

Measurement Variation of Aortic Pulse Wave Velocity in the Elderly

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Accurate and reproducible measures are required to study arterial stiffness in human populations. The reproducibility of aortic pulse wave velocity was evaluated in 14 participants from a population-based study of cardiovascular disease in the elderly. Three data files were collected per participant by each of two sonographers and files were read by two readers. Seven of the 14 participants returned for a second visit 1 week later to assess between-visit variability. Reproducibility was evaluated with Pearson and intraclass correlations and by the absolute value of the difference between replicate values. The overall reliability coefficient was $r_1 = 0.77$. Between-sonographer, between-

reader, and between-visit correlations were $r_p = 0.80$ to 0.87 , $r_p = 0.73$ to 0.89 and $r_p = 0.63$. The mean absolute value of the difference between replicates was 59.4 to 94.0 cm/sec and 88.7 to 112.8 cm/sec for sonographers and readers, respectively. These results indicate that the mean PWV measure is reproducible even when sonographers and readers are newly trained. *Am J Hypertens* 2001;14:463-468 © 2001 American Journal of Hypertension, Ltd.

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The elasticity of the central arteries converts the pulsatile action of the heart into continuous laminar blood flow to the cells of the body. The large arteries expand with each ventricular contraction, and their subsequent elastic recoil adds to the forward propulsion of blood. As we age, the arteries stiffen, resulting in changes to the dynamics of this system including increases in systolic blood pressure and a widening of the pulse pressure. Structural changes that occur with age include fragmentation and degeneration of elastin, increases in collagen, and a thickening of the arterial wall.¹ A progressive dilatation of the arteries accompanies this stiffening process. Arterial stiffening occurs at different rates for different individuals and can be viewed as a process of biological aging of the vascular system. The cause of increasing vascular stiffness with age in humans is not known. Differences in the progression of vascular stiffness with aging may be an important determinant of the development of hypertension, especially systolic hypertension, with the subsequent substantial risk of vascular disease.

Vascular stiffness can be measured in a number of

ways.² Many investigators have chosen to evaluate vascular stiffness through the calculation of pulse wave velocity.³⁻⁷ To measure pulse wave velocity, transducers that detect the pulse wave (either pressure or Doppler) are positioned at two different arterial sites. Velocity is estimated by dividing the arterial distance between these two points by the time it takes the pulse wave to travel from one transducer to the other. Stiffer arteries have higher pulse wave velocity, as the pulse wave travels faster in a stiffer vessel.

To study vascular stiffness in human populations, accurate and reproducible measures are required. The purpose of this report is to evaluate the reproducibility of aortic pulse wave velocity, as measured in our laboratory.

Methods

The Epidemiology Ultrasound Research Laboratory at the University of Pittsburgh develops and conducts noninvasive vascular testing for epidemiological research. To develop a protocol for the measurement of aortic pulse wave

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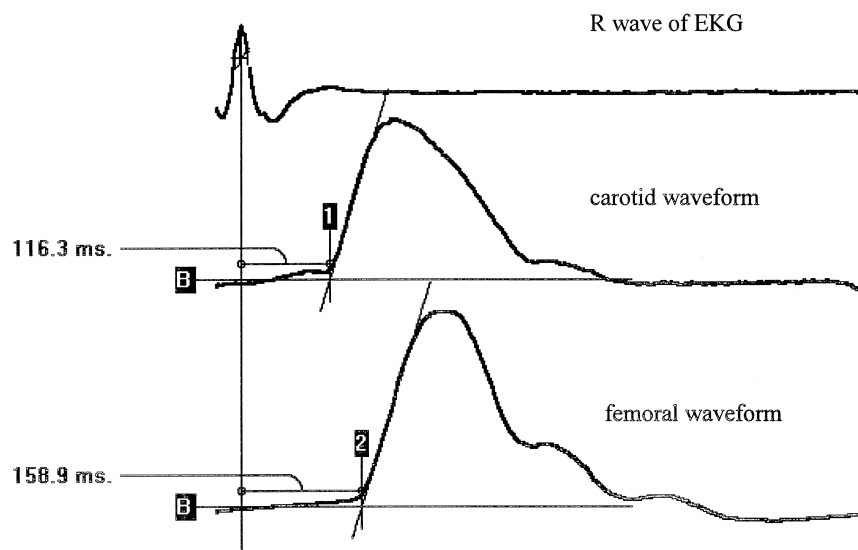


FIG. 1. Determination of time (in milliseconds) difference between foot of carotid waveform and foot of femoral waveform. Time difference = (time to femoral foot) – (time to carotid foot) = 158.9 – 116.3 = 42.6 msec.

velocity, a collaboration was initiated with the Laboratory of Cardiovascular Science, Gerontology Research Center at the National Institute on Aging. The techniques originally developed and used by this group³ were tested and refined for use in our laboratory.

The original protocol used two different pairs of arterial sites, an ascending aorta/femoral artery combination and a carotid artery/femoral artery combination. During early testing of this protocol, differences in reproducibility were observed depending on whether the aorta/femoral or the carotid/femoral site was used. For the aorta/femoral site, good reproducibility was achieved only when an experienced sonographer collected the pulse waves. When a less experienced sonographer was used, a high number of falsely elevated results were obtained because of an inability to position the unidirectional probe accurately to insonate the ascending aorta. Use of a bidirectional Doppler would facilitate proper probe placement at the ascending aorta. However, even with this equipment upgrade, a highly skilled sonographer would be required. Therefore, the carotid/femoral sampling sites were chosen, and the variability of the measurement was further reduced by using the mean of three separate data files for each participant rather than a single measure. Results using the carotid/femoral sites were similar between the experienced and inexperienced sonographers, but were more variable than results obtained by the experienced sonographer using the aorta/femoral sites.

The final protocol requires the participant to lie in a supine position for 5 min before testing during which time three EKG leads are attached. The participant is required to remain awake and to refrain from talking during the testing session. Two blood pressure readings are recorded using an automated device (Dinamap, Critikon Company, Tampa, FL). Two non-directional transcutaneous Doppler flow probes (model 810-a, 10 MHz, Parks Medical Elec-

tronics, Aloha, OR) are positioned at the right common carotid and right femoral arteries. A computer system displays and records output from the EKG and the two Doppler probes. The arterial flow waves from the two arterial sites are simultaneously recorded and the output is captured and stored in the computer system for subsequent scoring. Three data collection runs are performed, each obtaining 20 sec of simultaneously recorded carotid and femoral flow waveforms.

After the collection of the waveform data, the distance between the sampling sites (the carotid and femoral arteries) is measured with a tape measure. To reduce the influence of body contours on the distance measure, the tape measure is held above the surface of the body, parallel to the plane of the examination table. Three distances are measured: 1) from the second intercostal space to the sampling site on the right common carotid artery; 2) from the second intercostal space to the inferior edge of the umbilicus; and 3) from the inferior edge of the umbilicus to the sampling site on the right common femoral artery. The distance traveled by the waveform is calculated by subtracting the distance between the second intercostal space and the sampling site on the carotid artery from the sum of the other two distance measures.

The data are scored using software developed by the Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging. For each file, the reader deletes poor (unclear) waveforms, and the remaining waveforms are averaged to create composite waveforms for both the carotid and femoral pulse wave. A file is rejected if it has <10 acceptable waveforms (10 heartbeats) for averaging. The software averages the selected waveforms and determines the time from the R-wave of the EKG to the foot of each waveform (Fig. 1). The difference in timing between the two waves is the time component of the velocity equation. Aortic pulse wave

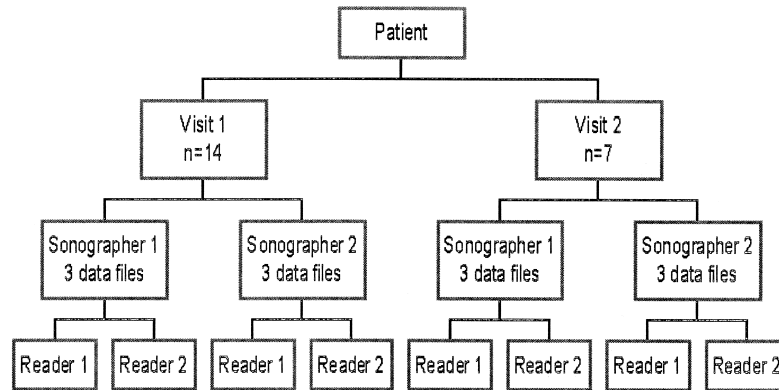


FIG. 2. Design of reproducibility study.

velocity is then calculated by dividing the distance traveled by the time differential between the two waveforms. Results from all usable data collection runs ($n = 3$) for each participant are averaged.

To test formally the reproducibility of this protocol, PWV measures were repeated on 14 participants from a population-based study of cardiovascular disease in the elderly. Six of the 14 participants were women and one participant was African-American. The average age at the time of the study was 77.5 years (range, 73 to 82 yr). Of the participants, 50% were hypertensive by history, use of antihypertensive medication, or blood pressure $\geq 140/90$. There were no significant differences between the participants selected for the reproducibility study and the remainder of the study population for race, sex, smoking, systolic or diastolic blood pressure, body mass index, or waist circumference.

The design of the study is represented in Fig. 2. Each participant had three data files collected by each of two sonographers, and the resulting data files were read by each of two readers. To assess between-visit variability, seven of the 14 participants returned for a second visit 1 week later, which followed the same protocol as the first visit. The total number of files collected was 252 (14 participants \times 3 files \times 2 sonographers \times 2 readers = 168) + second visit (7 \times 3 \times 2 \times 2 = 84). For both sonographers and readers, observer one was more experienced than observer two. Each reader evaluated the quality of the waveforms in each 20-sec data file, and waveforms that showed significant motion artifact were excluded. The remaining waveforms were averaged to provide a single composite waveform. If a data run had <10 "good" or clear waveforms, it was considered unusable. Results from the three data collection runs were averaged to produce the final PWV values for each participant for each visit by sonographer and reader.

A repeated measures analysis of variance (SAS software, Procedure VARCOMP, SAS v. 6.12, SAS Institute, Cary, NC) was used to partition the total variance into the components originating from between-sonographer differences, between-reader differences, and random error. The

significance of the sources of variation and possible interaction terms were tested using a random effects repeated measures (SAS software, [SAS, Cary, NC] Procedure GLM).⁸ To simplify the analysis, between-visit differences were examined by stratifying the results by sonographer and reader. The random-effects model $Y_{ijk} = \mu + P_i + S_{ij} + R_{ijk} + \epsilon_{ijk}$ was used where Y_{ijk} is the mean aortic PWV for the i th participant by the j th tech and k th reader; μ is the grand mean PWV of the study population; P_i is the i th participant effect, S_{ij} is the effect of the j th sonographer on the i th participant, R_{ijk} is the effect of the k th reader and j th sonographer on the i th participant and ϵ_{ijkl} is the residual error. P_i , S_{ij} , R_{ijk} and ϵ_{ijkl} are uncorrelated random variables with mean zero and variances (σ_P^2 , σ_S^2 , σ_R^2 , σ_e^2), respectively. Although the reliability estimates decrease slightly, sonographer and reader variation were treated as random effects rather than fixed effects, so that the resulting intraclass correlations would be generalizable to sonographers and readers other than those in this study.⁹

Reproducibility of aortic pulse wave velocity was estimated using the intraclass correlation coefficient of reliability.⁹⁻¹¹ The intraclass correlation coefficient is calculated as the ratio $\sigma_P^2/(\sigma_P^2 + \sigma_E^2)$, where σ_P^2 is the variability of the pulse wave velocity measure between participants, and $\sigma_E^2 = \sigma_S^2 + \sigma_R^2 + \sigma_e^2$ is the sum of the variation from the various sources of error. High values of the intraclass correlation coefficient indicate that most of the measurement variation is due to differences between participants and very little to the various sources of error. An overall intraclass correlation coefficient of reliability was calculated using this formula. To more closely evaluate the specific sources of error, pairs of records were evaluated holding other sources of error constant. For example, using only readings from the first visit by reader number 1, the results of sonographers 1 and 2 were compared. For each set of paired records, a standard Pearson correlation and the mean and standard deviation of the absolute value of the differences were calculated. Finally, all paired records were analyzed according to the recommendations of Bland and Altman for between-sonographer and between-reader reproducibility.¹²

Table 1. Reproducibility of pulse wave velocity*

	N	Pearson Correlation	Intraclass Correlation	Absolute Value of Difference in PWV (cm/sec)†
Between sonographers (reader constant)				
Reader 1	14	0.89	0.86	59.4 (55.1)
Reader 2	14	0.73	0.73	94.0 (108.6)
Between readers (sonographer constant)				
Sonographer 1	14	0.87	0.83	88.7 (50.5)
Sonographer 2	14	0.80	0.72	112.8 (71.6)
Between Visits (within participant)				
Sonographer 1				
Reader 1	7	0.63	0.62	168.8 (157.3)

* Sonographer 1 and reader 1 are more experienced than sonographer 2 and reader 2.

† Data reported as mean (SD).

Results

Three data files were collected per participant by each sonographers at each visit. Twelve of these data files from six participants were rated as unusable because of artifact or "noise" in the waveform collection, a discard rate of 4.8% (12/252). However, each participant had at least two usable data collection files for each visit and sonographer, except in two instances with only one usable data file for each visit and sonographer. The PWV was calculated as the mean result of the three data files per participant, excluding unusable files. Therefore, the reproducibility reported is for the mean of three files and not for a single measurement.

When all records ($n = 56$) from 14 participants, two sonographers and two readers from the first visit were analyzed, the overall intraclass correlation coefficient was 0.77. This reliability coefficient indicates that 77% of the variation in PWV was due to differences between participants. Less than 1% of the variation was due to the sonographer, 2% was due to the reader, and the remaining 20% of variation was due to random error. Repeated measures random-effects ANOVA indicated that patient differences were the only significant source of variation in PWV. Variations due to readers ($P = .69$), sonographers ($P = .35$), and visits were not significant, nor were any interactions found to be significant.

The Pearson and intraclass correlations and absolute value of the difference are presented in Table 1 for each source of error while holding the other sources of error constant. The contribution of sonographer variation was small for both readers. However, the experienced reader (observer 1) had slightly higher reproducibility compared to the inexperienced reader, with Pearson correlations of 0.89 ν 0.73 and intraclass correlations of 0.86 ν 0.73. Similarly, reader reproducibility was good, with slightly higher reproducibility (Pearson correlations of 0.87 ν 0.80 and intraclass correlations of 0.83 ν 0.72.) when waveforms were collected by the experienced sonographer. The better reproducibility of the experienced sonographer and experienced reader is also demonstrated by the smaller

mean and standard deviation of the absolute value of the differences for reader 1 and sonographer 1. This demonstrates the advantage of having a primary sonographer and a primary reader performing the work, particularly if prospective measures are planned.

Figure 3 illustrates the reproducibility between two observers for all measures at both visits, according to the recommendations of Bland and Altman.¹² The upper panels show the relationship between the two observers' results for between-sonographer comparisons and between-reader comparisons. The lower panels show the differences between the two observers against their mean. The plots show that 95% of the differences are within ± 1.96 standard deviations of the mean, which meets the criteria for repeatability.

Discussion

To study vascular stiffness successfully in human populations, the chosen measure must be reproducible. This study has demonstrated that aortic pulse-wave velocity can be measured in a reproducible manner when the PWV value is the mean of three files. Measurement variability due to the sonographer and reader was not found to contribute significantly to the overall variation in the measure. It is important to note that good results were achieved, even though one sonographer and one reader were relatively inexperienced. The best results were obtained when records from the experienced sonographer and reader were used, which emphasizes the importance of training and experience for both sonographers and readers. Good reproducibility was also found when measurements of the same participant were compared between two different visits. This suggests that pulse-wave velocity is relatively constant for a given participant and it is reasonable to expect to measure changes in this variable over time.

The reproducibility of PWV measured by our laboratory compares favorably with previous reports for PWV and other vascular stiffness measures that were also found to be reproducible according to the methods of Bland and

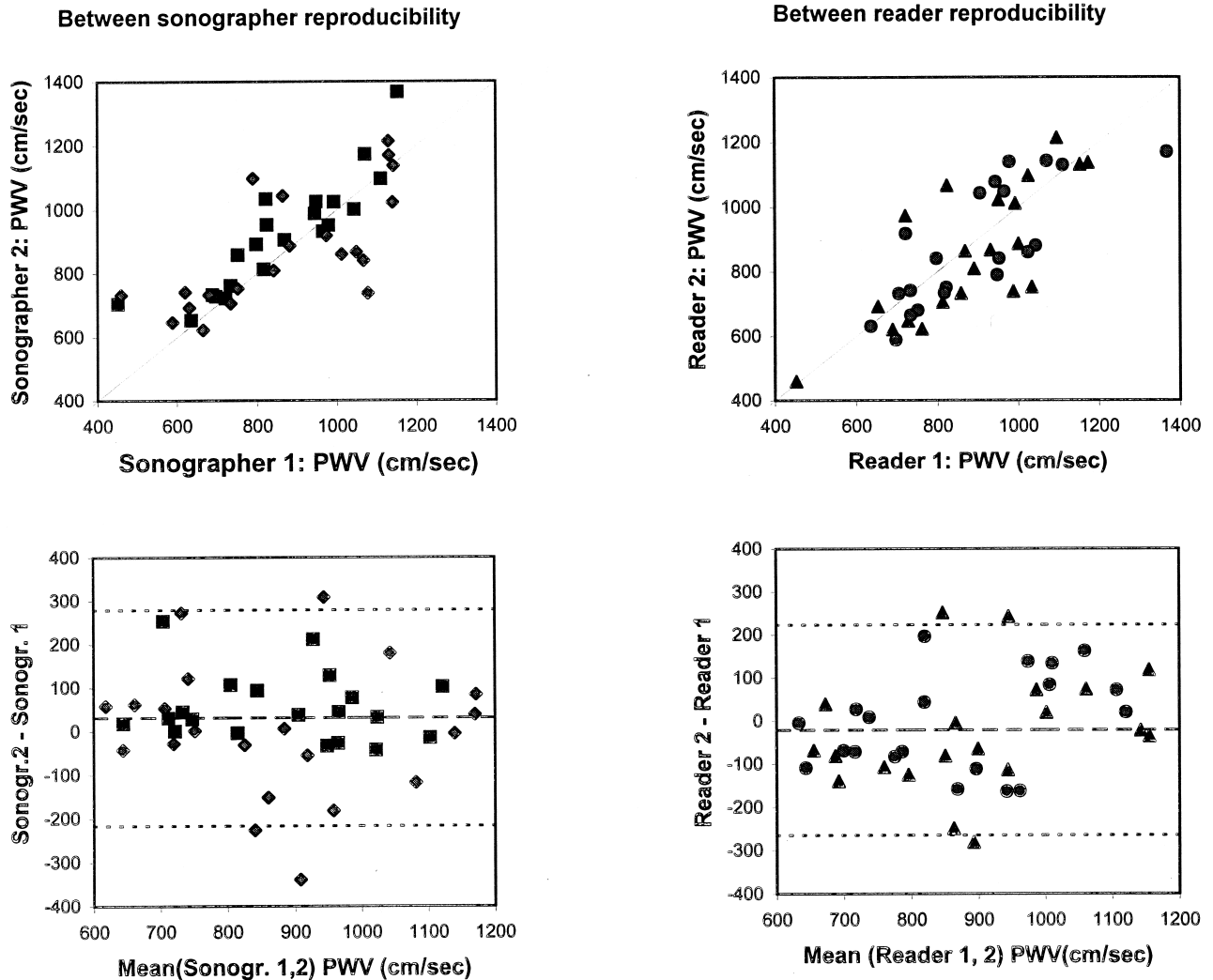


FIG. 3. Reproducibility of pulse wave velocity (PWV) between sonographers and between readers for all measures at both visits (■, reader 1; ◆, reader 2; ▲, sonographer 1; ●, sonographer 2). Upper panels show the relationships between sonographer and between reader. Lower panels are Bland-Altman plots, which shows the between-observer difference in measurements of PWV versus the mean of the measurements (—, mean; ---, ± 1.96 [SD]). To meet the definition of repeatability, $\geq 95\%$ of the differences should lie within 1.96 SD of the differences, as shown here.

Altman methods.¹³ The analysis presented here advances the previous reports on PWV by showing that reproducibility remains high even after accounting for multiple sources of measurement variation, including between sonographers, between readers and between visits. As expected, the reproducibility of pulse wave velocity was best when the sources of error were limited. Although each source of error is small in and of itself, their combined effect can have a substantial impact. Thus, it is recommended that a primary sonographer and a primary reader do the majority of work for a given study. In the case of a multicenter study, central reading is recommended.

The entity of vascular stiffness is receiving increasing recognition as an important correlate of atherosclerosis.¹⁴ Vascular stiffness has been found to be increased among individuals with high levels of cardiovascular risk factors¹⁵ and it has been found to correlate positively with extent of coronary atherosclerosis.¹⁶ Positive correlations

between vascular stiffness and stage of arterial disease have been found in animal studies.¹⁷ In addition, stiffening of the aorta has been shown to correlate with an increase in characteristic impedance¹⁸ and left ventricular hypertrophy.^{19,20} These findings were independent of age and arterial pressure.

This analysis suggests that the pulse wave velocity measure has good reproducibility, even when evaluating newly trained observers. Measures of vascular stiffness such as pulse wave velocity may eventually be of use in clinical practice to identify high risk individuals and to monitor effectiveness of antihypertensive therapy.

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