Noninvasive Assessment of Arterial Stiffness Should Discriminate Between Systolic and Diastolic Pressure Ranges


Abstract—Arterial stiffening plays an important role in the development of hypertension and cardiovascular diseases. The intrinsically nonlinear (ie, pressure-dependent) elastic behavior of arteries may have serious consequences for the accuracy and interpretation of arterial stiffness measurements and, ultimately, for individual patient management. We determined aortic pressure and common carotid artery diameter waveforms in 21 patients undergoing cardiac catheterization. The individual pressure-area curves were described using a dual exponential analytic model facilitating noise-free calculation of incremental pulse wave velocity. In addition, compliance coefficients were calculated separately in the diastolic and systolic pressure ranges, only using diastolic, dicrotic notch, and systolic data points, which can be determined noninvasively. Pulse wave velocity at systolic pressure exhibited a much stronger positive correlation with pulse pressure ($P<0.001$) and age ($P=0.012$) than pulse wave velocity at diastolic pressure. Patients with an elevated systolic blood pressure ($>140$ mm Hg) had a 2.5-times lower compliance coefficient in the systolic pressure range than patients with systolic blood pressures $<140$ mm Hg ($P=0.002$). Most importantly, some individuals, with comparable age or pulse pressure, had similar diastolic but discriminately different systolic pulse wave velocities and compliance coefficients. We conclude that noninvasive assessment of arterial stiffness could and should discriminate between systolic and diastolic pressure ranges to more precisely characterize arterial function in individual patients. (Hypertension. 2010;55:00-00.)

Key Words: arterial structure and compliance ■ pulse wave velocity ■ blood pressure measurement ■ systolic hypertension ■ carotid arteries

Decreased elasticity of the arterial wall plays an important role in the development of hypertension and related cardiovascular complications, such as heart failure, stroke, and renal failure.1–4 Therefore, noninvasive assessment of arterial stiffness has recently entered the European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension.5 Basic studies have shown that the elastic behavior of the arterial system is nonlinear, that is, arterial stiffness is pressure dependent.6–11 This intrinsic property of the arterial system may have serious consequences for the quantitative assessment of arterial stiffness, and changes therein, in response to age,12,13 physiological stress,7 and possibly antihypertensive treatment.14,15

Currently, arterial stiffness is assessed noninvasively either at the diastolic pressure level (aortic or carotid-femoral pulse wave velocity [PWV]) or estimated as an average over the diastolic-systolic pressure range. In the latter case, distensibility and compliance coefficients are calculated as, respectively, the relative and absolute changes in the cross-sectional area normalized to pulse pressure from diastolic minimum to systolic peak,16 tacitly assuming a linear pressure-area relationship. In ex vivo human cranial and femoral arteries, Hayashi et al16 found that the relationship between transmural pressure and vessel radius can be described by a single exponential relation. Meta-analysis of studies on the relationship between pressure and cross-sectional vessel area by Powalowski and Pensko9 confirmed this finding. However, Wolinsky and Glagov11 (in rabbit aorta, ex vivo) and Armen-tano et al8 (in dog aorta, in vivo) observed a more marked change in elasticity as a function of distending pressure, which is related to the ultrastructural interaction of elastin and collagen fiber networks in the tunica media. Viscous behavior of the arterial wall, associated with smooth muscle cell function, is observed ex vivo, especially with prolonged dynamic distension of the vessel, but appears insignificant in vivo if the waveforms are properly acquired and processed.18,19 To the best of our knowledge, the degree of nonlinearity of arterial stiffness in individual cardiovascular patients has not been studied in detail yet. Invasive measurement of pressure-area curves in vivo permits such a comprehensive description of arterial stiffness as a function of pressure.10,19,20 However, the challenge is to derive...
the pressure-dependent relationship for data obtained noninvasively.

The aim of the present study was to quantify the degree of nonlinearity of the arterial pressure-area relationship to evaluate its consequences for the (noninvasive) assessment of arterial elastic properties. We obtained carotid artery diameter and proximal aortic pressure recordings in patients undergoing cardiac catheterization. We used a dual exponential analytic model to derive incremental PWV for each individual, using all of the data points in the pressure-area range. To explore clinical applicability, we also calculated compliance and distensibility coefficients for the diastolic and systolic pressure ranges separately, on the basis of only diastolic, dicrotic notch, and systolic data points, which can be measured noninvasively with certain confidence. We discuss our findings with regard to the associations with pulse pressure, systolic blood pressure (SBP), and age within our study population and the potential for the application of noninvasive methods in clinical practice.

Materials and Methods

Study Population

Patients referred for a diagnostic coronary angiographic procedure were recruited in the outpatient clinic.21 Included patients were either suspected of coronary artery disease (anginal complaints) or had previous percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. All 21 of the patients gave written informed consent before enrollment. The study was approved by the joint medical ethical committee of Maastricht University and Maastricht University Medical Centre.

Protocol

Patients were prepared for the invasive diagnostic procedure following a standard protocol: overnight fast, refrainment from smoking, and prophylactic anticoagulation (Clopidogrel). Diabetes medication (Metformin), if any, was discontinued on the day of the examination; other medications were taken as usual. Age, weight, and height of the patients were copied from their clinical files. During antiseptic preparations and application of ECG electrodes, patients were in the supine position on the catheterization table, allowing localization of the left common carotid artery by means of a 7.5-MHz linear array/high-frame-rate ultrasound system (PICUS, ESAOTE Europe). All of the ultrasound recordings (see below) were obtained with the patients in this position. If the common carotid artery was located too deep for high-frame-rate image acquisition (because of dermal fat), the patient was excluded from the study. After percutaneous access was established by the intervention cardiologist, an angiographic guiding catheter (6F or 7F Wiseguide, Boston Scientific) was advanced over a guide wire and placed with the tip in the ostium of the targeted coronary artery. After initial coronary angiograms were obtained, the catheter was flushed with saline to wash out radiopaque contrast fluid, and the connection to the contrast pump was blocked to achieve the highest possible bandwidth for, and minimal ringing in, the aortic pressure signal. Bench testing of the fluid-filled system showed a flat frequency response from 0 to 25 Hz. At least 3 and maximally 5 repeated echo recordings of the left common carotid artery were obtained simultaneously with a continuous registration of aortic root pressure. The recording session took <4 minutes. After the last ultrasound recording, the angiographic procedure was continued.

Data Acquisition

During the common carotid artery echo recordings a B-mode image on the basis of 14 M-lines was depicted on the screen, and an online echo-tracking algorithm showed real-time anterior and posterior wall displacements. Pulse repetition frequency for each M-line was 800 Hz. For offline processing, the radiofrequency signal of the PICUS ultrasound scanner was fed into a dedicated PC-based acquisition system (ART.LAB, ESAOTE Europe) with a sampling frequency of 33 MHz. Aortic root pressure was recorded with a standard pressure transducer (Namic Custom angiographic kit, Namic) connected to the guiding catheter. The transducer was connected to a RADI pressure measurement console (RadiAnalyzer Xpress, RADI Systems), of which the output was connected to a cardiac-floating data acquisition system (Maastricht Programmable AcQuisition System, IDEE Instruments). Lead II of the patient ECG was relayed from the catheterization laboratory system (I-Connect, Fysicon Medical Technology) to both the Maastricht Programmable AcQuisition System and the PICUS ultrasound scanner to provide a synchronous time reference.

Signal Processing

The radiofrequency data acquisition and processing have been described in detail previously.22,23 Spatial and temporal estimation windows for wall echo tracking were 800 μm and 5 ms, corresponding with 34 and 4 sample points, respectively. Temporal estimation windows were 3 points overlapping, resulting in an effective sample rate of 800 Hz. We used 1 of the 14 M-lines to obtain diameter waveforms. Apart from the echo tracking, all of the data processing was performed in Matlab (version 7.5, Mathworks). Diameter and pressure waveforms were filtered by a 0-phase, low-pass filter with a cutoff frequency of 40 Hz. The second time derivatives of both signals were calculated over the recording length (7 seconds) by passing the signals through a 0-phase, second-order, high-pass filter (ie, a differentiator; cutoff at 100 Hz.). Signals were then segmented into separate beats with diameter and pressure beat pairs. Diameter waveforms were converted to cross-sectional area waveforms, assuming a circular cross-section: $A(t) = \pi d^2(t)/4$ (in millimeters squared). Misalignment in the time of pressure and area waveforms distorts the pressure-area curve. Bontoury et al.28 showed that hysteresis, indicating viscous wall behavior, is almost absent in vivo if the signals are properly assessed.19 Hysteresis is artificially created when a fixed time shift is applied to either one of the waveforms.20 To obtain proper pressure-area curves, we aligned the waveforms on the dicrotic notch (Figure 1). Timing of the dicrotic notch within the cardiac cycle can be determined accurately and reproducibly, if the signals have been acquired with an appropriate bandwidth (>20 Hz).24 In a preliminary experiment in a realistic hydrodynamic model of the arterial tree,26 we found that dicrotic notch-aligned pressure and area waveforms measured 19 cm apart in the proximal aorta did not exhibit hysteresis and yielded a pressure-area curve similar to the curve obtained from spatially aligned measurements (unpublished results).

Pressure and diameter waveforms and the pressure-area plots were visually checked per beat for signal quality and proper alignment. All of the beats showing a baseline shift over the beat (eg, because of wall tracking problems or arrhythmias) or excessive ringing because of catheter resonance or mechanical artifact (despite careful setup) were excluded. To suppress noise around the amplitude extremes, which would affect model fitting, both signals were additionally filtered by a second-order, 0-phase, low-pass filter with a cutoff frequency of 10 Hz. The pressure and diameter pulse waveforms are hardly affected by this filtering, because $\approx 98\%$ of the signal content is carried in the 0- to 10-Hz band.26 As argued above, hysteresis is hardly present in vivo, and, therefore, up and down slope pressure-area data essentially follow one and the same pressure-area curve. Preliminary analysis showed that including both slopes in the model fitting provides the most robust curve description. Because both limbs should confer equal weight to the model, both slopes were resampled into 100 pressure-area pairs, with the area samples rather than the time samples equidistantly spaced. The total of 200 pressure-area data points per beat was used to fit the model.

Model Definitions and Fitting Procedure

Modeling the measured data served 2 purposes: to obtain parameters that analytically describe individual curves within the diastolic-systolic pressure range and to derive smooth incremental PWV over this
range, which is difficult to achieve when using discrete data points. We used a model consisting of 2 summed exponential functions (dual exponential):

\[ p(A) = p_d e^{-\alpha_d \left(\frac{A}{A_d} - 1\right)} + p_e e^{-\alpha_e \left(\frac{A}{A_e} - 1\right)} \]

With \( p(A) \), pressure as a function of cross-sectional area \( A \); \( p_d \), diastolic pressure; \( A_d \), diastolic area; \( \alpha_d \) and \( \gamma \) stiffness indices; and \( A_{tha} \), cross-sectional area at which the second term of the model starts to contribute more than \( \varepsilon \) to the pressure given by the first term, \( p_d \cdot e^{\alpha_d \left(\frac{A}{A_d} - 1\right)} \), with \( \varepsilon \) being the threshold level, preset to 2 mm Hg.

Fitting of the dual exponential model was performed using an error minimization procedure (Matlab function “fmincon,” Matlab, MathWorks) under the following constraints: \( \alpha \) for dual term fitting is less than \( \alpha' \) when only the first term of the model is used to fit the data, and \( A_d < A_{tha} < A_s \), with \( A_s \) as systolic area. In some cases, the fitting procedure led to values of \( \gamma \) close to 0 and \( A_{tha} \) close to \( A_d \), indicating that the second component did not improve the fit. In these cases, the pressure-area curve is accurately described by a single exponential relation and, thus, \( \gamma \) and \( A_{tha} \) were said to be nonexistent, and only \( \alpha' \) is reported. To enable a comparison between individual patients (given any differences in \( A_d \)), the relative position of \( A_{tha} \) (in percentage) within the diastolic-systolic area range was expressed as follows: \( 100 \cdot \left(\frac{A_{tha} - A_d}{A_s - A_d}\right) \).

To express the final quality of the fit, root-mean-square error and the difference between measured and model SBP values (ΔSBP) were calculated per individual. Preliminary analyses included fitting of only the first term of the model to the data, which is equivalent to the model described by Powalowski and Pensko\(^{17}\) and Meinders and Hoeks.\(^{14}\) In one third of the patients, however, it did not accurately describe the curve as a whole (root-mean-square error of 4 to 8 mm Hg), nor did it capture SBP well (ΔSBP of −5 to −15 mm Hg). It should be stressed that it was not our objective to establish which model is most suitable or efficient to fit the data. Moreover, we specifically chose not to apply models that describe a pressure-area data outside the measured range, like the model of Langewouters et al.\(^{27}\) and as discussed by Vermeerch et al.\(^{27}\)

### Incremental PWV

Incremental PWV was derived from the model, using the Bramwell-Hill equation\(^{10,28}\):

\[ \text{PWV}(A) = \frac{\sqrt{\Delta p}}{\Delta A} \]

From the incremental PWV, maximum PWV (PWV\(_c\), at systolic pressure) and minimum PWV (PWV\(_d\), at diastolic pressure) were obtained. In addition, we calculated PWV averaged over the entire cardiac cycle (PWV\(_{mean}\)).

### Sectional Compliance and Distensibility

To investigate whether the nonlinearity of stiffness could also be quantified from measurements that can be obtained noninvasively,\(^{24,29,30}\) we selected only diastolic, systolic, and dicrotic notch data points (Figure 1) to calculate diastolic (CC\(_{low}\)) and systolic (CC\(_{high}\)) compliance coefficients:

\[ \text{CC}_{low} = \frac{A_{DN} - A_d}{p_{DN} - p_d}, \quad \text{CC}_{high} = \frac{A_s - A_{DN}}{p_s - p_{DN}} \]
with d, DN, and s referring to diastolic minimum, diastolic notch level, and systolic maximum, respectively, in the pressure (p) and area (A) waveforms.

Similarly, we obtained sectional distensibility coefficients DC_{low} and DC_{high} by dividing the sectional compliance coefficients by their respective minimum cross-sectional areas (A_d and A_{DN}).

### Statistical Analysis

Data are presented as mean±SD. For the model parameters, we determined the precision by calculating the intraindividual, intermeasurement SD, averaged over all of the patients. Associations of model parameters and model-derived incremental PWV with pulse pressure and age were evaluated by Pearson correlation; possible differences in trends were tested by F test (GraphPad Prism 4, GraphPad Software Inc). To analyze whether patients with elevated SBP exhibit lower arterial compliance in both the diastolic and systolic pressure ranges compared with patients with normal systolic SBP, we divided our study population into 2 groups on the basis of a systolic pressure cutoff of 140 mm Hg.31 Differences between groups were analyzed by 2-tailed Mann–Whitney and Wilcoxon signed-rank tests, respectively. A P<0.05 was considered statistically significant.

### Results

Patient characteristics are given in Table 1. Figure 1 illustrates clearly a compressed area waveform compared with the pressure waveform, indicating considerable nonlinear wall elasticity in this particular case. Figure 2 shows an example of a patient (age 37 years) in whom the pressure-area curve was described well by a single exponential relation (Figure 2A) and one (age 81 years) in which the dual exponential model was required to provide an accurate description of the pressure-area relationship (Figure 2B). Figure 2C shows the relative position of both curves in the pressure-area plane. The intraindividual variability of the model parameters (“precision,” Table 2) was below the intersubject variability, indicating that discrimination of differences between subgroups is feasible. Model fit root-mean-square error was 3.2±1.3 mm Hg, and the SBP error was <5 mm Hg for all of the patients (ΔSBP=2.2±1.7 mm Hg). Aside from relative A_{Br} (P<0.001), none of the model parameters was signifi-
Figure 3. PWV is significantly more strongly associated with pulse pressure (A) and age (B) than PWVd. Mean PWV shows an intermediate association. PWV is the incremental PWV derived from the 2-exponential model. For pulse pressure, the slopes of the 3 trends are all different (P<0.0007) and for age as well (P=0.012); #P<0.001, ^P=0.003, §P=0.016. Correlation (Pearson, r) between age and pulse pressure was weak (r=0.29; P=0.2).

Table 3. Elevated SBP Is Associated With Reduced Arterial Compliance in the Systolic Pressure Range

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low SBP &lt;140 mm Hg</th>
<th>High SBP &gt;140 mm Hg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>8/0</td>
<td>7/6</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120±16</td>
<td>160±18</td>
<td>0.23</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±16</td>
<td>79±10</td>
<td>0.23</td>
</tr>
<tr>
<td>CChigh-mm²/kPa</td>
<td>0.66±0.34</td>
<td>0.26±0.20*</td>
<td>0.002</td>
</tr>
<tr>
<td>CClow-mm²/kPa</td>
<td>0.78±0.46</td>
<td>0.65±0.42</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. DBP indicates diastolic blood pressure; CChigh and CClow sectional compliance coefficients for the systolic and diastolic pressure range, respectively.

*P=0.0002, CChigh vs CClow within the high SBP group.

Discussion

The present study demonstrates that central arterial stiffness may be significantly nonlinear in patients with established cardiovascular disease. PWV at the SBP level exhibited a much stronger association with pulse pressure and age than PWV at the diastolic pressure level. Correspondingly, we found that, particularly in patients with elevated SBP, arterial compliance is progressively reduced in late systole. Notably, differences in systolic stiffness and compliance between individuals were not attributable to blood pressure alone. These findings suggest that systolic stiffness may provide information additional to diastolic stiffness for the characterization of arterial function in cardiovascular patients.

Our findings clearly demonstrate in patients the nonlinear elastic behavior of central arteries as documented previously in experimental studies.6,11 The bearing of the mechanical forces in the arterial wall exhibits a gradual transition from elastic at lower pressures toward collagen at higher pressures.6,11 With our dual exponential model, we could accurately describe the pressure-area relations at both lower (α') and higher (γ) pressure levels within the diastolic-to-systolic range. In contrast to Armentano et al.6 we are hesitant to directly link α' or γ to fiber content, because this would disregard the dynamic orientation of the ultrastructure under variable stress and the contribution of smooth muscle tone.11,13 We did, however, find that the position of the major bend in the pressure-area curve (ie, relative Arel) was inversely correlated with systolic and pulse pressures, which may well reflect the progressive contribution of collagen to artery wall stiffness at greater transmural pressures. In addition, it is known that, with aging, elastic arteries dilate, whereas the wall stiffens.32 This pattern is illustrated in Figure 2C, in which the older patient has a much greater
diastolic area, increased nonlinearity, and a relative $A_{\text{thr}}$ of 29%. Moreover, the latter parameter tended to decrease with age, which suggests that elastin fragmentation and secondary collagen deposition$^{7,13,32}$ are responsible for the progressive difference between systolic and diastolic PWV with age, as observed in the present study.

Aortic PWV and carotid artery compliance and distensibility have been shown to reflect normal vascular aging$^{13,33}$ and accelerated stiffening because of manifest cardiovascular disease.$^{2,3,34,35}$ In our patients, diastolic PWV increases 0.08 m/s per year, which corresponds well with rates reported previously for aortic PWV.$^{12,36}$ The increase in PWV measured at systolic pressure, however, is $>3$ times greater, namely, 0.28 m/s per year. This pattern cannot be explained completely by a pulse pressure increase with age, because the latter association was rather weak and not significant in our study population. Apparently, systolic PWV may be more suited to quantify changes in arterial stiffness with age than diastolic PWV. It would be worthwhile to investigate whether carotid-femoral PWV can be obtained at higher pressures to improve the (early) prediction of cardiovascular events in populations at risk.

Aortic or carotid-femoral PWV, currently considered the gold standard for measuring arterial stiffness,$^5$ has been shown to correlate well with other cardiovascular risk factors and mortality.$^{34-35,37}$ The method is based on foot-to-foot transit time measurement and, therefore, quantifies arterial stiffness at diastolic blood pressure. Ideally, stiffness should also be measured at systolic pressure, but the systolic peak is unsuitable as a time reference point for transit time measurement (and, therefore, for PWV measurement), because its timing within the cardiac cycle is poorly defined. As we showed recently, the dicrotic notch is a good alternative as a time reference point to measure PWV locally, because it is less susceptible to interference from peripheral reflections.$^{38}$ Considering that the dicrotic notch pressure level is between mean and SBP,$^{39}$ dicrotic notch-based PWV may be a promising noninvasive measure of local (i.e., carotid and femoral) artery stiffness in the systolic pressure range.$^{24}$ Alternatively, our results suggest that noninvasive assessment of systolic and diastolic compliance and distensibility, requiring dicrotic notch identification, is feasible using carotid artery echo-tracking and applanation tonometry.

From the ventricular-arterial interaction perspective, it is worth considering the contribution of systolic arterial compliance to cardiac afterload. Systolic compliance was particularly low in the patients with a systolic pressure $>140$ mm Hg, suggesting that the heart ejects the last portion of stroke volume ($\approx 30\%$) in a 2.5-times stiffer arterial tree. Although carotid artery compliance is not synonymous with proximal arterial compliance, it is reasonable to assume that the degree of nonlinear stiffness observed at the carotid artery level is similar to that in the aorta,$^7$ considering that Studinger et al.$^{40}$ observed in humans similar distensibility in the carotid artery and the aortic arch. Thus, our findings suggest that the increased central arterial stiffness in late systole may in fact additionally contribute to cardiac risk in patients with systolic hypertension and, therefore, should be considered as a therapeutic target.$^{15}$ In antihypertensive treatment, the (pressure-independent) effects of arterial stiffness reducing drugs have to be considered.$^{14,41,42}$

**Perspectives**

The present study shows that nonlinear arterial stiffness is present and quantifiable in cardiovascular patients. Notably, our patients likely had some stress-related increase in sympathetic drive during catheterization, affecting central arterial hemodynamics. Therefore, the present findings can only tentatively be extrapolated to other, noncatheterized patients. The question can be posed whether the systolic PWV or compliance coefficient provides additional information other than what systolic or pulse pressure will do. Our findings indicate that blood pressure effects alone do not explain the difference between systolic and diastolic stiffness and its progression with age. This strongly suggests that systolic and diastolic stiffness measures should be combined with blood pressures to fully characterize arterial function. Moreover, this approach may potentially improve identification and selection of proper antihypertensive drugs, reducing arterial stiffness as well, in patient management. Additional studies in selected, controlled populations are required to establish the added value of discriminating between systolic and diastolic arterial stiffness in vascular medicine.

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**Disclosures**

None.

**References**


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