A Comparison Between Systolic and Diastolic Pulse Contour Analysis in the Evaluation of Arterial Stiffness

Ernst-R. Rietzschel, Eva Boeykens, Marc L. De Buyzere, Daniel A. Duprez, Denis L. Clement

Abstract—Several methodologically independent measures of arterial stiffness derived from either the systolic or diastolic segments of the arterial pulse have been proposed. The exact nature of the large and small artery elasticity indices (C1 and C2, respectively) derived from diastolic pulse contour analysis remains largely unexplored, although C2 has controversially been termed to be “oscillatory” and “reflective.” We investigated the relation between C2 and, respectively, a prototype of arterial reflectivity (ie, the augmentation index, AIx) and a covariate of arterial reflectivity (body height). A validated transfer function is used to transform a tonometrically obtained radial pressure wave into an ascending aortic pressure wave, from which AIx is derived using systolic pulse contour analysis. Diastolic pulse contour analysis using a modified Windkessel model is used to derive C1 and C2. One hundred subjects, who were free from atherothrombotic disease and 19 to 77 years of age, with a wide pressure range (97 to 186/52 to 104 mm Hg) were studied. Mean values of C1, C2, Alx, and body height were, respectively, 13.8±4.3 mL/mm Hg×100, 128.5±24.9%, and 169±9 cm. Coefficients of variation were 32.8% for C1, 33.3% for C2, and 6.7% for Alx. C2 was significantly and inversely correlated to AIx (r=-0.707, P<0.001). Both Alx and C2 were correlated to body height (r=-0.487, P<0.001, and r=0.514, P<0.001). In conclusion, the results of this study provide the first clinical evidence that validates a probable biophysical equivalent of the C2 element of a third-order, 4-element modified Windkessel model. We suggest that C2 is, at least in part, a measure of arterial wave reflectance. However, although short-term reproducibility of Alx is excellent, C2 showed markedly increased variability with the devices used. (Hypertension. 2001;37:e15-e22.)

Key Words: arteries ■ pulsatile flow ■ wave reflections ■ Windkessel model ■ hypertension, diagnosis ■ reproducibility of results

Hemodynamics research has shifted away from a steady-flow approach toward a pulsatile flow approach, because the former was less predictive in relation to cardiovascular morbidity and mortality.1–5 The growing importance of pulsatile pressure indices (systolic blood pressure [SBP] and pulse pressure) paralleled the notion that not only increases in systemic vascular resistance (SVR) but also increases in pulse pressure (systolic blood pressure [SBP] and pulse pressure) paralleled the notion that not only increases in systemic vascular resistance (SVR) but also increases in arterial stiffness are important in the pathophysiology of hypertension.6,7 This interest in the arterial cushioning function of pulsatile flow has given us a myriad of arterial working definitions of arterial stiffness have been introduced: parameters of compliance or distensibility, which essentially express changes in mono-dimensional, bidimensional, or tridimensional space for a given pressure difference; parameters quantifying speed of wave propagation along an arterial segment (pulse-wave velocity); and parameters of global vascular elastic behavior derived from the arterial pressure pulse waveform.

Given the complexity of the latter approach, simplified mathematical models have been developed.9 The arterial pressure pulse waveform can be regarded as the result of incident (anterograde) and reflected (retrograde) pressure waves.11–13 Wave reflection occurs at sites of discontinuity in calibre (bifurcations, branching points, and arterioles) or discontinuity in elastic properties (atherosclerosis) along the arterial tree.14 Changes in amplitude and timing of wave reflections play a key role in aortic hemodynamics and, on a broader level, give us information on how the arterial vasculature affects the heart.15–19 The SphygmoCor BPAS-1/A device (model SPT-301, PWV Medical Pty Ltd) calculates a number of parameters of ventriculo-arterial coupling and wave reflectance, of which the augmentation index (AIx) is preeminent.11,20,21 Another approach in analyzing the arterial pulse is to regard the waveform as a basic pattern of exponential decay on which damped oscillations are superimposed, building on the “Grundform” - “Grundschiungung” concept pioneered by Otto Frank.22 The Windkessel models of the vasculature9,23–25 typify this last approach, and one of these is used by the recently introduced HDI/Pulsewave CR-2000 (Hypertension Diagnostics Inc) to quantify the circulation in terms of SVR, large artery elasticity index (C1), small artery elasticity index (C2), and inductance (L).24–27

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Recently, in the field of arterial stiffness, several authors have underscored the need, in addition to uniformity of terminology, for comparisons of techniques to ascertain which methodology (or methodologies) best suits the different research questions facing us. Indeed, comparative data between different stiffness indices or devices is very scarce, and, more specifically, data assessing the parameters of Windkessel modelling with reflectivity indices are currently lacking.

The goal of this study is to compare 2 methodologically different techniques, predominantly analyzing either the diastolic decay or the systolic segment of the arterial waveform, to describe global vascular elastic behavior. Specifically, C2 as a putative biophysical equivalent of wave reflectance will be assessed. Short-term reproducibility of the 2 techniques used is also analyzed within a single population with a wide pressure and age range.

Methods

Subjects
We enrolled 100 healthy white subjects (41 men, 59 women) with wide age and blood pressure ranges (mean age 46.0 ± 15.1 years and range 19 to 77 years; mean SBP 129 ± 19 mm Hg and range 97 to 186 mm Hg; mean diastolic blood pressure [DBP] 73 ± 11 mm Hg and range 52 to 104 mm Hg). Mean body height was 169 ± 9 cm with a mean weight of 71.6 ± 14.4 kg and a resulting mean body mass index (BMI) of 25.5 ± 4.9 kg/m². Uncomplicated hypertension was present in 32 subjects, and of these, 27 were currently taking antihypertensive medication. None of the subjects had taken any vasoactive drugs in the past 24 hours before the examinations. Any history of cardiac or vascular disease (including cerebrovascular, renovascular, and peripheral vascular disease) was an exclusion criterion. None of the subjects suffered from known endocrine, hepatic, or renal disease. All subjects gave informed consent to be enrolled in the study, which was approved by the local medical ethics committee.

Study Protocol
The experiments were performed between 8:00 and 10:00 AM after an overnight fast and abstinence from tobacco, alcohol, tea, or coffee. The subjects were allowed 30 minutes of supine rest after which the measurements were performed.

SphygmoCor/PWV Blood Pressure Analysis

System BPAS-I/A
Pressure pulse waveforms at the level of the radial artery were recorded using a high-fidelity, transcutaneous, single-unit, handheld applanation tonometer with an external coplanar micromanometer tip (Millar Instruments). Under optimal conditions for applanation (ie, when the flat tonometer end with coplanar sensor flattens the wall of an artery at the operational part of the sensor, thus eliminating tangential forces) pressure waves measured noninvasively are virtually identical to those recorded with a high-fidelity intra-arterial transducer. To overcome the problem of differences in hold-down pressure of the applanation tonometer, the peripheral pressure waveforms are calibrated with a pressure value determined by a mercury sphygmomanometer at the brachial artery. An averaged radial pressure waveform derived from an 8-second recording is subsequently used to derive a corresponding ascending aortic pressure waveform using a validated general transfer function (GTF). From this ascending aortic waveform the AIx is calculated as the height of the second systolic peak above the wave foot divided by the height of the first systolic peak above the wave foot expressed as a percentage.
Arterial Stiffness Indices, CET, and SV With Coefficients of Variation in 100 Healthy Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Coefficient of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ax, %</td>
<td>128.5±24.9</td>
<td>71.0–186.0</td>
<td>6.7%</td>
</tr>
<tr>
<td>C1, mL/mm Hg · 10</td>
<td>13.8±4.3</td>
<td>6.1–28.8</td>
<td>32.8%</td>
</tr>
<tr>
<td>C2, mL/mm Hg · 100</td>
<td>5.9±3.1</td>
<td>1.3–14.8</td>
<td>33.3%</td>
</tr>
<tr>
<td>CET, ms</td>
<td>348.3±26.6</td>
<td>258.5–421.0</td>
<td>3.6%</td>
</tr>
<tr>
<td>SV, mL</td>
<td>80.8±14.1</td>
<td>44.0–120.5</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

estimated using multivariate linear regression. A value of $P<0.05$ was considered statistically significant.

Results

The Table summarizes the arterial stiffness indices (C1, C2, and AIx), estimates of CET, and stroke volume (SV) obtained by the HDI/Pulsewave CR-2000, as well as coefficients of variation of these parameters. Univariate correlates of C2 comprised ($P<0.01$, except when indicated otherwise) MAP ($r=-0.622$), SBP ($r=-0.587$), age ($r=-0.566$), body height ($r=0.514$), DBP ($r=-0.516$), pulse pressure ($r=-0.442$), body surface area ($r=-0.266$), and BMI ($r=-0.207$, $P<0.05$). Univariate correlates of AIx comprised ($P<0.01$) age ($r=0.659$), MAP ($r=0.555$), body height ($r=-0.487$), SBP ($r=0.483$), DBP ($r=0.469$), pulse pressure ($r=0.320$), BMI ($r=0.304$), and body surface area ($r=0.197$).

In addition to confounders withheld from the univariate analysis (MAP, age, and body height), gender and a history of hypertension/habitual antihypertensive drug use were identified: Women had significantly a lower C2 (5.0±2.6 versus 7.2±3.5 mL/mm Hg ×100, $P<0.01$) and significantly higher a Ax (135±24 versus 119±24%, $P<0.01$) than men. Subjects who habitually took antihypertensive drugs had a significantly lower C2 (4.2±2.8 versus 6.3±3.1 mL/mm Hg ×100 for drug-free subjects, $P=0.011$) and a nonsignificantly higher AIx (137±18 versus 126±26% for drug-free subjects, $P=0.09$). However, in a multivariate regression analysis neither gender nor habitual antihypertensive drug use added to a model that included MAP, age, and body height. Colinearities could be inferred because women, despite similar age and blood pressure compared with men, were significantly shorter ($P<0.01$) and subjects who habitually took antihypertensive drugs had significantly higher blood pressures ($P<0.01$), were older ($P<0.01$), and were shorter ($P<0.01$) than their drug-free counterparts.

The regression plots between AIx, C2, and body height are shown in Figure 1. The correlations between body height and AIx and C2 remained significant after correction for blood pressure and age ($r=-0.345$, $P<0.01$, and $r=0.314$, $P<0.01$, respectively, for AIx and C2 versus height).

Ax was significantly and inversely correlated with C1 ($r=-0.424$, $P<0.001$) and C2 ($r=-0.707$, $P<0.001$, Figure 2). After controlling for age, height, and blood pressure (MAP), AIx and C2 were still significantly and inversely correlated ($r=-0.312$, $P<0.001$). The correlation between C1 and AIx was lost after correction for age ($r=-0.161$, $P>0.05$).

Coefficients of variation were calculated and averaged 6.7% for AIx, 32.8% for C1, and 33.3% for C2 (Table). Bland-Altman plots were constructed for AIx, C1, and C2 and demonstrate that the 95% confidence interval of the percentual variation varied from −12.4% to +13.8% for AIx, from −63.3% to +69.1% for C1, and from −57.9% to +72.8% for C2. Figure 3 depicts Spearman correlations between first and second measurement of each parameter on the left and corresponding Bland-Altman plots on the right. Differences (absolute and percent) between the dual measurements of C1, C2, and AIx were calculated; no correlations were found between the differences of C1, C2, and AIx and age, height, weight, blood pressure, or heart rate (HR). Variability in measurement of C1 was not a predictor of variability in measurement of C2 and vice versa.

To identify the reasons for divergence and the apparent relative overestimation of C2 in a subgroup of subjects, further analysis was performed on the standardized residuals'
z scores of the regression between C2 and AIx. Distance from the regression line between C2 and AIx, expressed as z scores, correlated significantly \((P<0.01)\) with HR \((r=0.380)\), MAP \((r=0.310)\), and body height \((r=0.267)\). Mean z scores of standardized residuals for MAP and HR quartiles are shown in Figure 4 (between group differences analyzed using 1-way ANOVA; \(P<0.01\) and \(P=0.014\) for MAP and HR, respectively). A stepwise gradient of the z scores in both HR and MAP quartiles can be clearly seen.

**Discussion**

This study is the first to compare 2 methodologically different techniques, analyzing either the diastolic decay or the systolic segment of the arterial waveform, to describe global vascular elastic behavior. Our results demonstrate that C2 and AIx are significantly and inversely correlated, which raises the possibility that in addition to AIx, C2 could also be a descriptor of reflective phenomena.

However, before reaching this conclusion, possible confounders of the relation between C2 and AIx should be addressed. In addition to the covariates of C2 and AIx previously identified in literature (age and blood pressure), we investigated the effect of body height, because arterial wave reflections are not only dependent on arterial stiffness but are also related to the length of the arterial path and a fortiori to body height.\(^{11,42-44}\) We found significant correlations between body height and C2 and AIx. The correlation between C2 and body height has not been described previously and is approximately of the same magnitude as the inverse correlation we confirmed between AIx and body height, which has been described previously. In these reports, shorter stature was associated with an increase in magnitude and earlier return of reflected waves due to a shorter arterial tree. In contrast, body height had only marginal effects on nonwave reflection–related stiffness indices. Because of a theoretical relation between body size and HR, on the basis of data from comparative physiology (ie, increasing HR with decreasing body size of the species), as well as on scarce human data, we took care to exclude an effect of HR.\(^{45-47}\)

After adjustment, the correlation between C1 and AIx was lost; however, the correlation between AIx and C2 did not change significantly after correction for age, height, and blood pressure. The concept of wave reflectance is preeminent in a controversy in literature concerning the nature of C2, which has (arbitrarily) been termed to be “oscillatory” and “reflec-
The controversy endures because first it has not been possible to convert the C1 and C2 capacitances of the electrical analogue to a distinct anatomical or physiological substrate. With regard to this point, the authors themselves stated: “Each model element may not explicitly describe a single vascular property but should be viewed as contributing to the resulting pressure waveform.”

Second, wave reflection of any kind in a Windkessel model is, from a theoretical point of view, impossible, because pulse-wave velocity is assumed to be infinite. However, the correlation between C2 and AIx combined with the individual relations to body height, which were inverse but of similar magnitude, does suggest that C2 is, at least in part, an expression of wave reflectance and thus is, at least in part, a measure of “small arterial” and hence dependent of effects on SVR. On the basis of the results, C2 values were less than the effects of the nitrovasodilators (nitroprusside and nitroglycerin) largely in combination with the individual relations to body height, which independently from the waveform analysis (the “A” indices) will increase values of C1, C2, and L (see Appendix). The overestimating gradient produced by decreasing HR cannot be explained by the effect on SVR. A lower HR would (because of a lower CO and thus higher pressures and/or slower HRs) give rise to a gradient that favors relative overestimation of C2. The inverse holds for higher blood pressures or faster HRs (Figure 4). The pressure-dependent gradient can be explained on the basis of the calculation of SVR. Lower MAP values yield lower SVR values, which independently from the waveform analysis (the “A” indices) will increase values of C1, C2, and L (see Appendix). The overestimating gradient produced by decreasing HR cannot be explained by the effect on SVR. A lower HR would (because of a lower CO and thus higher SVR) be expected to cause a relative underestimation of C2. These findings are contrary to the observed data, and we can only surmise a potent, opposite effect of HR on the derivation of the “A” values.

### Short-Term Reproducibility

A short-term reproducibility analysis was performed and the results indicate a wide gap between the coefficients of variation of C1 and C2 (33% and 34%, respectively) and of AIx (7%). The level of variability for AIx is very similar to values previously reported. Causes of variability could occur at 3 separate stages (signal acquisition, signal calibration and waveform analysis), which will therefore be individually addressed.

### Signal Acquisition

Both devices use a tonometer for recording the radial arterial pulse wave. The SphygmoCor BPAS-1/A device uses a Millar hand-held tonometer with an external micromanometer tip. There is general agreement that applation tonometry can accurately reproduce intra-arterial waveforms (when conditions of correct applation are achieved, which seems to be the case in the majority of subjects). The study by Sato et al showed an excellent relation between invasive and tonometric signals with a flat gain up to 7Hz, which covered most of the frequency ranges of interest. However, AIx retains some dependency on the high-frequency content of the signal (8 to 10 Hz). Noise reduction accomplished by introducing a low-pass filter in the system in the range of 9 to 12Hz could therefore be responsible for underestimation of AIx obtained noninvasively compared with invasively obtained AIx. The HDI/Pulsewave CR-2000 device uses a proprietary tonometer (see Methods) in combination with a “holding and positioning device” and an angulated “wrist stabiliser,” which ensures a constant wrist position and a complete stability of position after the tonometer has been applied, in contrast with the

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**Figure 4.** Z scores of standard errors of standardized residuals of the regression line between the C2 and the AIx for MAP quartiles (top) and HR quartiles (bottom). * indicates P<0.05. Depicted are z scores with standard errors and quartile means (mm Hg, top; bpm, bottom)
SphygmoCor BPAS-1/A pencil probe, which has to be manually held in position. Consecutive measurements with the tonometer kept in fixed position might be very reproducible but do not comply with daily reality, neither in cross-sectional population studies (or as proposed in risk stratification) nor in longitudinal interventional or observational studies. Therefore, we opted to completely remove the tonometers from the skin between measurements. In these conditions, the only theoretical advantage of the stabilized HDI tonometer is a more constant position within a single measurement. This theoretical advantage was, however, not translated into improved reproducibility in our population. Because variability in measurement of C1 was not a predictor of variability in measurement of C2 and vice versa, acquisition of the signal or bad-signal quality does not seem to be the prime suspect in the greater variability of the HDI/Pulsewave CR-2000. There is no published information on the HDI proprietary tonometer regarding the accuracy of the tonometrically obtained radial artery waveform compared with intra-arterial recordings.

Signal Calibration
In both devices, the peripheral pressure waveforms obtained at the radial artery are calibrated with a blood pressure value determined at the brachial artery. This potentially introduces a systematical error because it assumes equivalence between radial and brachial pressures. Although there is a degree of systolic amplification from brachial artery to radial artery, the differences in pressure are likely to be very small and probably insignificant in comparison to the error introduced by noninvasive blood pressure measurement per se. Furthermore, this systematical error occurs only in the SphygmoCor BPAS-1/A device with regard to the central aortic pressure data; because AIx is an expression of the relative height of 2 parts of the same waveform, this systematical error is not present in the calculation of AIx. In contrast, all “A”-dependent components of the modified Windkessel model (C1, C2, and L) are pressure dependent, because SVR (calculated as MAP/CO) is used in the calculation of all 3. Inaccuracies in measurement of MAP will therefore introduce inaccuracies in SVR and a fortiori in C1, C2, and L.

Waveform Analysis
In the SphygmoCor BPAS-1/A, an averaged radial pressure waveform is derived from an 8-second recording, which is used to derive a corresponding ascending aortic pressure waveform using an integral GTF. Because AIx is calculated on the ascending aortic waveform, the accuracy of AIx hinges on the accuracy of these GTFs. Since initial publication, several authors have independently produced similar GTFs and provided validating evidence. GTFs were obtained in individuals in steady state and during hemodynamic transients (after vasodilatation with nitroglycerine and during handgrip maneuvers) and used to synthesize ascending aortic pressure waves, which were compared with invasively recorded pressure waves. Induction of hemodynamic transients, despite producing marked variations in hemodynamic status, had only a marginal effect on the calculated GTFs, which remained practically identical to steady-state GTFs. Kara-manoglu et al constructed patient-specific transfer functions, but these proved to be only marginally better than a GTF in matching ascending aortic pressure data. The authors concluded that clinically acceptable predictions of central aortic pressure and waveform could be obtained by mathematical manipulation of radial pressure waves using a single GTF and that this seems to hold true in a wide variety of hemodynamic states. These conclusions are, however, not universally accepted, and the main criticisms are the small number of subjects in the validating studies, the variations in methodology in the cited validating studies, and the inherent problems related to the noninvasive calibration of the radial artery waveform as discussed above.

In the HDI/Pulsewave CR-2000 device, a 30-second collection of radial artery waveform data are analyzed using a third-order, 4-element modified Windkessel model of the circulation, matching the diastolic pressure decay using a proprietary nonlinear curve-fitting routine. The advantages and shortcomings of Windkessel models are well known and described in literature. Three main problems with the methodology should be addressed. First, the model assumes a measurement-site independence, a assumption that has been shown to be unfounded by the study of Fogliardi et al. Second, the model seems to be critically dependent on which segment of the diastolic decay curve is used, and wide variations of “A” values can be produced by small differences in portions of the diastolic decay used for parameter estimation. Third, induction of hemodynamic transients seems to exacerbate the problems created by the assumption of measurement-site independence.

Causes for the increased variability of the HDI/Pulsewave CR-2000 device could theoretically be found at several stages. However, taking into account that variability in C1 was not a predictor of variability in C2 and vice versa and that the device has reproducible measurements of SV and CO reflecting good reproducibility of CET, which is also derived from the same radial waveform with minimal variability, it must be assumed that signal acquisition or bad signal quality does not seem to be the prime suspect in the greater variability of the HDI/Pulsewave CR-2000 device. Furthermore, only a minimum of variability can be attributed to biological variations in blood pressure or HR between measurements in supine subjects at rest during a 5-minute time frame (the measurements were, as expected for subjects in supine rest, small: in the order of 3% to 4% blood pressure or HR variability, accounting for at most 8% to 9% of the variability of C1 or C2 in a stepwise multiple regression analysis). It therefore seems likely that the proprietary parameter estimating algorithm of the HDI/Pulsewave CR-2000 is primarily responsible for the variability of C1 and C2. Although reproducibility does not imply validity, in future clinical or validating studies with stiffness devices, power calculations on the number of subjects needed for inclusion are likely to be several times larger for the HDI/Pulsewave CR-2000 device.

In conclusion, the results of this study provide the first clinical validating evidence for a probable biophysical equivalent of the C2 element of a third-order, 4-element modified Windkessel model. We suggest that C2 is, at least in part, a measure of arterial wave reflectance. However, although
Appendix

Formulas

\[ SV = -6.6 + 0.25 \times (ET \times 35 - 0.62 \times HR) \]
\[ + 40.4 \times BSA - 0.51 \times A \]

\[ [ET (ms); Weight (kg); Height (cm); Age (y); BSA (body surface area) = 0.007184 \times Weight^{0.66} \times Height^{0.33}] \]

\[ CO (L/min) = SV \times HR \times 1000 \]

\[ SVR = \frac{dyne \times sec}{cm^2} = \frac{MAP}{CO} \]

\[ P(t) = A_1 e^{-A_2 t} + A_4 e^{-A_5 t} \cos(A_3 t + A_6) \]

Where \( A_1 \) (mm Hg) and \( A_2 \) (mm Hg) and \( A_3 \) (rad) represent initial conditions (i.e., conditions at the start of diastole). \( A_4 \) (sec \(^{-1}\)) expresses the dominant exponential nature of the curve. \( A_5 \) (sec \(^{-1}\)) is proposed to be damping of pressure oscillation, and \( A_6 \) (sec \(^{-1}\)) to be frequency of pressure oscillations.

\[ C_1 (mL/mm Hg \times 10) = 2A_2(A_2 + A_3)^2 + A_2SVR(A_2 + A_3)(A_3^2 + A_4^2) \]

\[ C_2 (mL/mm Hg \times 100) = 1/1000(2A_2 + A_3) \]

\[ L (mm Hg \times sec^2/mL) = SVR \times (2A_2 + A_3)^2 / 2(A_2^2 + A_3^2 + A_4^2) \]

References


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