Validity and Reliability of Diastolic Pulse Contour Analysis (Windkessel Model) in Humans

Timothy S. Manning, Barbara E. Shykoff, Joseph L. Izzo, Jr

Abstract—The present study assessed (1) the impact of the measurement site (lower versus upper extremity) on the corresponding compliance variables and (2) the overall reliability of diastolic pulse contour (Windkessel-derived) analysis in normal and hypertensive subjects. Arterial tonograms were recorded in the supine position from the radial and posterior tibial arteries in 20 normotensive (116±12/68±8 mm Hg) and 27 essential hypertensive subjects (160±16/94±14 mm Hg). Ensemble-averaged data for each subject were fitted to a first-order lumped-parameter model (basic Windkessel) to compute whole-body arterial compliance (C_A) and to a third-order lumped-parameter model (modified Windkessel) to compute proximal compliance (C_1) and distal compliance (C_2). Despite high-fidelity waveforms in each subject, the first-order Windkessel model did not yield interpretable (positive) values for C_A in 50% of normotensives and 41% of hypertensives, whereas the third-order model failed to yield interpretable C_1 or C_2 results in 15% of normotensives and 41% of hypertensives. No between-site correlations were found for the first-order time constant, 2 of the 3 third-order model curve-fitting constants, or C_A, C_1, or C_2 (P>0.50). Mean values for all 3 compliance variables were higher for the leg than the arm (P<0.05 each). We conclude that differences in Windkessel-derived compliance values in the arm and leg invalidate whole-body model assumptions and suggest a strong influence of regional circulatory properties. The validity and utility of Windkessel-derived variables is further diminished by the absence of between-site correlations and the common occurrence of uninterpretable values in hypertensive subjects. (Hypertension. 2002;39:963-968.)

Key Words: diastole ■ compliance ■ models, statistical ■ plethysmography ■ hemodynamics

Increased stiffness (decreased compliance) of the aorta and large blood vessels is associated with wide pulse pressure, systolic hypertension, and increased cardiovascular risk.1-3 Because wide pulse pressure and systolic hypertension are late manifestations of the arteriosclerotic process, there is significant interest in the development of more sensitive compliance measurements that can detect premature vascular stiffening at an earlier stage of the process. Our laboratory has undertaken a systematic analysis of 3 of these noninvasive compliance methods: systolic pulse contour analysis, plethysmography, and diastolic pulse contour analysis.4 Using these 3 methods in over 100 subjects, we have found that the respective compliance and reflectance values correlate poorly across methods and have concluded that either the biologic information that each method provides is intrinsically different or that major methodological artifacts exist.4

The first method that we have subjected to additional methodological validation is diastolic pulse contour analysis.5-8 Diastolic pulse contour analysis is based on the assumption that the circulation can be represented by 1 (first-order model) or 2 (third-order model, including an interposed inertance function) capacitors arranged in parallel with a resistor (Figure 1). In these models, vascular elastic recoil (compliance) is represented by the capacitor(s). By fitting the diastolic decay portion of an individual’s arterial waveform to a first-order model (basic Windkessel) or third-order model (modified Windkessel), compliance variables can, theoretically, be derived.

The specific purpose of the present studies was to address issues of validity and reliability of Windkessel-derived compliance variables. We tested a specific assumption of this lumped-parameter model: that compliance estimates obtained from all peripheral measurement sites should be equal.6,7 Different compliance estimates obtained from 2 different sites would imply that regional, as well as systemic, factors influence the results. We also investigated the reliability of the system. This last issue is significant because analysis criteria and clinical reliability have not been published during the development of existing proprietary systems that measure arterial compliance.

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Methods

Subjects
The study was approved by an institutional review committee, and the subjects gave written informed consent. The study procedures followed were in accordance with institutional guidelines. A sample-size calculation was performed before the study. Based on an effect size equal to 0.5, an a level equal to 0.05 for a nondirectional test and 1-β equal to 0.9; the required sample size is approximately 44 subjects. Twenty normotensive subjects (median age 35, range 26 to 79 years) and 27 hypertensive subjects (median age 56, range 43 to 78 years) volunteered for testing. Systolic blood pressure ranged from 96 to 136 mm Hg (mean±SD 116±12 mm Hg) in the normotensive subjects and from 142 to 194 mm Hg (mean±SD 160±16 mm Hg) in the hypertensive subjects. Diastolic blood pressure ranged from 52 to 84 mm Hg (mean±SD 68±8 mm Hg) in the normotensive subjects and from 70 to 118 mm Hg (mean±SD 94±14 mm Hg) in the hypertensive subjects.

Waveform Acquisition
High-fidelity pressure waveforms were obtained noninvasively from the radial and posterior tibial artery by applanation tonometry using a Millar tonometer (Millar Instruments, Inc). The SphygmoCor Blood Pressure Analysis System (PWW Medical, Ltd) was used to amplify the signal and ensemble average the waveform data. Applanation tonometry can be used to record pressure waveforms from any peripheral artery that can be supported by a bony structure. Gently flattening but not collapsing an artery with a tonometer balances circumferential forces in the arterial wall, and the resulting contact force between the artery and the tonometer is equal to intra-arterial pressure. To minimize the effects of movement artifact on wave morphology, pressure waveforms were first assessed visually by a technician and then submitted to analysis by the SphygmoCor software, which reports a quality control parameter for diagnostic waveform variability. If diastolic waveform variability exceeded 10%, new data were obtained immediately. Pressure waveforms that failed the quality control parameter were rejected. Only data sets where both radial and posterior tibial artery waveforms were obtained were used in the statistical analysis. The order of tonometry measurements was alternated among subjects.

First-Order Model (Basic Windkessel)
The basic Windkessel model, a first-order lumped parameter model, assumes that the time constant (τ) of the monoeXponential pressure decay is determined by the product of systemic vascular resistance and aortic compliance. In the electrical analogue (Figure 1A), voltage (v) is analogous to pressure in the aorta, the capacitor (C_a) to whole-body arterial compliance, electrical current (i) to blood flow, and the resistor (R) to systemic vascular resistance. The standard first-order model equation for diastolic pressure (voltage) as a function of time is

\[ P(t) = A_1 \exp \left( \frac{-t}{\tau} \right) + A_3 \]

where \( A_1 \) represents end-systolic pressure, \( A_3 \) is mean circulatory pressure and \( t \) is time. The fitted parameter of interest is the time constant (\( \tau \)). When the resistance (R) is known, the whole-body arterial compliance is calculated as

\[ C_a = \frac{\tau}{R} \]

Third-Order Model (Modified Windkessel Model)
The third-order lumped-parameter model\(^{5-7}\) assumes that compliance of the arterial system can be partitioned into central and distal compartments, where central compliance is distinct from distal compliance. In the electrical analogue (Figure 1B), voltage (v) is analogous to mean pressure in the aorta, the first capacitor (C_1) to central, proximal, or large artery compliance, electrical current (i) to blood flow, inductance (L) to inertsance of a column, of blood, the second capacitor (C_2) to distal or small artery compliance, and the resistor (R) to systemic vascular resistance.\(^{6,7}\) The third-order model equation for diastolic pressure (voltage) as a function of time is

\[ P(t) = A_1 \exp \left( -A_2 t \right) + A_3 \exp \left( -A_4 t \cos(A_5 t + A_6) \right) \]

where \( A_1 \) and \( A_2 \) are damping constants, whereas \( A_5 \) is the frequency of oscillation. \( C_1 \) and \( C_2 \) were calculated using the following equations:

\[ C_1 = \frac{2A_1(A_1^2 + A_3^2)}{\left[ R(A_1^2 + 2A_1A_2 + A_2^2)(A_4^2 + A_5^2) \right]} \]

\[ C_2 = \frac{1}{R(2A_1 + A_3)} \]

In both the first- and third-order model equations, \( R \) is an estimate of systemic vascular resistance and demonstrates the high degree of theoretical dependence of \( C_2 \) on \( R \). For this study, it was not necessary to calculate \( R \) because intraindividual comparisons were used; accordingly, an arbitrary constant \( R \) value of 1500 dyne \cdot s \cdot cm\(^{-2}\) was used to calculate \( C_a \), \( C_1 \), and \( C_2 \) at each site.

Data and Statistical Analysis
In both models, the beginning of diastole was defined as the lowest point of the dicrotic notch (ie, the point after which the pressure began to rise again before decaying exponentially). The end of diastole was defined as the point where the diastolic pressure was no longer monotonically decreasing. The curve-fitting constants for each model were estimated by an iterative procedure using Marquardt’s algorithm (nonlinear regression). Curve fits were accepted if the coefficients were significantly different from zero (\( P<0.05 \)). The variables \( C_a \), \( C_1 \), and \( C_2 \) were calculated using Eq. 2, 4, and 5, respectively. Only data sets where both radial and posterior tibial artery waveforms could be fitted were used.

The \( \chi^2 \) statistic was used to test equality of proportions for the first- and third-order models. Pearson correlation coefficients were calculated to assess the linear relationship between the radial and
Results

Waveforms obtained from the radial artery were distinctly different from corresponding waveforms obtained from the posterior tibial artery (Figure 2), as expected. Coefficients of variation of ensemble-averaged blood pressures within a given individual were less than 5% (radial artery 3.7±1.7%, posterior tibial artery 4.2±2.2%). The mean values, standard deviations, and correlation coefficients for the first-order time constant (τ), third-order curve fitting constants (A2, A4, and A5), and each model’s compliance estimates (C_A, C_1, and C_2) are presented in Table 1. C_A, C_1, and C_2 estimates are presented graphically in Figures 3A, 4A, and 5A, respectively.

Data Correspondence to Model

As shown in Table 2, diastolic waveforms from 11 of 27 hypertensive subjects and from 10 of 20 normotensive subjects could not be described adequately by the first-order model. Waveforms from 11 of 27 hypertensive subjects (not the same individuals) and 3 of 20 normotensive subjects could not be described adequately by the third-order model. The third-order model fit the diastolic waveform data better than the first-order model ($\chi^2[1]=13.55, P<0.05$). Within the normotensive and hypertensive groups, the ability of the first- and third-order models to fit the data were independent of blood pressure and age. The lack of fit in either model was not related to the nominal quality control parameters from the SphygmoCor system, which did not eliminate any tracings from further analysis.

Time Constant (First-Order Model)

The correlation coefficient between sites for τ was not statistically significant ($P=0.97$), and a significant difference in mean values was observed between the radial and posterior tibial artery ($P=0.027$, power=0.62, $r=0.18$).

A2, A4, and A5 (Third-Order Model)

The correlation coefficients between sites for A2 and A4 were not statistically significant ($A_2$ $P=0.08$, $A_4$ $P=0.72$), whereas significant differences were observed between the mean values obtained from the radial and posterior tibial artery for $A_2$ ($P=0.002$, power=0.89, $r=0.26$) and $A_4$ ($P=0.0001$, power=0.99, $r=0.47$). A significant correlation was observed between radial $A_5$ and posterior tibial $A_5$ ($P=0.001$). There

| TABLE 1. Curve-Fitting Constants and Model Parameter Compliance Values for Individuals in Whom First and Third-Order Models Could Be Fit |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Radial          | Posterior Tibial| $r$ Values      |
| First-Order Model (n=26)        |                 |                 |                 |
| $\tau$ (s$^{-1}$)               | $0.395\pm0.175$ | $0.534\pm0.245^*$ | $-0.006$        |
| Error in $\tau$                | 11±7%           | 19±10           |                 |
| $C_A\times10^{-4}$ (cm$^2$·dyne) | $2.63\pm1.17$  | $3.56\pm1.63^*$ | $-0.006$        |
| Third-Order Model (n=33)        |                 |                 |                 |
| $A_2$ (s$^{-1}$)                | $0.4\pm0.2$     | $0.3\pm0.1^*$   | 0.31            |
| Error in $A_2$                 | 5±5.0%          | 8±10%           |                 |
| $A_4$ (s$^{-1}$)                | 9±4             | 5±2*            | 0.07            |
| Error in $A_4$                 | 8±3%            | 11±8%           |                 |
| $A_5$ (s$^{-1}$)                | 15±5            | 14±3            | 0.64**          |
| Error in $A_5$                 | 7±5%            | 4±3%            |                 |
| $C_A\times10^{12}$ (cm$^2$·dyne)| $2\pm1$        | $3\pm1^*$       | $-0.11$         |
| $C_A\times10^{15}$ (cm$^2$·dyne)| $4\pm2$        | $8\pm3^*$       | 0.04            |

$\tau$ indicates time constant; $C_A$, whole-body arterial compliance; $A_2$ and $A_4$, damping constants; $A_5$, frequency of oscillation; $C_1$, large artery compliance; $C_2$, small artery compliance; $r$, correlation coefficient between radial and posterior tibial values.

*P<0.05 between groups; **P<0.05.
was no significant difference between sites for A (P=0.21, power=0.24, =0.05).

C A (First-Order Model)
The correlation coefficient between sites for C A was not statistically significant (r=0.006, P=0.97, r²=0.00004; Figure 3A), but a significant difference was observed between the radial and posterior tibial artery (P=0.027, power=0.62, =0.18). The Bland-Altman plot for C A (Figure 3B) quantifies the limits of agreement between measurement sites: 4.9×10⁻⁴ to 3.1×10⁻⁴ dyne · s · cm⁻¹. The 95% confidence intervals for the upper and lower limits of agreement are 7.4×10⁻⁴ to 2.5×10⁻⁴ dyne · s · cm⁻¹ and −0.66×10⁻⁴ to −2.5×10⁻⁴ dyne · s · cm⁻¹, respectively.

C 1 and C 2 (Third-Order Model)
The correlation coefficients between sites were not statistically significant for either C 1 (r=−0.11, P=0.55, r²=0.01; Figure 4A) or C 2 (r=0.04, P=0.81, r²=0.002; Figure 5A). There were significant differences in C 1 (P=0.04, power=0.54, =0.12) and C 2 (P=0.0001, power=1.0, =0.61) between the radial and posterior tibial artery. The Bland-Altman plots for C 1 (Figure 4B) and C 2 (Figure 5B) quantify the limits of agreement between measurement sites: 2.44×10⁻⁴ to −4.29×10⁻⁴ dyne · s · cm⁻¹ and 2.19×10⁻⁴ to −9.41×10⁻⁴ dyne · s · cm⁻¹, respectively. For C 1, the 95% confidence intervals for the upper and lower limits of agreement are 1.32 to 3.56 dyne · s · cm⁻¹ and −5.41 to −3.17 dyne · s · cm⁻¹, respectively. For C 2, the 95% confidence intervals for the upper and lower limits of agreement are 0.39 to 3.99 dyne · s · cm⁻¹ and −7.61 to −11.21 dyne · s · cm⁻¹, respectively.

Discussion
Precise quantitation of arterial compliance variables is the cornerstone of future identification of individuals in whom premature vascular stiffening signals increased systolic blood pressure and increased cardiovascular risk. Present data, however, strongly suggest that the problems encountered in using Windkessel-derived diastolic pulse contour analysis in humans are similar to those reported in dogs, where the third-order model has been found to yield “unreliable estimates of arterial compliance.”12 Our results show that the lumped-parameter Windkessel models yield different results from the upper and lower limb. These differences probably represent the influences of regional circulatory properties and suggest that a simple “systemic measurement” of whole-body, proximal or distal compliance cannot be reliably obtained from peripheral tonography and diastolic pulse contour analysis.
From a theoretical perspective, diastolic pulse contour analysis indirectly estimates arterial compliance by fitting the diastolic portion of an arterial waveform to a lumped-parameter model. This lumped-parameter model of whole-body compliance is valid only if (1) the pressure wave speed is high enough so that all segments of the large and small arteries are pressurized simultaneously, and (2) no reflection sites exist. Under these 2 conditions, peripheral pressure waveforms at different arterial sites differ only in scale, and thus, compliance variables calculated from any site would be equivalent. However, pressure changes do not occur instantaneously throughout the arterial tree and the arterial tree is not a reflectionless system. Under these conditions, peripheral pressure waveforms at different arterial sites differ only in scale, and thus, compliance variables calculated from any site would be equivalent. However, pressure changes do not occur instantaneously throughout the arterial tree and the arterial tree is not a reflectionless system. Instead, after each systole, a pressure wave travels downstream with variable intrinsic velocities that depend on local arterial wall properties. Reflected waves emanate from points of significant impedance mismatch, and the summation of antegrade and retrograde waves determines the morphology of the composite arterial waveform at any given point along the arterial tree. Because of differences in the length of individual arteries, the number of regional reflection sites, and the stiffness of the individual arterial walls, the morphology, timing, and magnitude of reflected waves are intrinsically different in the wrist and ankle. Thus, Windkessel-derived compliance values in the upper and lower extremities would not be expected to be similar because they represent local, as well as systemic, vascular properties. The validity of these statements is supported by the current data.

The assumption of site-independence has never been fully tested for the basic or modified Windkessel model in man, and existing data are conflicting in animals. In dogs, both similar and different compliance values have been reported when aortic and femoral measurement sites were compared. We chose peripheral sites from the upper and lower limbs where the different morphology of the pressure pulses is due to different regional patterns of wave reflection. In the pulse wave morphology of Figure 2A, the second peak is probably a reflected wave, which violates the assumption of the first-order model (ie, that the diastolic pressure decay is monoeponential) and alters the Windkessel calculation. In the case of the third-order model, the presence of a reflected wave exerts an even stronger influence on the decaying sinusoid calculation than on the overall sinusoid decay.

The reliability of obtaining Windkessel-derived compliance values is also of significant concern. Our results are probably not due to methodological artifacts. Both the radial and posterior tibial measurement sites are well situated for tonometry, with each artery properly supported between a bony structure and the tonometer. Even though we were able to obtain high-fidelity arterial waveforms with no apparent artifact, some data could not be fit to the Windkessel equations in many subjects without yielding uninterpretable results, such as negative or “zero” coefficients and compliance values (Table 2). Retrospective analysis of tracings in

![Figure 5. Scatter plot (A) and Bland-Altman plot (B) for the posterior tibial and radial small artery compliance estimate. The solid line in A is the line of identity. C1 indicates small artery compliance.](image)

### Table 2. Descriptive Data for First-Order and Third-Order Models

<table>
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<th>Model Fit Data</th>
<th>Model Did Not Fit Data</th>
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<td>First-Order Model</td>
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<td>Normotensives (n=20)</td>
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<td>Hypertensives (n=27)</td>
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<tr>
<td>Total</td>
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</tr>
<tr>
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<td>Total</td>
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<td>Hypertensives (n=16)</td>
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</table>
| SP indicates systolic pressure; DP, diastolic pressure.
individuals in whom negative compliance values were obtained demonstrated the presence of late-diastolic wave peaks of uncertain origin. These large peaks strongly influence the calculation, converting the sinusoid from a decay pattern (positive compliance value) to an amplification pattern (a negative compliance value).

The model fit was excellent for the data reported. For the first-order model, the coefficient of determination ($r^2$) averaged 0.99 ± 0.04 and 0.99 ± 0.003 for the radial and posterior tibial artery waveforms, respectively. For the third-order model, $r^2$ averaged 0.94 ± 0.03 and 0.96 ± 0.02 for the radial and posterior tibial artery waveforms, respectively. The diastolic waveform variability averaged less than 5% at each measurement site, and the curve-fitting constants derived from the first- and third-order lumped-parameter models had low curve-fitting errors (Table 1).

The poor reliability is also not due to the slight methodological differences between our system and the commercially available HDI/Pulsewave CR-2000 (Hypertension Diagnostics, Inc) system. We have previously reported excellent concordance between the two modified Windkessel-based techniques in individuals in whom interpretable compliance values could be obtained.4

The significant intersite differences observed in this study cannot be attributed to excessive variability in either the radial or posterior tibial diastolic waveforms and probably represent true differences in the respective arterial walls. The first-order model time constant ($\tau$) and third-order model curve fitting constants ($A_2$ and $A_4$) were significantly different between the radial and posterior tibial artery. Because the constants were not correlated, the difference between sites was not systematic. The time constant ($\tau$), the curve-fitting constants ($A_2$ and $A_4$), and their derived compliance values ($C_2$, $C_1$, and $C_2$) were not only uncorrelated between sites, but significantly different as well. The third-order model curve-fitting constant $A_5$, which describes the frequency of oscillation, was correlated between sites, suggesting that the lack of correlation in other compliance variables could be due to the time delay between the incident and reflected wave. The $A_5$ correlation further suggests that the same reflection sites are found in both the upper and lower extremity.

Our results do not rule out the possibility that the compliance variables ($C_2$, $C_1$, and $C_2$) can serve as biomarkers of arterial dysfunction or disease. Abnormal changes in $C_2$ have been reported to be altered by aging, hypertension, and congestive heart failure.15 However, the physiological meaning of Windkessel-derived compliance values remains unclear.

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References
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