with lowest CV values. The largest differences in AI and CV values occur for the 12 subject.

Table 3: CV values obtained for each subjects independently of session and carotid side of measurement.

Subjects	CV (%)
1	26.1
2	14.7
3	8.9
4	33.3
5	9.2
6	17.8
7	14.7
8	21.9
9	11.8
10	13.6
11	17.2
12	33.7

3.3 Angiography Subjects

The ADW comparison between both methods (invasive and non-invasive) is shown in Figure 4. A small segment (3-4 s) was chosen from each method before and after carotid intervention. It is possible to note the physiological alterations in both methods after carotid intervention. The DN, RP, and SP associated time

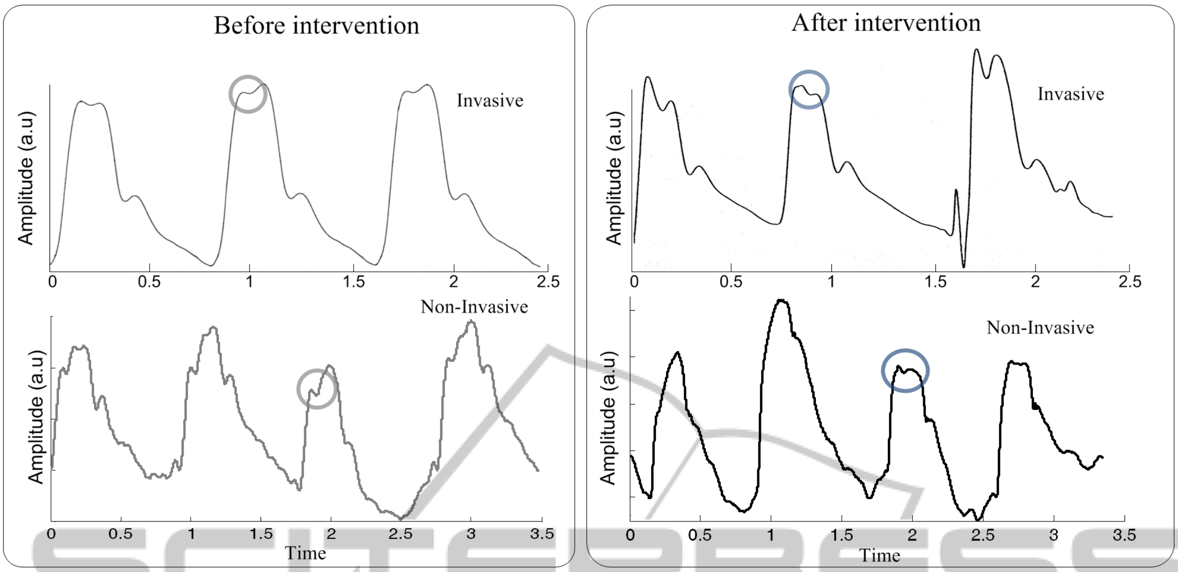

Figure 4: Set of three-four pulses detected invasively and non-invasively after and before carotid intervention. RP arrival time for each one is represented by gray and blue circles, corresponding respectively to ADW collected before and after carotid intervention.

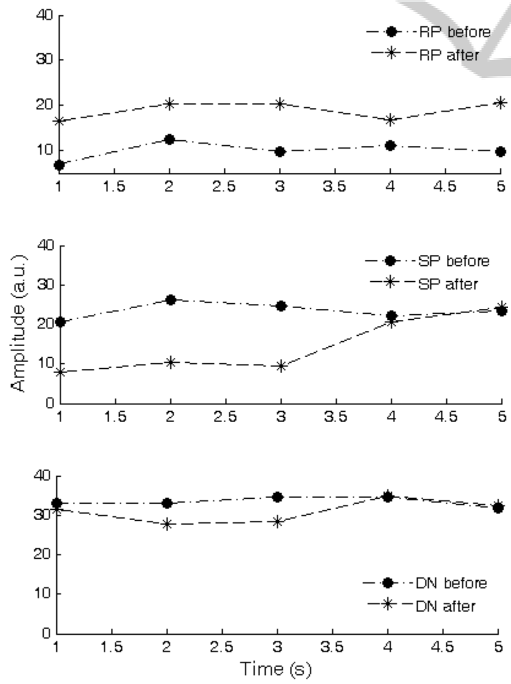

Figure 5: SP, RP and DN time parameterization comparison before and after carotid intervention.

were measured for the non-invasive method before and after carotid procedure and the data are presented in Figure 5. DN associated time changed little, as expected due to the absence of known cardiac valves complications. However, visible changes occur in the RP and SP analysis. Before the catheterization procedure, the RP occurs early, while SP appears later but after the carotid intervention this tendency was inverted leading to the occurrence of *normal* ADW patterns characteristics from healthy subjects (SP occurs first, and then RP). This fact seems to indicate that the anomalous reflection waveform disappeared with the carotid intervention, as indicated by blue circles in Figure 4. The main purpose of this case study was to prove that our probe is able to monitor physiological alterations, such occurs in stenosis situations.

4 DISCUSSION

The analysis of pulse variability for ADW measurements showed good results. There were no signicant differences within each pair over the range of measurements for any of the variables. The AI values observed for each one of the subjects shows differences in mean value for the subjects (#2, #8, #12), but correlated with high CV value leads to the assumption that physiological variations are the main cause. These results are according (Luo et. al., 2011) that demonstrate that the differences are only significative after 40/50 years. This is the main limitation of the present study. Vascular dysfunction of the left and right carotid arteries is affected by the age, among other factors. So, left and right carotid signals need to be further analysed to include different age groups and correlations with other parameters, such as biochemical parameters.

5 CONCLUSIONS

The present study investigated the viability of ADW assessment using a cardiac prototype in a wide number of subjects, comprising real clinical environment. The study of different groups during data analysis demonstrates the ability in different patterns comparison for each group. The data variability results showed good repeatability for the SP, RP and DN. Therefore, this prototype could be an interesting tool to use in the screening of arterial complications caused by the arterial stiffness development. This fact was also proved by the analysis of a stenosis case study where the clinical alterations were reliably monitored by our probe.

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