Assessment of Central and Peripheral Arterial Stiffness

Studies Indicating the Need to Use a Combination of Techniques


**Background:** Several new techniques exist for measuring arterial stiffness, but their association with central pulse wave velocity (PWV), an established measure of central arterial stiffness, has not been compared in the same study. The aim of this study was to compare the agreement of the new techniques with central PWV.

**Methods:** Fifteen men with coronary artery disease (59 ± 2 years of age) and 15 healthy men (28 ± 1 years of age) were recruited. The following measures were performed in a random sequence and repeated after 1 week: central and distal pulse wave velocity (PWV), large and small artery compliance (C1 and C2, respectively), and stroke volume/pulse pressure (SV/PP) (measured by HDI/PulseWave CR-2000), augmentation index (AIx) and central pulse pressure (CPP) (Sphygmocor), stiffness index (SI) (Micro Medical Pulse Trace), systemic arterial compliance (SAC) (area method), and brachial PP (Dinamap). Methods were compared using correlation coefficients and Bland-Altman analysis.

**Results:** Although all measures of arterial stiffness except PWV correlated significantly with central PWV (P < .01 for each), Bland-Altman analysis showed poor agreement (confidence interval [CI] > 3 Z-scores) between central PWV and C1, C2, SV/PP, and SAC. There was good agreement (CI > 2 Z-scores) between central PWV and SI, AIx, CPP, and brachial PP. The coefficient of variation was lowest with central PWV (7.6%), brachial PP (8.0%), and SV/PP (8.6%) and was significantly higher (P < .05) in increasing order with C1 (11.3%), C2 (15.6%), SI (17.8%), SAC (19.3%), AIx (22.4%), and CPP (25.3%).

**Conclusions:** Based on our study findings, C1, C2, SV/PP, and SAC show poor agreement with central PWV, an established measure of central arterial stiffness. Indices of this type should therefore be useful in providing a more complete understanding of arterial stiffness. In comparison, SI, AIx, and CPP are more closely related to central arterial stiffness. Am J Hypertens 2005;18:249–260 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Arterial stiffness, arterial compliance, central pulse wave velocity, methodologic comparison.

Stiffness of the arterial circulatory system is increased in patients with coronary artery disease,\(^1\) influences the threshold for myocardial ischemia,\(^2–4\) and relates to ventricular hypertrophy\(^5\) and endothelial function of both small\(^6\) and large arteries.\(^7\) Because of its size and elasticity, the aorta is the principal determinant of systemic arterial compliance (SAC)\(^8\) and therefore arterial stiffness. Accordingly, several surrogate measures of large-artery stiffness including stroke volume/pulse pressure,\(^9\) brachial artery pulse pressure,\(^10\) and central pulse wave velocity (PWV)\(^11\) have been shown to be predictive of all-cause and cardiovascular mortality.

The physiologic and pathophysiologic relevance of arterial stiffness, along with implications for therapy of this condition, have led to widespread interest in its measurement resulting in greater availability of commercial devices. Several of these devices aim to provide a global evaluation of arterial stiffness.\(^12–14\) There is no gold standard for assessing arterial stiffness,\(^15\) and the various methods are based on diverse assumptions (Table 1). In


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<th>Principles and features</th>
<th>Formula (units)</th>
<th>Measurement technique</th>
<th>Assumptions*</th>
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<tr>
<td>Systemic arterial compliance (SAC)</td>
<td>Basic 2-element Windkessel model of the arterial circulation (arterial compliance and total peripheral resistance, R); Ignores effects of wave reflection.</td>
<td>( A_d/R \times (P_{es} - P_{ed}) ) (mL/mm Hg)</td>
<td>Carotid pulse tracing, Doppler flow and echocardiography</td>
<td>Simultaneous pressure and flow changes occur throughout arterial circulation. Pressure independence of compliance. Venous pressure is zero and zero arterial inflow in diastole.</td>
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<tr>
<td>Central pulse wave velocity PWV</td>
<td>Calculated from transit time (( \Delta t )) and transit distance (L) of pressure waveform traveling between two arterial sites. PWV increases with increasing arterial wall stiffness (( \sim \sqrt{\text{elastic modulus or } 1/\text{distensibility}} )). Provides a regional measure of arterial stiffness.</td>
<td>PWV - ( L/\Delta t ) (m/sec)</td>
<td>Applanation tonometry at two separate sites.</td>
<td>Pulse transit distance (L) can be determined from body surface measurements. “Foot of wave” to “foot of wave” measures (( \Delta t )) are adequate surrogates for higher harmonics.</td>
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<tr>
<td>Peripheral pulse wave velocity PWV</td>
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<tr>
<td>Sphygmocor Augmentation index (Aix)</td>
<td>Difference in pressure between first and second peaks (( \Delta P )) of the central pressure waveform. Expressed as a percentage of PP. Value is usually negative in young healthy subjects (inflexion occurs during diastole) but positive in older subjects, (inflexion occurs during systole) due to increased arterial stiffening/wave reflection.</td>
<td>AIX = (( \Delta P/PP )) \times 100%</td>
<td>Applanation tonometry at carotid or at radial artery with a transfer function.</td>
<td>Use of an undisclosed generalized transfer function to estimate central waveforms. Adjusted to a common heart rate by an undisclosed method.</td>
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<td>CR2000</td>
<td>Central pulse pressure (PP)</td>
<td>Systolic-diastolic aortic pressure (mm Hg)</td>
<td>Piezoelectric pressure sensor</td>
<td>Stroke volume derived from nomogram.</td>
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<td>Capacitive or “large” artery compliance (C1)</td>
<td>Change in volume (ΔV)/change in pressure (ΔP) during diastolic decay (mL/mm Hg)</td>
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<td>Pressure independence of compliance</td>
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<td>Oscillatory or “small” artery compliance (C2)</td>
<td>ΔV/ΔP during oscillations around diastolic decay (mL/mmHg)</td>
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<td></td>
<td>Stroke volume/PP</td>
<td>Estimated SV/brachial PP (mL/mm Hg)</td>
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<td>Pulse Trace</td>
<td>Stiffness index (SI)</td>
<td>Peak to peak time/Height of subject (m/sec)</td>
<td>Finger photoplethysmography</td>
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<td></td>
<td>Time interval between the peaks of forward and backward traveling waves divided by height. Relates to pulse wave velocity and wave reflection.</td>
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</table>

Alx = augmentation index; BP = blood pressure; C1 = large artery compliance; C2 = small artery compliance; PP = pulse pressure; PWV = pulse wave velocity; SAC = systemic arterial compliance.

* Where applicable, all devices are calibrated from brachial sphygmomanometry.
particular, methods can be generally described as either propagative models, which relate to wave speed or wave reflection or both, or nonpropagative models. Models incorporating wave reflection are believed to be influenced by both central and peripheral arterial stiffness. Central stiffness is most commonly assessed using central PWV, which is related to the square root of the elastic modulus; it is a robust measurement and predictive of cardiovascular outcome in hypertensive and nonhypertensive populations. The present study therefore examined the extent of agreement between central PWV and other methods to establish their dependence on either central stiffness or distal stiffness and wave reflection. The other methods examined were: SAC obtained from simultaneous pressure and flow using a two-element Windkessel model (the “area” method); compliance estimated from a radial pressure waveform using a three-element Windkessel and a nomogram to estimate stroke volume (HDI/Pulse Wave CR2000 [manufacturer information provided in Methods]); systolic pressure augmentation and pulse pressure in the central aorta predicted from the radial waveform by a generalized transfer function (Sphygmocor pulse wave analysis system); distal pulse wave velocity; a stiffness index using finger photoplethysmography (Micro Medical Pulse Trace); and brachial pulse pressure obtained using an oscillographic device (Dinamap). The reproducibility of the various methods among both healthy subjects and those with coronary artery disease (CAD) was also examined.

Methods
Study Population
Fifteen patients with CAD (age 59 ± 2 years; mean ± SEM) and 15 healthy volunteers (age 28 ± 1 years) were studied. The CAD patients were recruited from a database of previous study volunteers and the healthy subjects recruited by means of advertisements. All CAD patients had previously been identified as having at least one angiographically identified stenotic lesion of a major coronary artery. The healthy volunteers were not known to have a history of CAD or risk factors for cardiovascular disease. Antihypertensive medication received by the CAD subjects included β-blockers (n = 11), angiotensin-converting enzyme inhibitors (n = 7), and angiotensin II receptor antagonists (n = 2). The CAD subjects were also receiving medication in the form of statins (n = 10), fibrates (n = 1), anti-platelets (n = 9), calcium antagonists (n = 3), digoxin (n = 1), and nitrates (n = 2). Five of the healthy volunteers were taking vitamin supplements but none were using prescribed medication. The Alfred Healthcare Group Ethics Committee approved the study and all subjects gave written consent.

Study Design
Subjects were studied after an overnight fast on two separate occasions at an interval of 1 week and at the same time of day. Tests were performed in a random sequence using a Latin-square design and were repeated in the same order at the second visit. The same operator tested each subject on both occasions with each method. All β-blocking agents and nitrates were discontinued for 24 h before the study, and other medications remained unaltered between visits.

Indices of Arterial Stiffness
Studies were performed in a clinical research laboratory at a constant ambient temperature (20° to 22°C). Subjects lay supine for all measurements of arterial compliance. The characteristics and features of the individual techniques are shown in Table 1, and details of the measurement procedures are described below.

Determination of PWV
Central and distal PWV were determined by simultaneous applanation tonometry of the carotid and femoral arteries and of the femoral and dorsalis pedis arteries, respectively. Data were digitized (2000 Hz/channel) and acquired using in-house custom-written software. The time of travel between applanation points (Δt) was calculated from the foot of each waveform, detected as the maximum of the second derivative, and was averaged over four to six cardiac cycles. Distances measured as straight lines between sampling sites on the body surface with a tape measure were used to calculate the distance traversed (D). The distance between the manubrium sternum and femoral sampling site, minus the distance from the manubrium sternum to the carotid was used to estimate the distance traversed for central PWV. The PWV was calculated as D/Δt.

Measurement of C1, C2, and SV/PP With HDI/Pulse Wave CR2000 Cardiovascular Profiling System
Radial artery waveforms were recorded for 30 sec on the right arm of each subject with an arterial tonometer sensor array (Hypertension Diagnostics Inc./Pulse Wave CR-2000 Research Cardiovascular Profiling System, Minneapolis, MN). Pulse contour analysis of the diastolic pressure decay was used to estimate large and small artery compliance (C1 and C2, respectively). Total SAC was also estimated using SV/PP, where SV = stroke volume and PP = brachial artery pulse pressure. The SV is estimated using ejection time, heart rate, body surface area, and age. Brachial artery pulse pressure was calculated from the mean of a minimum of 10 recordings (Dinamap, 1846 SX, Critikon, Tampa, FL) obtained throughout the arterial compliance measurements.

Measurement of AIX and Central PP With Sphygmocor Pulse Wave Analysis System
A radial artery blood pressure (BP) waveform was obtained for 13 sec using a Sphygmocor pulse wave analysis system.
system (SCOR-Px, AtCor Medical, NSW, Australia). An aortic artery waveform was derived from the radial artery waveform using a generalized transfer function. The aortic waveform was calibrated using a single simultaneously recorded brachial artery CV measurement (Dinamap, 1846 SX, Critikon) from the left arm. Diastolic and mean arterial pressures were assumed to remain constant throughout the arterial tree. The aortic or central augmentation index (AIx) was calculated as the ratio of the pressure difference between the “shoulder” of the wave and “peak” systolic pressure (∆P) and the pulse pressure (PP) according to the formula: AIx = (∆P/PP) × 100. Values were considered as positive if the “shoulder” occurred before the peak pressure and as negative if the shoulder occurred after the pressure peak). All AIx values were corrected for differences in heart rate from 75 beats/min using a proprietary algorithm. Central pulse pressure (central PP) was calculated as the difference between the estimated aortic systolic and diastolic pressures.

Determination of Stiffness Index With Micro Medical Pulse Trace System

A digital volume pulse (DVP) was obtained using the Pulse Trace system (Micro Medical, Gillingham, Kent, UK). An infrared light–transmitting unit was placed on the index finger of the subject’s right hand and photoplethysmograph recordings were obtained for 15 sec before analysis. The first derivative with respect to time of the DVP was used to identify the first notch or inflexion point of the waveform. The time (∆t) between this point and the first peak is used to calculate the stiffness index (SI) according to the following formula: SI (m/sec) = height of subject (m)/∆t(sec).

Determination of SAC by Area Method

We assessed SAC using the “area” method as previously described. The method requires measurement of volumetric blood flow and associated driving pressure. Briefly, measurements of aortic flow velocity were obtained using continuous Doppler velocimetry (Multi-Dopplex MDI, Huntleigh Technology, Luton, UK), and right carotid pressure was simultaneous measured by applanation tonometry (SPT-301, Millar Instruments, Houston, TX). Brachial arterial pressure was also measured (Dinamap, 1846 SX, Critikon) to permit calibration of the carotid arterial pressure contour using brachial mean and diastolic CV and to derive carotid systolic CV. Aortic volume flow was obtained by multiplying the mean velocity flow by the left ventricular outflow tract area, measured by two-dimensional echocardiography (Hewlett-Packard Sonos 1500, Hewlett-Packard, Andover, MA).

Assessment of Anthropometric Data and Lifestyle

Height, weight, waist/hip ratio, alcohol intake, physical activity, medication use, and family history of CAD were recorded on one of the subjects’ two visits. Subjects were instructed not to change their usual dietary and alcohol intake, level of physical activity, and other aspects of lifestyle between visits.

Biochemical Measurements

Fasting venous blood samples were collected for serum glucose, lipids, and lipoprotein concentrations, which were determined enzymatically with a Cobas-BIO centrifugal analyzer (Roche Diagnostic Systems, Basel, Switzerland).

Statistical Analysis

Results are presented as mean ± SEM. Group differences in within-subject coefficient of variation and mean values were compared using F-ratios and analysis of variance, respectively. Comparison between techniques was assessed using Pearson correlation coefficients and Bland-Altman analysis. Confidence intervals (CI) were determined for differences in Z-scores between central PWV and each of the other indices of arterial stiffness. Z-scores express individual test results in terms of standard deviations above or below the mean value, thus allowing them to be compared on the same dimensionless scale. Fixed and proportional bias between methods was examined using weighted least-squares regression of the Z-scores.

Results

Study Population

Table 2 shows the characteristics of the 15 CAD patients and 15 non-CAD volunteers. The CAD patients were shorter (P = .02) and their body mass index, waist circumference, and waist/hip ratio were all significantly higher (P < .001 and P < .001 respectively) than those of the healthy volunteers. Diastolic CV and mean arterial CV were both higher (P = .04 and P = .05 respectively) and total cholesterol and LDL cholesterol significantly lower (P = .02 and P = .03 respectively) in the CAD patients than in the healthy volunteers. The CAD patients also displayed nonsignificantly elevated glucose and nonsignificantly lower HDL cholesterol, characteristic of subjects with the metabolic syndrome.

Stiffness Indices: Group Comparisons, Sensitivity, and Specificity

Table 3 shows the mean values for arterial stiffness and corresponding CV values for each method and each group. As expected, with the exception of PWV, measures of stiffness were all higher among the CAD subjects compared with the healthy volunteers. However, these values failed to reach significance for SAC, SV/PP, and brachial PP (measured by Dinamap). Because mean arterial pressure (MAP) was also an independent predictor of each stiffness index, except for C2 (P = .06) and SI (P = .30), the ANOVA between groups was repeated with adjustment for MAP. The degree of the
difference in mean values between groups was unchanged except for C1 (*P = .13*).

Table 4 shows the area under the receiver operating characteristic (ROC) curve for each test for discriminating between the two groups of subjects. The ROC was <0.9 for AIx (0.99), SI (0.95), C2 (0.92), and central PWV (0.91) and was >0.7 for central PP (0.78), C1 (0.72), and aortic compliance (0.70). The sensitivity and specificity of each test based on the mean value of all subjects is also shown in Table 4. For AIx, SI, C2, and central PWV, the sensitivity and specificity were both >70%.

### Stiffness Indices: Repeatability

Among all subjects, the coefficient of variation (CV) for repetitive examinations was lowest for central PWV (7.6%) and was significantly higher (*P < .05*) for C1 (11.3%), C2 (15.6%), SI (17.8%), SAC (19.3%), AIx (22.4%), and central PP (25.3%) (Table 3). The CV for C2 and central PP were significantly higher (*P < .05*) and the CV for AIx was significantly lower (*P < .05*) in the CAD group than in the healthy volunteers. The CV for the single brachial PP reading that was used to calibrate measures of central PP was 13.9% in the healthy subjects and 19.6% in the CAD subjects (*P = NS*).

### Correlational Analysis

Correlations among the groups were examined with data pooled from the two study groups (Table 5). All measures of arterial stiffness were significantly correlated with central PWV (*P < .01* for each). In addition, strong associations existed between measures related to small artery compliance or peripheral wave reflectance and those of central PWV. That is, C2 was associated with central PWV (r = −0.77, *P < .001*), AIx (r = −0.75, *P < .001*), and SI (r = −0.65, *P < .001*). The SI was also associated with AIx (r = 0.80, *P < .001*) and was still associated with AIx and C2 after adjustment for central PWV (r = 0.67, *P < .001* and r = −0.39, *P = .04*, respectively).

#### Bland-Altman Analysis Results

There was no fixed or proportional bias between central PWV and any of the other measures. The 95% CI for differences in Z-scores between central PWV and brachial PP, central PP, SI, and AIx indicated close agreement (CI < 2 SD) (Fig. 1). The CI for central PWV versus C1, C2, SAC, and SV/PP were between 3 and 4 SD (Fig. 2), indicating poor agreement. There was close agreement between AIx and both SI and C2 (CI = 1.27 and 1.87 SD, respectively) (Fig. 3), and between brachial and central pulse pressure (CI = 1.30 SD). Moderate agreement was found between central and distal PWV (CI = 2.21 SD).

### Discussion

Interest in the biomechanical properties of the aorta and other large arteries has increased markedly in recent years. As a result, a number of different methods and devices for evaluating such properties are now available. However, there is limited experience regarding comparison and repeatability of multiple indices of arterial stiffness within the same study population. In the current study we have demonstrated limited agreement among the various indi-
Table 3. Means and coefficients of variations of arterial stiffness among healthy subjects and coronary artery disease (CAD) patients

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Variable</th>
<th>Mean (±SEM)</th>
<th>CAD patients</th>
<th>Healthy subjects</th>
<th>All subjects</th>
<th>Coefficient of variation (%)</th>
<th>CAD patients</th>
<th>Healthy subjects</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applanation</td>
<td>Central PWV (m/sec)</td>
<td>10.0 ± 0.7</td>
<td>6.3 ± 0.2*</td>
<td>8.2 ± 0.5</td>
<td></td>
<td>7.1</td>
<td>7.4</td>
<td>7.6</td>
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<td></td>
<td>Distal PWV (m/sec)</td>
<td>8.9 ± 0.2</td>
<td>9.3 ± 0.4</td>
<td>9.1 ± 0.2</td>
<td></td>
<td>10.7</td>
<td>10.9</td>
<td>12.3†</td>
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<tr>
<td>“Area” method (Liu 1986)</td>
<td>SAC (mL/mm Hg)</td>
<td>0.56 ± 0.07</td>
<td>0.71 ± 0.06*</td>
<td>0.64 ± 0.05</td>
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<td>13.8</td>
<td>21.3</td>
<td>19.3†</td>
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<td></td>
<td>C1 (mL/mm Hg × 100)</td>
<td>14.5 ± 1.2</td>
<td>18.3 ± 1.1†</td>
<td>16.4 ± 0.8</td>
<td></td>
<td>12.0</td>
<td>11.1</td>
<td>11.3†</td>
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<tr>
<td></td>
<td>C2 (mL/mm Hg × 100)</td>
<td>5.0 ± 0.6</td>
<td>10.1 ± 0.6*</td>
<td>7.6 ± 0.7</td>
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<td>24.6</td>
<td>11.6§</td>
<td>15.6†</td>
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<td></td>
<td>SV/PP (mm Hg)</td>
<td>1.72 ± 0.15</td>
<td>1.88 ± 0.08</td>
<td>1.80 ± 0.08</td>
<td></td>
<td>7.8</td>
<td>8.2</td>
<td>8.6</td>
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<tr>
<td>Pulse Trace</td>
<td>SI (m/sec)</td>
<td>12.0 ± 0.6</td>
<td>6.9 ± 0.5*</td>
<td>9.4 ± 0.6</td>
<td></td>
<td>15.2</td>
<td>20.7</td>
<td>17.8†</td>
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<tr>
<td>Sphygmocor</td>
<td>AIx (%)</td>
<td>23.0 ± 2.2</td>
<td>-8.2 ± 3.4*</td>
<td>7.4 ± 3.5</td>
<td></td>
<td>14.2</td>
<td>37.5§</td>
<td>22.4†</td>
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<td></td>
<td>Central PP (mm Hg)</td>
<td>46 ± 4</td>
<td>34 ± 2‡</td>
<td>40 ± 2</td>
<td></td>
<td>31.9</td>
<td>12.6§</td>
<td>25.3†</td>
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<td></td>
<td>Brachial PP (mm Hg)</td>
<td>57 ± 5</td>
<td>53 ± 2</td>
<td>55 ± 2</td>
<td></td>
<td>9.5</td>
<td>6.3</td>
<td>8.0</td>
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</table>

CAD = coronary artery disease; SV/PP = stroke volume/pulse pressure; other abbreviations as in Table 1.

* P < .001 (ANOVA); † P < .05 between test and central PWV (F-ratios); ‡ P < .05 (ANOVA); § P < .05 between groups (F-ratios); ¶ Heart rate corrected to 75 beats/min; || P < .01, (ANOVA)

Pulse wave velocity is inversely related to arterial distensibility and compliance, whereas nonagreement implied dependence on more distal aspects of arterial stiffness or wave reflection by alterations in the estimates of compliances of arterial stiffness, which appears to depend on the circulatory model from which the indices are derived. We have also demonstrated considerable differences in the variability of the techniques. Bland-Altman plots revealed a considerable variation in the level of agreement, which cannot be dependent on the underlying assumptions of the models, as such indices provide a global assessment of arterial stiffness assuming that the arterial circulation can be lumped into parameters, namely C1, C2, SV/PP, and SAC. Windkessel models provide a global assessment of arterial stiffness assuming that the arterial circulation can be lumped into parameters, namely C1, C2, SV/PP, and SAC. Windkessel models are simultaneous and instantaneous throughout the circulatory model from which the indices are derived. Indeed, although the true agreement demonstrated significant associations between central PWV and most of the indices, the effects of wave reflection on more distal aspects of arterial stiffness or wave reflection by alterations in the estimates of compliances of arterial stiffness, which appears to depend on the circulatory model from which the indices are derived. We have also demonstrated considerable differences in the variability of the techniques. Bland-Altman plots revealed a considerable variation in the level of agreement, which cannot be dependent on the underlying assumptions of the models, as such indices provide a global assessment of arterial stiffness assuming that the arterial circulation can be lumped into parameters, namely C1, C2, SV/PP, and SAC. Windkessel models provide a global assessment of arterial stiffness assuming that the arterial circulation can be lumped into parameters, namely C1, C2, SV/PP, and SAC. Windkessel models are simultaneous and instantaneous throughout the circulatory model from which the indices are derived. Good agreement was demonstrated between central PWV and AIx, providing a better indicator of the true agreement compared to each method. Thus, poor agreement was observed between central PWV and most of the indices, the effects of wave reflection on more distal aspects of arterial stiffness or wave reflection by alterations in the estimates of compliances of arterial stiffness, which appears to depend on the circulatory model from which the indices are derived. Good agreement was demonstrated between central PWV and AIx, providing a better indicator of the true agreement compared to each method. Thus, poor agreement was observed between central PWV and most of the indices, the effects of wave reflection on more distal aspects of arterial stiffness or wave reflection by alterations in the estimates of compliances of arterial stiffness, which appears to depend on the circulatory model from which the indices are derived. Good agreement was demonstrated between central PWV and AIx, providing a better indicator of the true agreement compared to each method. Thus, poor agreement was observed between central PWV and most of the indices, the effects of wave reflection on more distal aspects of arterial stiffness or wave reflection by alterations in the estimates of compliances of arterial stiffness, which appears to depend on the circulatory model from which the indices are derived.
was expected, as central pressure augmentation is known to be dependent on PWV. The extent of wave reflection within each subject together with the degree of random error are likely to have been responsible for the residual variation between central PWV and central pressure augmentation. There was also close agreement between central PWV and SI, an index thought to provide a composite measure of PWV. The stiffness index (SI), which is derived from the digital volume pulse (DVP), resembles the carotid pressure wave and varies similarly in response to vasodilator and vasoconstrictor drugs. In addition, a simple linear relationship exists between the DVP and the peripheral pressure wave, irrespective of the presence of hypertension or the effects of vasodilation produced by glyceryl tri-nitrate. Indices obtained from the DVP, such as SI, may therefore be a useful surrogate for those derived from either peripheral or carotid waveforms. The good agreement between SI and central PWV and the strong associations with AIx and C2 independently of PWV, support the use of the SI as a simple alternative measure of arterial stiffness that takes into account the effects of wave reflection in addition to wave velocity.

Like its counterpart C1 (denoting large artery compliance), C2 (denoting small artery compliance) is a mathematical construct derived from Windkessel modeling. Bland-Altman analysis revealed poor agreement between C2 and central PWV, indicating the dependence of C2 on factors other than central stiffness. There was, however, good agreement between C2 and AIx. These two indices were significantly associated with each other independently of central PWV. Our results are in close agreement with the association previously reported by Rietzschel et al using the Sphygmocor and CR2000 devices. The significant association between C2 and AIx is also independent of AIx being derived from a directly measured or

<table>
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<tr>
<th>System</th>
<th>Central PWV</th>
<th>“Area” method</th>
<th>C1</th>
<th>C2</th>
<th>SV/PP</th>
<th>SI</th>
<th>AIx</th>
<th>Central PP</th>
<th>Brachial PP</th>
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<td>&quot;Area&quot; method</td>
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<td>CR2000</td>
<td>-0.57*</td>
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</tr>
<tr>
<td>SAC</td>
<td></td>
<td>-0.71*</td>
<td>0.54*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>-0.77*</td>
<td>0.46†</td>
<td>0.69*</td>
<td>0.65*</td>
<td>0.62*</td>
<td>0.88*</td>
<td>0.50*</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>-0.65*</td>
<td>0.62*</td>
<td>0.88*</td>
<td>0.50*</td>
<td>-0.65*</td>
<td>-0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV/PP</td>
<td>-0.58*</td>
<td>-0.35</td>
<td>-0.31</td>
<td>-0.65*</td>
<td>-0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>0.75*</td>
<td>-0.55*</td>
<td>-0.50*</td>
<td>-0.75*</td>
<td>-0.75*</td>
<td>-0.39†</td>
<td>0.80*</td>
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<tr>
<td>AIx</td>
<td>0.72*</td>
<td>-0.45†</td>
<td>-0.49*</td>
<td>-0.50*</td>
<td>-0.46*</td>
<td>0.40†</td>
<td>0.55*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central PP</td>
<td>0.66*</td>
<td>-0.46†</td>
<td>-0.52*</td>
<td>-0.24</td>
<td>-0.68*</td>
<td>0.05</td>
<td>0.23</td>
<td>0.79*</td>
<td></td>
</tr>
<tr>
<td>Brachial PP</td>
<td>0.36</td>
<td>-0.14</td>
<td>-0.17</td>
<td>-0.29</td>
<td>-0.23</td>
<td>0.48*</td>
<td>0.28</td>
<td>0.28</td>
<td>0.25</td>
</tr>
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</table>

SI = stiffness index; other abbreviations as in Table 1.
* P < .01; † P < .05.
reconstructed aortic pressure waveform. Thus, although the exact physical origins of C2 remain uncertain, our data and those of others support the dependence of C2 on hemodynamic changes affecting central aortic pressure and the extent of wave reflection, rather than on the speed of wave transmission. This is also suggested by data showing that the shape of the pressure waveform (and hence C2), but not aortic PWV, is significantly altered by the administration of glyceryl trinitrate.

Because our two groups of subjects were not matched for age, we are not able to determine the ability of the indices to identify the presence of CAD. However, it is reasonable to assume that older subjects with CAD will have stiffer arteries than younger subjects without CAD and that this should be reflected in the results. Although stiffness was higher in the CAD group for all measures, indices of arterial stiffness related to wave reflectance (ie, AIX, C2, and SI) discriminated better between the two groups of subjects than the more predominantly central measures of SAC, C1, and SV/PP. Similar conclusions were obtained when assessing the overall sensitivity and specificity of the techniques using the area-under-ROC-curve analysis. However, it is not possible for us to determine to what extent these differences were due to differences in stiffness or to differences in variables such as age. The non-uniform dependence of the different techniques on factors such as age may have heightened the ability of some techniques to differentiate between the groups. Weber et al recently demonstrated the important effect of age on AIX in CAD subjects; in that study, AIX was greater in subjects <60 years of age with CAD but not different among subjects >60 years. Similarly, statin therapy increases compliance but does not change central PWV. None of our control subjects were receiving statin therapy as compared with ten of the 15 CAD subjects. Non-uniform dependence of the measures on height, hypertensive therapy, endothelial function, or the presence of atherosclerosis or the metabolic syndrome might also have influenced our results. However, despite these limitations, prospective data are consistent with our observations. Thus, C2 is more predictive of cardiovascular events than C1, and AIX has been shown to be an

FIG. 1 Bland-Altman plots of central pulse wave velocity (PWV) versus brachial pulse pressure (PP), central PP, stiffness index (SI) and augmentation index (AIX). Units for each test were expressed as Z-scores representing standard deviations from the mean value. Horizontal lines represent means ± 2 SD for estimated difference between central PWV and other methods.
independent predictor of all-cause and cardiovascular mortality. The predictive value of the speed of wave transmission is also established.

The comparison of repeatability among various devices requires an appreciation of a number of factors. Except for central PWV and the SI, the other indices of stiffness all
required calibration using brachial artery sphygmonanometry. Their repeatability thereby included a component of brachial artery PP. Likewise, measurement of SAC requires direct estimation of stroke volume in addition to carotid pressure, whereas the stroke volume required for C1, C2, and SV/PP (using CR2000) is obtained from a nomogram. The latter is dependent only on age, height, estimated ejection time, and heart rate and varies little in comparison with direct estimation of stroke volume. Similarly, AIx was normalized to a heart rate of 75 beats/min and was therefore not dependent on heart rate. Allowing for these considerations, the variability of SAC was within the expected range for technical and biological variation and in accordance with previous data using healthy subjects.  

Repeatability of pulse wave velocity has been assessed extensively and has generally been reported to be approximately 10% or less using differing devices. Variability in central PWV in the older subjects is not clear but was therefore not dependent on heart rate. Allowing for these considerations, the variability of SAC was within the expected range for technical and biological variation and in accordance with previous data using healthy subjects.

In conclusion, several indices of arterial stiffness, ie, SI, AIx, and CPP, relate closely with an established measure of central arterial stiffness, central PWV. The lack of agreement between central PWV and C1, C2, SV/PP, and SAC can be considered an indication that these methods may provide information that is useful in addition to central PWV. A more accurate and integrated picture of arterial stiffness may therefore be obtained by using a combination of techniques based on different models.

We thank AtCor Medical for kindly providing a SphygmoCor Pulse Wave Analysis System: Models SCOR-Px and SCOR-Vx. We gratefully acknowledge Marcus Somerville and Christoph Gatzka for their technical assistance and Melissa Formosa, Lucy Rudolph, and Leonie Johnston for their technical and nursing assistance.

References