Reproducibility of Pulse Wave Analysis and Pulse Wave Velocity in Healthy Subjects

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Keywords: Optical Probe, Waveform Distension, Pulse Wave Analysis, Pulse Wave Velocity, Reproducibility.

Abstract: The hemodynamic parameters extracted from pulse pressure waveform, by pulse wave analysis (PWA) and pulse wave velocity (PWV) are strong independent predictors of cardiovascular morbidity. The aim of this study is to investigate the reproducibility of pulse pressure profile and arterial stiffness indicators, i.e., Augmentation Index (AIx), Subendocardial Viability Ratio (SEVR), maximum rate of pressure change (dP/dt_{max}), Ejection Time Index (ETI), as measured using a contactless optical system. Reproducibility was evaluated in 13 healthy subjects by two senior operators ('A' and 'B') that acquired signals in alternate order (ABAB or BABA). The PWV result showed a good inter and intra-operator reproducibility. The mean difference between the two operators is 0.1570 m/s with a SD of 0.8160 m/s, this difference represents approximately 3.49% of the arithmetic average of the means obtained by each operator per trial. Between trials, differences of less than 8% of the mean PWV value for each operator were obtained. PWA repeatability results are considered high for HR, strong for Aix and moderate for dP/dt_{max}. The newly developed optical system showed good reproducibility as evaluated by both inter-operator and intra-operator methods.

1 INTRODUCTION

Cardiovascular diseases are the main cause of death in the general population. For this reason, the identification of risk factors at an early preclinical stage of disease is an important clinical issue.

Besides, also markers of arterial stiffness such as Pulse Wave Velocity (PWV) and Pulse Wave Analysis (PWA) comprised of Augmentation Index (AIx), Subendocardial Viability Ratio (SEVR), maximum rate of pressure change (dP/dt_{max}), Ejection Time Index (ETI), have been shown, in recent studies, to be strong independent predictors of cardiovascular morbidity (Crilly et al., 2007).

Several standard techniques are widely used for estimation of pulse pressure waveform and main hemodynamic parameters, however, all of them require direct contact with the patient's skin at the artery site, this procedure may distort the waveform integrity. The optical solutions represent a significant improvement to overcome this limitation for measuring the distension waveform of the carotid artery due to their truly non-invasive nature (Pereira et al., 2011a; Pereira et al., 2011b; Pereira et al., 2012).

In peripheral arteries, like the carotid, the pressure wave travels across the arterial tree in a compliant way, forcing the blood vessels to distend elastically according to the pressure wave profile and imparting a visible distension effect. The distension waveform and the pressure waveform have an analogous wave contour and, therefore, can reciprocally be used for pulse wave analysis (Laurent et al., 2006; Pereira et al., 2013a; Pereira et al., 2013b).

In previously studies, the optical system proved to be reliable in detecting the arterial distension waveform. In order to evaluate the capability of the developed optical device to accurately detect the pulse waveform several studies was developed (Pereira et al., 2011b, Pereira et al., 2013b).

This study investigates the reproducibility of pulse pressure profile, and both inter-operator (systematic differences among the observers) and intra-operator (deviations of a particular observer's score on a particular patient) variability analysis

Pereira T., Santos I., Pereira T., Santos H., Almeida V., Pereira H., Correia C. and Cardoso J..
Reproducibility of Pulse Wave Analysis and Pulse Wave Velocity in Healthy Subjects.
DOI: 10.5220/0004802502210228
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2014), pages 221-228
ISBN: 978-989-758-011-6

were performed. Thus the aim of the present study is to assess intra- and inter-operator reproducibility. Reproducibility was evaluated in 13 healthy subjects by two senior operators, and evaluates the degree of closeness of the repeated measurements made on the same subject either by the same instrument.

This is a prospective study and similar studies of this kind presents a sample of the same magnitude (Protogerou et al., 2012; Vappou et al., 2011).

The reproducilbity study covering inter-operator and intra-operator variability analysis. Inter-operator variability refers to systematic differences among the observers. Intra-operator variability refers to deviations of a particular observer's score on a particular patient that are not part of a systematic difference.

This work contributes to the design a protocol for this type of non-invasive probes used in determination of hemodynamic parameters, which contains the required guidelines to assessment test for the operator variability.

2 MATERIALS AND METHODS

2.1 Technology

The proposed probes were developed to measure the arterial pulse wave profile at the carotid site and are based on the reflectance fluctuations of the skin surface during the underlying pulse wave propagation (Pereira et al., 2011b; Pereira al., 2012).

The illumination source is provided by light emitting diodes (LEDs) with 635 nm and the light detection is performed by two photodetectors, placed at a specific distance of 20 mm apart (see Figure1), to assess the pulse pressure waveform at two distinct spots, ensuring the accurate determination of local pulse transit time (PTT) and thus, of the local PWV.

Figure 1: Structure of optical probe inside the plastic box.

The enclosing box contacts the skin, to stabilize and maintain constant the distance between the photodector and the artery site (3 mm), however in the local of measurement there is no contact and consequently no distortion of signal.

The signals were digitized with a 16-bit resolution data acquisition system (National Instruments, USB6210®) with a sampling rate of 20 kHz and stored for offline analysis using Matlab® (R2011a).

2.2 Study Population

The group consisted of 13 healthy human volunteers, normotensive and with no documented history of cardiovascular disorders or diabetes that had undergone signal acquisitions with the optical probe. The characteristics of the volunteers are presented in Table 1.

Table 1: Main characteristics of the sample.

Parameters	Range values
n (Males/Females)	13 (7/6)
Age (years)	24.1 ± 2.2
Height (cm)	166.6 ± 8.0
Weight (kg)	63.8 ± 12.8
BMI (kg/m^2)	22.8 ± 2.9
Brachial SBP* (mmHg)	113.5 ± 12.5
Brachial DBP* (mmHg)	73.2 ± 9.1
Heart Rate* (bpm)	65.4 ± 11.4

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* Measure in brachial, with commercial sphygmomanometer (blood pressure cuff).

2.3 Study Protocol

Two trained blinded operators (further referred as ‘A’ and ‘B’) alternatively undertook 2 measurements each, in the same location, using the same probe in the same day, over a short period of time. The subjects rested for 10 minutes in supine position, reached the physiological baseline conditions, both operators measured blood pressure (BP) before each measurement and acquired signals in alternate order (ABAB or BABA). Each trial consisted of few acquisitions, usually between 2 and 4, and the values of each trial were further averaged.

Similar reproducibility studies have been carried out with same protocol, that accepted as rigorous approach this evaluation of PWA and PWV repeatability (Crilly et al., 2007; Frimodt-Moller et al., 2008). As expected BP, pulse pressure waveform and consequently the hemodynamic indices remained, are stable during the assessment period. The sequence of operator was random, which reduce bias will have tended to compromise intra-operator variability. The study protocol was approved by the ethical committee of the Centro Hospitalar e Universitário de Coimbra, Portugal. All the subjects were volunteers and gave a written informed consent.

2.4 Hemodynamic Measurement

The assessment of the cardiovascular system condition based on multi-parameters allows a more precise and accurate diagnosis of the heart and the arterial tree condition. The multiple parameter risk response score is a useful tool to categorize patients for selection of appropriate interventions. The optical system allows the determination the several parameters based in the pulse pressure wave profile, and possible to overcome errors in the determination of one of the parameters. Risk indicators, can be determined from the main parameters extracted from waveform and its time characteristics and pulse wave velocity.

In the pulse wave analysis, AIx is the most widely researched index and is defined as the ratio of blood pressure amplitudes at the timings of the reflection point (RP) and systolic peak (SP), thus resulting in RP/SP expressed as a percentage. A convention for the signal of AIx, defines when the reflected wave arrival occurs earlier than the systolic peak the AIx have positive value while a negative value of AIx indicates that the reflected wave arrives after the systolic peak (Crilly et al., 2007).

The Subendocardial Viability Ratio, or Buckberg Index, varies between 119 and 254% in healthy subjects, and is a parameter that estimates the myocardial oxygen supply–demand relative to the cardiac workload and is an indicator of subendocardial ischaemia (Crilly et al., 2007).

The ejection time, also referred to as Left Ventricular Ejection Time, corresponds to the ventricular systolic ejection time between the aortic valve opening and closing. Its ratio to the total duration of the cardiac cycle represents the ETI (%) and varies between 30 and 42% in healthy individuals (Kara, Okandan et al., 2004).

The dP/dt_{max} parameter reports the maximum rate of pressure change in the systolic upstroke and gives information about the initial velocity of the myocardial contraction, which is also an index of myocardial performance and the range of values expected for a healthy population is 772 ± 229 (mmHg/s) (Miller et al., 2007).

2.5 Signal Processing

The pulse wave velocity was calculated using the PTT determined by the cross-correlation method between the signals from the two photodetectors.

A set of cyclic waveforms coming from one of the channels, undergo segmentation and normalization to the diastolic–systolic pressure interval. The signal segmentation is performed using the wave foot, detected by the minimum, and was based on an automated peak detection function in Matlab® (Peakdetect from the Mathworks, by Tom McMurray). The average pulse are digitally low-pass filtered (with a cut-off frequency of 30 Hz), which removes the noise, thus allowing the signal differentiation. The developed algorithm for waveform features determination is based on differential calculus and was applied to the remarkable points as a tool to quantify arterial pressure waveform features (Korpas et al., 2009).

An assessment of arterial brachial pressure by conventional measurement using a sphygmomanometer was conducted prior and after the exam for calibration purposes. These values were used to calibrate the carotid pressure waveform as recommended and according to the calibration method proposed by Kelly and Fitchett (Kelly & Fitchett, 1992).

2.6 Statistical Analysis

The data are reported as mean values ± standard error with 95% confidence intervals and percentages were used to describe qualitative variables. The Bland-Altman approach for '95% limits of agreement' was used in inter and intra-operator differences in paired measurements.

Reproducibility was assessed by Intraclass Correlation Coefficients (ICC), Coefficients of Variation (CV), Standard Error of Measurement (SEM) and Limits of Agreement (LA) (Euser et al., 2008; Vanmolkot et al., 2005).

Intraclass correlation coefficient was computed for repeatability studies, based on one-way analysis of variance (ANOVA). ICC describes how strongly measurements in the same group resemble each other. The CV expresses the variation between measurements in relation to the mean value of all measurements. The LA provides direct information about the absolute measurement error. The standard error of measurement takes the amount of measurement error into consideration (Bartlett & Frost, 2008). Statistical analysis was performed by SPSS® software (SPSS Inc., Chicago, Illinois).

3 RESULTS

3.1 PWV Results

The normality of the variables distribution for each trial/operator were assessed using the test of normality Shapiro-Wilk, all the sets of PWV values follow a normal distribution (Significance value ≥ 0.169, $p<0.05$). The correlation between the PWV values obtained by both operators is plotted in Figure 2a.

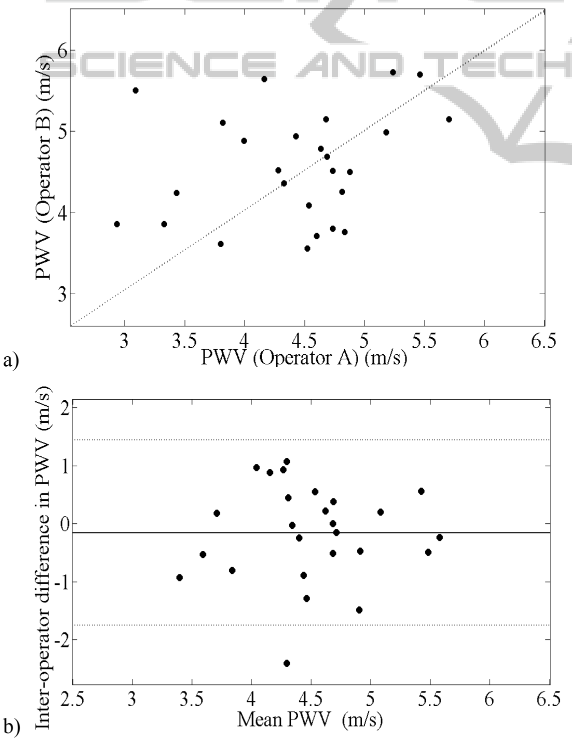

Figure 2: Comparison between two operators (A and B). (a) Correlation between the operators for PWV measurements. (b) Bland-Altman plot displays the inter-operator difference for the two operators as a function of the mean of the determined PWV.

The mean difference between the two operators is 0.1570 m/s with a SD of 0.8160 m/s as shown in a Bland-Altman plot (Figure 2b). This difference represents approximately 3.49% of the arithmetic average of the means obtained by each operator per trial.

Considering all measurements there is only one that has a difference greater than 2 m/s, and just 4 measurements have a difference higher than 1 m/s. According to Figure 2 the acceptable intra-operator PWV differences (<1 m/s) are observed in 22 measurements (85%).

The between-operator ICC of 0.602 (95% from 0.12 to 0.82) revealed a moderate agreement between classes (measurement made by operator 'A' and operator 'B').

Considering variance results, in Table 2, there is no evident variation depending on the operator. However, considering the values between trials, the trial 2 shows lower variance comparing to trial 1 for each operator. Furthermore, the coefficients of variation obtained for inter-observer and intra-observer reproducibility were less than 15%.

The graph represented in Figure 3 shows that values obtained by operator 'A' are very similar to the operator 'B'. Also the mean values for PWV from different trials of each operator have very close values.

In spite of this apparent difference, the ICC for both trials per operator shows that for operator 'A' there is a moderate agreement between trial 1 and 2 (ICC=0.674; 95% CI from 0.01 to 0.82) and for operator 'B' this coefficient has a similar value of agreement (ICC=0.654; 95% CI from -0.17 to 0.89).

Table 2: PWV mean values obtained by each operator A and B, per trial.

Trial	Ope	Range (min-max) (m/s)	Mean (m/s)	SD (m/s)	Var
1	A	(3.090-5.463)	4.263	0.734	0.539
	B	(3.616-5.699)	4.629	0.714	0.510
2	A	(2.932-5.710)	4.568	0.649	0.422
	B	(3.558-5.729)	4.517	0.663	0.440

Ope: operator; SD: standard deviation; Var: variance.

To better understand the variability of the PWV values, the values obtained within each operator and between trials are represented in the Figure 4.

No significant association between the PWV intra-operators values was found after a correlation analysis. The average difference between the two trials assessed by the operator A was -0.3049 m/s with a SD of 0.7388 m/s as shown in a

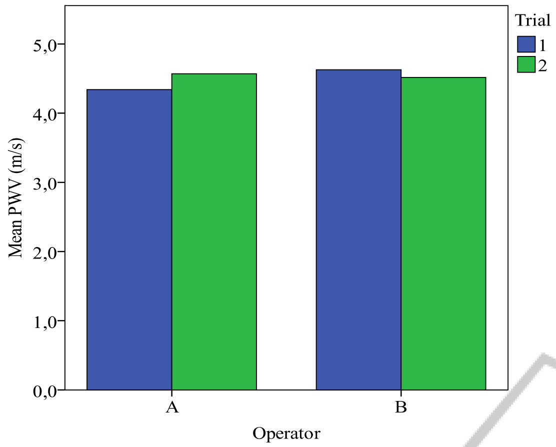

Figure 3: Bar graphs for mean values of PWV by operator.

with a SD of 0.7388 m/s as shown in a Bland-Altman plot in Figure 4 b). This limit of agreement (from -1.78 to 1.17 m/s) represents at most 6.9% of the mean PWV for this operator.

The average difference between the two trials assessed by operator B was 0.1123 m/s with a 0.6801 SD of m/s as shown in a Bland-Altman plot in Figure 4 c). This limit of agreement (from -1.25 to 1.47 m/s) represents at most 7.6% of the mean PWV value for operator B.

3.2 PWA Results

Relatively to the other PWA parameters the values determined in this dataset by the optical system are shown in Table 3.

The standard deviation of measurement errors is therefore a reflection of the reliability of the test response (Bartlett & Frost, 2008). The SEM is expressed in the actual units of measurement, making it easy to interpret, i.e. the smaller the SEM, the greater the reliability and the values obtained for HR, AIx and ETI parameter are low values, only in the case of dP/dt_{max} and SEVR were presents slightly higher values for the SEM.

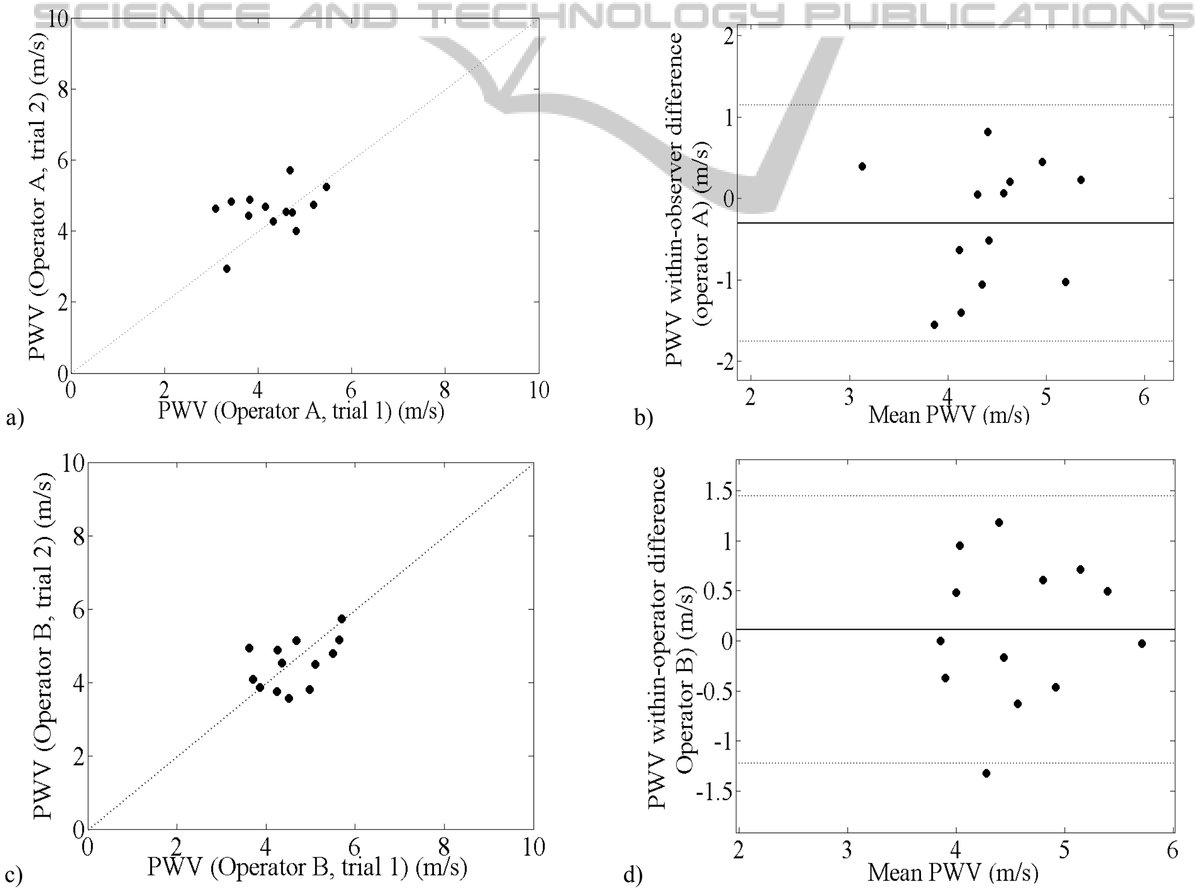

Figure 4: Comparison between two trials for two operators. (a) Correlation of PWV between two trials acquired by Operator A. (b) Bland-Altman plot displays the intra-operator difference for the Operator A. c) Correlation of PWV between the two trials acquired by Operator B. d) Bland-Altman plot displays the intra-operator difference for the Operator A.

Table 3: Mean values of PWA hemodynamic parameters for each operator.

	Ope	Mean	SEM	(95% CI)	SD
HR (bpm)	A	65.41	1.47	62.48 to 68.35	11.18
	B	64.95	1.79	61.34 to 68.57	11.90
AIx (%)	A	-1.57	1.70	-5.15 to 2.00	13.61
	B	-4.19	1.89	-7.99 to -0.39	12.51
SEVR (%)	A	149.4	9.38	130.98 to 168.53	71.20
	B	152.9	13.04	126.63 to 179.84	86.53
dP/dt_{max} (mmHg/s)	A	328.4	20.75	286.92 to 370.00	158.00
	B	347.7	19.59	308.29 to 387.25	129.94
ETI (%)	A	42.24	1.96	38.31 to 46.16	14.93
	B	42.61	2.27	38.04 to 47.18	15.04

3.2.1 Inter-Operator Repeatability

The proximity of the mean values Inter-operator is expressed in the ICC results (Table 4). Some parameters showed good agreement. As one can observe, the HR and dP/dt_{max} had shown high ICC values, concordant with almost perfect agreement. On the other hand for SEVR and ETI parameters, the determined low ICC is congruent with fair agreement. Concerning AIx, its corresponding ICC values show a moderate level of between-operator agreement.

In Figure 5 the results for AIx measurements for all subjects for operator ‘A’ and operator ‘B’ are represented. It is visible that there are not major differences between AIx values obtained by the two operators for each subject. The results in the figure show a common trend between the values obtained for AIx parameter by two operators measurement for each subject.

A positive Augmentation Index could indicate a case of arterial stiffness. With an increase in stiffness there is a faster propagation of the forward pulse wave as well as a more rapid reflected wave, a positive AIx means that the reflected wave arrival occurs earlier than the systolic peak is. Depending on the AIx value (positive or negative) the pulse wave type is defined as follows: when a negative value occurs the pulse shows characteristic of healthy subjects and when a positive value occurs the pulse have characteristic of subjects suffering from arterial stiffness (Almeida et al., 2013).

Table 4: Inter-operator repeatability of PWA: based in the differences correspond to ‘Operator A’ measurement minus ‘Operator B’ measurement).

	ICC[a]	(95% CI)	Mean diff	SD (2SD)	Limits of agreement[b]
HR (bpm)	0.976	0.95 to 0.99	-0.279	3.52 (7.03)	-7.31 to 6.75
AIx (%)	0.734	0.41 to 0.88	-1.929	10.01 (20.02)	-21.95 to 18.09
SEVR (%)	0.472	-0.20 to 0.77	7.173	152.26 (304.52)	-151.75 to 166.09
dP/dt_{max} (mmHg/s)	0.581	0.09 to 0.81	-2.660	14.96 (29.91)	-263.61 to 345.44
ETI (%)	0.442	-0.24 to 0.75	0.014	0.09 (0.19)	-32.57 to 27.25

[a] Intraclass correlation coefficient (ICC) using an absolute agreement definition.

[b] Limits of agreement for differences= mean difference ± 2SD.

Mean diff means Mean of difference between measures.

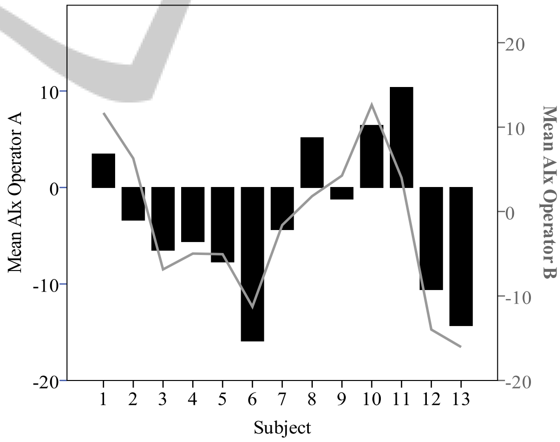

Figure 5: Trends in AIx measurements: mean of values for each subject by operator A and operator B.

3.2.2 Intra-Operator Repeatability

Comparing the ICC results from Table 5 with those presented in Table 4, which are referent to within-operator differences, one could see that there are no major discrepancies, except for AIx that has a lower ICC and dP/dt_{max} that is slightly higher.

Table 5: Intra-operator repeatability of PWA, based in the differences corresponds to ‘trial 1’ measurement minus ‘trial 2’ measurement.

	ICC[a]	(95% CI)	Mean diff	SD (2SD)	Limits of agreement[b]
HR (bpm)	0.926	0.83 to 0.97	1.837	5.73 (11.46)	-9.62 to 13.30
AIx (%)	0.448	-0.23 to 0.75	-2.398	13.00 (26.00)	-28.40 to 23.61
SEVR (%)	0.473	-0.20 to 0.77	-4.804	79.53 (159.05)	-163.86 to 154.25
dP/dt_{max} (mmHg/s)	0.678	0.27 to 0.86	6.902	141.85 (283.70)	-276.80 to 290.60
ETI (%)	0.494	-0.16 to 0.78	0.740	14.63 (29.27)	-28.53 to 30.00

4 CONCLUSIONS

The reproducibility study was performed in 13 volunteers by two trained operators. Both operators measured BP before each measurement and acquired trials in alternate order. This measurements reproducibility study has demonstrated a subjective component based on the measurement techniques used by different operators.

The main limitations of this study are its small size and the inclusion of healthy volunteers rather than patients. However it is common to evaluate emerging techniques in volunteers initially and these studies are important platforms for further method improvement and subsequent patient studies.

The PWA repeatability results are considered high for HR, strong for AIx, moderate for dP/dt_{max} and low for SEVR and ETI. Actually, for all analysis the resulting values for dP/dt_{max} and SEVR differ substantially from the ones presented as reference and show the lower values for reproducibility evaluation, probably originated by the calibration method used.

The PWV results had a good inter and intra-operator reproducibility judged by the Bland-Altman plots as well as the test of differences between measures. The two photodetectors (placed at a precise and well-known distance of 20 mm), detect the pulse wave propagation, along the arterial segment. This distance could be a limitation only in cases was a small segment of carotid artery is accessible, which difficult the position of two photodetectors centered on the artery.

The factors such as the position of two photodetectors in the carotid vessel, tremors in the hands of an operator, respiratory movements of the volunteers could introduce differences in the measurements between operators and trials. These factors might affect the measurements and are possible to quantify making changes in the probe by the introducing an accelerometer or a respiratory band in the volunteers, however escaped to the objective of this work.

The newly developed optical system showed good reproducibility as evaluated by both inter-operator and intra-operator methods. This study could be extended by comparing PWV and PWA values from patients with vascular risks.

The cohort size is only 13 but it is enough to draw conclusions about both inter-operator and intra-operator variability analysis, however the present results and clinical implications need to be confirmed by larger studies that enable the predicted ability of the optical system and including population with heterogeneity characteristics: age, blood pressure, BMI, cardiovascular diseases.

ACKNOWLEDGEMENTS

The authors acknowledge the support from Fundação para a Ciência e Tecnologia (FCT) for funding (SFRH / BD / 79334 / 2011). Project developed under the initiative of QREN, funding by UE/FEDER, through COMPETE - Programa Operacional Factores de Competitividade.

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