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Repeatability of Pulse Wave Velocity or How Acceptable is a Single Measurement of Arterial Stiffness

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ABSTRACT: Pulse wave velocity (PWV) is a parameter of arterial stiffness, important in the evaluation of risk for cardiovascular diseases. Single measurement in case of good repeatability is time-saving in large population-based studies. The rationale for this study was to investigate the repeatability and show possible acceptability of single arterial stiffness measurement using special device - Arteriograph. Repeatability of Arteriograph was investigated in few studies. However the extended complex assessment was not applied. PWV of 85 subjects were measured in duplicate. Data was distributed between normal (NBP) and high (HBP) blood pressure groups. Statistical evaluation was performed according to good practice recommendation for estimation of repeatability of numerical variables: the intraclass correlation coefficients showed overall excellent reliability (>0.9), paired t-test for mean of differences and Bland-Altman plot was without deviation in NBP and with systematic discrepancy in HBP. However, the clinical categorization was without marked differences in both groups. In comparison with the recommendations of American Heart Association the PWV by median of duplicates showed a good repeatability in HBP and NBP (0.3 and 0.08 m/s, accordingly). According to the ARTERY Society recommendation the mean of differences for PWV was excellent in NBP (-0.1 m/s) and acceptable in HBP (0.3 m/s); SD of differences in NBP and HBP (0.6 and 0.6 m/s, accordingly) was acceptable. Our study showed the acceptability of a single measurement on Arteriograph in setting of population-based study. Caution should be taken in interpreting the individual results of the subjects with high blood pressure.

KEYWORDS: Arteriograph, Arterial stiffness, Pulse wave velocity, Repeatability

I. INTRODUCTION

The role of arterial stiffness in the development of cardiovascular diseases has attracted more and more attention in recent years.^[1, 2] Several invasive and non-invasive approaches have been developed for the investigation of arterial stiffness. One of non-invasive techniques based on the oscillometric measurement is used in commercially available device Arteriograph (TensioMed Ltd., Budapest, Hungary). Arteriograph software provides several parameters for the assessment of arterial stiffness, among which pulse wave velocity is the mostly used. The growing use of pulse wave velocity in clinical practice puts forward the special requirements for both the simplification of the procedure of measurements and its quality. The quality of measurements depends mainly on the technical characteristics of the device and on the effect of the investigators and also on variable conditions of investigated subjects and environment. The Arteriograph technique was successfully validated against invasive measurements,^[1, 3] as well as against non-invasive applanation tonometry and piezoelectronic techniques.^[4-6] While the overall effect of the investigator, device, patient- and environment-dependent conditions, which manifested as the difference between the values of the repeated

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 7, July 2017

over a short period of time measurements and expressed in terms of repeatability, has not been completely validated on Arteriograph.

Currently, there is the recommendation of experts based on consensus opinion to perform arterial stiffness measurements in duplicate, what is expected to be useful and effective.^[1] Undoubtedly the repeatability influences the clinical interpretation, which can be critical for the assessment of arterial stiffness results in individual subjects. In this case the categorization of one measurement as normal and the other as abnormal is not acceptable.^[7] However, a single measurement could be financially reasonable in the setting of population-based studies.

To our knowledge there are only a few studies on the investigation of Arteriograph repeatability and none on the assessment of the repeatability by extended statistical analysis and the evaluation of the effect of the repeatability on clinical categorization of pulse wave velocity values.^[8, 9] The task of current investigation was to evaluate the acceptability of a single measurement on Arteriograph for arterial stiffness assessment. To achieve this aim the repeatability of pulse wave velocity was assessed by statistical evaluation of the values of two consecutive measurements performed by one investigator. To verify whether each of two consecutive measurements provides equivalent clinical assessment of arterial stiffness, the clinical categorization of each value of pulse wave velocity in pairs of duplicate was assessed.

II. RELATED WORKS

There are little data in the literature on the target repeatability in the assessment of arterial stiffness by one device. "ARTERY Society guidelines for validation of non-invasive hemodynamic measurement devices" (Wilkinson IB, *et al.*) gives the recommendations for mean differences and SD in the comparison of different devices.^[14] The target difference in duplicate measurements of one device is indicated in the "Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness" (Townsend RR, *et al.*).^[1]

Recently, the most similar with our investigation studies on repeatability of Arteriograph were conducted on healthy persons by Ring M, *et al.*,^[8] and on subjects with diabetes by Krogager C, *et al.*^[9] However, extended statistical analysis and clinical categorization of duplicate values were not applied in these works and also number of investigated persons was significantly smaller than in our study.

III. MATERIALS AND METHODS

Subjects and study design

The current investigation was performed as a preliminary research of the cross-sectional population based study of arterial stiffness and biochemical markers of atherosclerosis in Tallinn population. The study was performed in accordance with the Helsinki Declaration of 1983 and approved by the Tallinn Medical Research Ethics Committee of National Institute for Health Development of Estonia (Nr 1005). Informed consent was obtained from all individual participants included in the study.

100 subjects from the list of main study participants were invited for this study. The arterial stiffness measurements by Arteriograph were performed on 87 subjects who responded to the invitation to participate in the investigation.

Subject condition was standardized according to the recommendation on general user procedures for arterial stiffness devices.^[10] Investigation was performed between 09:00 am and 11:00 am in a quiet room at temperature-controlled condition of 23-25°C. Participants spent at least 10 min rest in the supine position before the examination. All the subjects were an overnight fast and without morning antihypertensive medications. Smoking, caffeine-containing products and alcohol consumption were not allowed 24h before the investigation.

Two consecutive (duplicate) measurements of blood pressure and pulse waves were performed with the interval of 2-3 minutes on each subject by one experienced investigator using Arteriograph. The quality of pulse waves was verified by visual inspection and according to recommended for Arteriograph target standard deviation of PWV, calculated automatically by the device. Pulse waveforms with early and late systolic wave and regular sequence, without saw toothed curves were considered as visually acceptable. The recordings with standard deviation of pulse wave velocity in ranges of equal or higher than 0 and lower than 1.1 m/s were considered as technically acceptable.

The data on all the accepted measurements were distributed between two groups. The groups were formed taking into consideration the magnitude of blood pressure at first measurement and according to the recommendation of ESC/ESH

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 7, July 2017

Hypertension Guidelines 2013 for office blood pressure. ^[11] Data on the subjects with systolic blood pressure (SBP) \geq 140 mmHg and/or diastolic blood pressure (DBP) \geq 90 mmHg were combined into the group named as high blood pressure group (high BP) and data on the subjects with SBP < 140 mmHg and/or DBP < 90 mmHg – into the normal blood pressure group (normal BP).

Repeatability of pulse wave velocity measurements was evaluated by statistical analysis of differences in duplicates. The final decision about the reliability of a single measurement was made considering the results of repeatability and clinical categorization of the duplicate values of pulse wave velocity.

Description of the determination of pulse wave velocity by Arteriograph

Arteriograph (TensioMed Ltd., Budapest, Hungary) is a commercially available non-invasive oscillometric device. Arteriograph registers the periodic blood pressure oscillations on the brachial artery of the upper arm, beneath the cuff, at a single location. Blood pressure is recorded before and after getting a cuff pressure in excess of 35 mmHg over the systolic blood pressure. Fluctuations of blood pressure are computerized into pulse wave curves and analyzed by software of the device. The software decompounds pulse waves to the early systolic, late systolic and diastolic waves and registers the onset and peaks of the waves. The time difference between the peaks of the first systolic and the second reflected waves represents the pulse wave transit time (RT) from the left ventricle of heart to the reflection point at bifurcation of abdominal aorta and back. It is assumed that the distance travelled by a pulse wave during this time is approximately related to the duplicate distance between jugular notch and symphysis measured on the body surface. The ratio of this distance to the RT is calculated by software of the Arteriograph and is named as aortic pulse wave velocity (PWV).

Statistical analysis for the assessment of the repeatability of pulse wave velocity

The descriptive statistics of the study parameters, normality of distribution of differences and paired t-test for the means of differences with calculation of differences between duplicate measurements, mean difference, standard deviation of differences and confidence intervals were estimated by SPSS statistical software version 17.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered as statistically significant. The intraclass correlation coefficients were estimated using MedCalc statistical package version 14.8.1 (MedCalc Software, Ostend, Belgium; <http://www.medcalc.org>; 2014), based on the same rates for all subjects, absolute agreement, two-way model. The Bland-Altman plot of agreement between duplicate measurements on each subject was constructed by the above-mentioned MedCalc statistical package version 14.8.1. No subjects or outliers were excluded from any part of the statistical analysis.

Clinical categorization of pulse wave velocity

The software of Arteriograph automatically categorizes the values of PWV as optimal, normal, increased and abnormal. All the optimal and normal values of pulse wave velocity were categorized as normal and all of the increased and abnormal values as abnormal.

IV.RESULTS

The measurements of 85 subjects passed quality control assessment successfully and were accepted for the analysis. The measurements of 2 subjects were excluded from the study because of the irregular sequence of pulse waves.

Basic characteristic of the parameters under study

Basic characteristic of the first measurement of each pair of duplicate recordings performed by Arteriograph, as well as age of the investigated subjects are shown in Table 1. Data are distributed between high BP (n=49) and normal BP (n=36) groups. The means and ranges of age in these groups are very close to each other.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 7, July 2017

Table 1 Basic characteristic of the parameters under study

	Units	N	Minimum	Maximum	Mean	Std. Deviation
Age (high BP)	years	49	27	64	53	11
Age (normal BP)	years	36	26	64	51	11
SBP1(normal BP)	mmHg	36	104	139	125	8,9
SBP1(high BP)	mmHg	49	128	251	161	20,9
DBP1(normal BP)	mmHg	36	51	87	77	7,2
DBP1(high BP)	mmHg	49	72	139	92	12,2
PWV1 (normal BP)	m/s	36	3,4	11,5	7,4	2,28
PWV1 (high BP)	m/s	49	4,0	17,4	9,3	2,84

For the assessment of the repeatability by statistical analysis the differences between duplicate measurements of PWV were estimated and normality of their distributions was evaluated by Shapiro-Wilk test for normality. Differences of PWV in investigated groups were normally distributed at significance level of $P \geq 0.05$ ($P=0,286$ and $P=0.107$ in high BP and normal BP group, accordingly).

Assessment of the intraclass correlation coefficients

The intraclass correlation coefficient (ICC) of duplicate measurements is a test-retest reliability index and reflects the degree of correlation as well as agreement between measurements. ICC analysis compares the variability of duplicate measures of each subject with the total variation across all measurements and all cases, ICC greater than 0.9 indicate excellent reliability.^[12]

Table 2 Intraclass Correlation Coefficients

PWV Diff	Intraclass correlation	95% Confidence Interval
High BP (n=49)	0,9741	0,9546 to 0,9853
Normal BP (n=36)	0,9671	0,9370 to 0,9831

Table 2 shows the ICC of duplicate measurements for the investigated groups. The PWV duplicates demonstrated excellent reliability (ICC >0.9) among the duplicate measurements in each pair and across all the pairs in both groups.

Assessment of the paired t-test for the mean of differences

Estimation the means of differences between duplicate measurements of PWV are shown in Table 3.

Table 3 Paired Samples Test for differences

	Units	Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean of Diff	Std. Deviation	Std. Error Mean	Lower	Upper			
PWV Diff (normal BP)	m/s	-,11861	,58084	,09681	-,31514	,07792	-1,225	35	,229
PWV Diff (high BP)	m/s	,28571	,57031	,08147	,12190	,44953	3,507	48	,001

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

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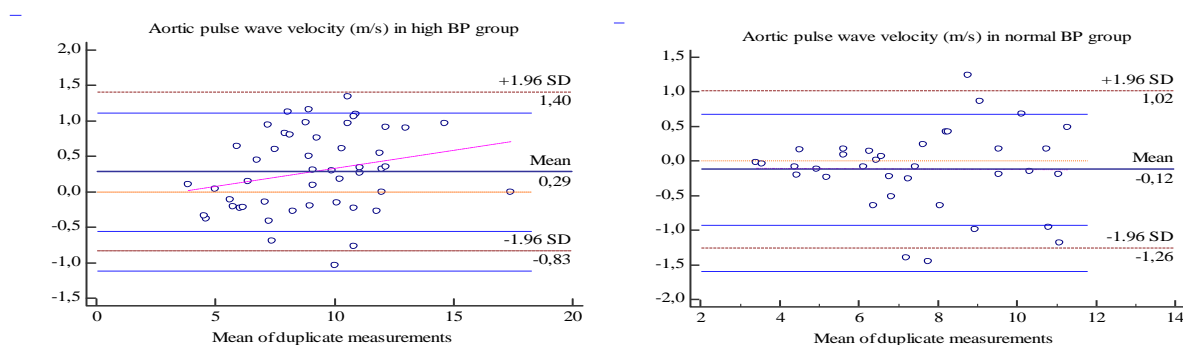
Vol. 6, Issue 7, July 2017

Table 3 demonstrates that the mean of differences between two consecutive measurements of PWV was not significant in normal BP group and was found statistically significant ($p=0.001$) in high BP group, even being very close to zero (0.29).

Assessment of the Bland – Altman plot for agreement between duplicate measurements

Bland-Altman plot displays the pattern of agreement between the duplicate measurements. The differences of the paired measurements are plotted on the graphic against their means. Two standard deviations of the mean of differences are represented as the limits of agreement. Also the 95% confidence intervals for the lower and upper limits of agreement are shown on the plot.

Figure 1 Bland-Altman plots for agreement between duplicate measurements of PWV in high BP and normal BP groups



Bland and Altman have recommended that 95% of the points should lie within the limits of the agreement.^[13] Accordingly, PWV duplicate measurements in both groups are in good agreement, with no outliers. The mean of differences is very close to zero in these groups. The scatters of differences are almost evenly distributed around the mean in a normal BP group. However they showed the tendency of prevalence the negative differences at smaller values and positive differences as the PWV increases in high BP group.

Assessment of the clinical meaning of duplicate measurements

In the group with normal BP clinical categorization of PWV values was without discrepancies between first and second measurements in all 36 subjects. In the group with high BP there was one case from 49 investigated (2%) of the different categorization of duplicate PWV values, with first value categorized as normal and second – as increased.

V. DISCUSSION

To our knowledge, whereas a few studies on repeatability have been carried out, the present study is the first that demonstrates the repeatability of Arteriograph technique, using extended statistical analysis, clinical categorization and other available in literature recommendations for validation of non-invasive hemodynamic measurement devices. The number of investigated subjects ($n=85$) in our study was in absolute accordance with the recommendation for device validation of minimum 83.^[1, 14] The repeatability was assessed following the good practice recommendation for the evaluation of repeatability of the numerical variables, based on extended statistical analysis,^[15] including the intraclass correlation coefficients, paired t-test for the mean of differences and Bland-Altman plots of agreement. Statistical analysis was followed by the comparison of clinical categorization of duplicate values.

Repeatability by extended statistical analysis

Our study demonstrated the excellent repeatability of PWV in the investigation of subjects in normal BP group. The repeatability in high BP group was with some deviations in statistical results and clinical categorization.

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 7, July 2017

The assessment by intraclass correlation coefficients showed the excellent reliability in both groups. The assessment by paired t-test for the mean of differences of duplicate PWV in normal BP group did not show any evidence of systematic difference. The PWV in a high BP group indicated systematic difference between duplicate measurements, although with near to zero mean value. The same systematic effect in high BP group appeared during the investigation by Bland-Altman agreement. Although the means of differences were close to zero, the differences themselves showed a slight to moderate tendency of being dependent on the value of a mean in a high BP group.

Comparison of clinical categorization of duplicate values

The assessment of statistical significance alone without clinical assessment is not sufficient in medical research and may lead to incorrect conclusions. Therefore clinical classification of the PWV values was also considered for final decision. Clinical categorization of duplicate values of PWV in a normal BP group was without discrepancies. In a high BP group there was only one case of different clinical assessments of PWV duplicates. Thus, despite the observed systematic difference in the results of some statistical tests, we did not observe the marked deviation in clinical categorization of PWV duplicates.

Comparison with available in literature recommendations for validation of non-invasive haemodynamic measurement devices

According to practical recommendation the differences in duplicate measurements should not exceed 0.5 m/s using the median value. [1] Our data indicated a good repeatability: the median of duplicate PWV measurements was 0.3 m/s and 0.08 m/s in a high BP and a normal BP group, accordingly. According to the recommendation of ARTERY Society for the comparison of different devices, the mean differences of ≤ 0.5 and < 1 m/s and SD of ≤ 0.8 and ≤ 1.5 m/s were considered as excellent and of acceptable accuracy, accordingly. [1] In our study the repeatability of one device was investigated, thus we suggested the corresponding targets should be at least two to three times smaller. This assumption allowed us to assess our results for mean differences of PWV as excellent in normal BP group (-0.1m/s) and acceptable in high BP group (0.3m/s); our results for SD of differences – as acceptable (0.6 and 0.6m/s in normal BP and high BP groups, accordingly).

Considering all the above mentioned facts the repeatability of PWV was recognized as appropriate to make a conclusion about the adequacy of a single measurement for arterial stiffness assessment in setting of population study.

Comparison of repeatability in our investigation with other studies

Table 4 shows the comparison of our results with the studies on repeatability of Arteriograph available in literature. The intraclass correlation coefficient was not calculated in these studies, the assessment of repeatability was based mainly on the mean of differences with standard deviation of differences and distributions of differences on Bland-Altman plot. Also clinical categorization of repeated values and dependence of the repeatability on the blood pressure of subjects were not assessed.

The mean age of the subjects in these studies was comparable with our results; however the number of the investigated was significantly smaller than in our study. One study showed repeatability only in healthy subjects, other – in subjects with diabetes. The repeatability of PWV duplicates in all our groups was comparable with above mentioned studies.

Table 4 Comparison of repeatability in our investigation with other studies

	n	Age	Clinical parameters high BP vs normal BP	Mean differences \pm Standard deviation of the difference	Tendency of Diff to be dependent on magnitude of mean (Bland –Altman plot)
Current study, one investigator, interval 2-3min	49	53 \pm 11	High BP	0,3 \pm 0,6 m/s**	Moderate
	36	51 \pm 11	Normal BP	-0,1 \pm 0,6 m/s*	Not dependent

International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Website: www.ijirset.com

Vol. 6, Issue 7, July 2017

Study Ring M, <i>et al</i> , ^[8] one investigator, interval 30 min	8	48±15	Healthy	-0,2±0,4 m/s ***	Not dependent
Study Krogager C, <i>et al</i> , ^[9] records consequently	19	64±8	All BP + Type 2 diabetes	0,1±0,5 m/s*	Not dependent
	11	67±10		-0,2±0,6 m/s*	Not dependent

Non significant *

Significant at p=0,001**

Unreported significance ***

VI.CONCLUSION

We demonstrated a good repeatability of Arteriograph technique and thus showed an acceptability of a single measurement on Arteriograph for the assessment of arterial stiffness in setting of population-based study. To our knowledge, our investigation is a first study of repeatability on Arteriograph using extended methodology of good practice recommendation for the evaluation of repeatability of the numerical variables, assessment of the clinical categorization of the results and available in literature recommendations for validation of non-invasive hemodynamic measurement devices.

Our results also pointed out that procedure of measurement and technique of Arteriograph in assessment of individual results of arterial stiffness in subjects with high blood pressure needs further investigation.

Study limitations

Relatively small amount of investigated subjects in each group did not allow us to perform the analysis of the repeatability dependent on age and sex of subjects, separately.

Financial support

This investigation was financially supported by the Estonian Ministry of Education and Research under institutional research financing IUT 19-2.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Tallinn Medical Research Ethics Committee of National Institute for Health Development of Estonia (Nr 1005) and with the 1983 Declaration of Helsinki.

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Vol. 6, Issue 7, July 2017

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