Noninvasive Method for Determination of Arterial Compliance Using Doppler Echocardiography and Subclavian Pulse Tracings
Validation and Clinical Application of a Physiological Model of the Circulation

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Background The Poiseuillian model of the arterial system currently applied in clinical physiology does not explain how arterial pressure is maintained during diastole after cessation of pulsatile aortic inflow. Arterial pressure-flow relations can be more accurately described by models that incorporate arterial viscoelastic properties such as arterial compliance. Continuous pressure and flow measurements are needed to evaluate these properties. Since the techniques used to date to acquire such data have been invasive, physiological models of the circulation that incorporate these properties have not been widely applied in the clinical setting. The purpose of this study was (1) to validate noninvasive methods for continuous measurement of central arterial pressure and flow and (2) to determine normal reference values for arterial compliance using physiological models of the circulation applied to the noninvasively acquired pressure and flow data.

Methods and Results Simultaneously acquired invasive and noninvasive aortic pressures (30 patients), flows (8 patients), and arterial mechanical properties (8 patients) were compared. Pressure was measured by high-fidelity catheter aortic micromanometer (invasive) and calibrated subclavian pulse tracing (noninvasive). Aortic inflow was determined from thermodilution-calibrated electromagnetic flow velocity data (invasive) and echo-Doppler data (noninvasive). Arterial compliance was determined for two- and three-element windkessel models of the circulation using the area method and an iterative procedure, respectively. Once validated, the noninvasive methodology was used to determine normal compliance values for a reference population of 70 subjects (age range, 20 to 81 years) with normal 24-hour ambulatory blood pressures and without Doppler-echocardiographic evidence for structural heart disease. The limits of agreement between invasive and noninvasive pressure data, compared at 10% intervals during ejection and nonejection, were narrow over a wide range of pressures, with no significant differences between methods. Invasive and noninvasive instantaneous aortic inflow values differed slightly but significantly at the start of ejection (P<.05), but during the latter 90% of ejection, values for the two methods were similar, with narrow limits of agreement. Total vascular resistance and arterial compliance values derived from invasive and noninvasive data were similar. Arterial compliance values for the normal population using the two-element model (C2E) ranged from 0.74 to 2.44 cm²/mm Hg (mean, 1.57±0.38 cm²/mm Hg), with a beat-to-beat variability of 5.2±3.9%. C2E decreased with increasing age (r=−.73, P<.001) and tended to be higher in men (1.67±0.41 cm²/mm Hg) than in women (1.51±0.35 cm²/mm Hg, P=.07). Compliance values for the three-element model (C3E) were predictably smaller than for the two-element model (mean, 1.23±0.30; range, 0.59 to 2.16 cm²/mm Hg, P<.001 versus C2E) but correlated with C2E values (r=.81, P<.001) and were also inversely related to age (r=−.56, P<.001). Ridge regression and principal component analyses both showed the compliance value to be a composite function whose variation could be best predicted by consideration of simultaneous values for five major hemodynamic determinants: heart rate, mean flow, mean aortic pressure, minimal diastolic pressure, and end-systolic pressure. Multivariate analysis revealed age and sex to be independent predictors of compliance (P<.01 for both). There were no differences in compliance between black and white subjects.

Conclusions Noninvasive methods can be used to acquire the hemodynamic data necessary for clinical application of physiological models of the circulation that incorporate arterial viscoelastic properties such as arterial compliance. The strong inverse linear relation between model-based compliance estimates and age mandates incorporation of this demographic parameter into any framework that is developed for the clinical evaluation of arterial viscoelasticity. (Circulation. 1994;89:2688-2699.)

Key Words • echocardiography • arterial compliance • pressure

For any given aortic inflow, the morphology and dimensions of aortic pressure are entirely determined by the mechanical properties of the arterial system.1-3 To understand the hemodynamic interactions between the heart and the vasculature, it is necessary to characterize the arterial mechanical properties that determine the relation between central arterial pressure and flow.4 Since these properties cannot be measured directly in the intact organism, they must be determined indirectly, from continuous pressure and
volume-flow measurements using various models of the circulation.\textsuperscript{2,5-8} Traditionally, clinicians have modeled the arterial system according to Poiseuille's equation as a simple hydraulic circuit in which pressure is a function of flow and resistance only.\textsuperscript{4,9,10} However, this paradigm does not explain how the pulsatile flow wave generated by left ventricular contraction is converted into the sustained aortic pressure wave that is essential for normal organ perfusion.\textsuperscript{2,20} The systemic pressure-flow relation can be more accurately described by models that incorporate viscoelastic properties of the circulation, such as arterial compliance.\textsuperscript{3,5,11}

Since Stephen Hales' 18th-century analogy of the proximal arterial circulation to a "windkessel" (capacity chamber) that stores a proportion of the hemodynamic energy discharged by the cardiac pump during systole for subsequent sustained delivery to the periphery during diastole,\textsuperscript{4,10,12} numerous models of the circulation have been developed to characterize the relation between arterial pressure and flow. A paucity of invasive data in humans and the absence to date of noninvasive methodology for the acquisition of continuous pressure and flow measurements presumably account for the failure of these models to gain clinical eminence thus far. Since these data have not been readily accessible to clinicians, vascular viscoelastic properties such as arterial compliance are not incorporated in the current conceptual framework for evaluation of cardiovascular pathophysiology. As a result, the potential diagnostic and therapeutic benefits that might accrue from the clinical application of more physiological models of the circulation are not well appreciated. There also appears to be a generic communication gap between those who develop arterial models and those who must apply them in the clinical setting. The model makers have focused their attention on model accuracy (which is by definition proportional to mathematical complexity) rather than on providing clinically accessible, functional models that can be easily applied at the bedside.

The aims of this study were (1) to validate noninvasive methods for continuous measurement of central arterial pressure and flow and (2) to determine normal reference values for arterial compliance, using simple physiological models of the circulation applied to the noninvasively acquired pressure and flow data.

Methods

Study Design

The study was divided into two parts, both of which were approved by the Institutional Review Board of the University of Chicago Hospitals: (1) validation of noninvasively acquired hemodynamic data and (2) determination of arterial compliance values in normal subjects.

Study Population

All patients and subjects were screened clinically and by Doppler echocardiography before admission to the study. Individuals with evidence for regional wall motion abnormalities or valvular disease were excluded. Specific care was taken to ensure that aortic valves were anatomically normal with preserved leaflet excursion and without Doppler evidence for aortic regurgitation or stenosis.

Validation of Noninvasively Acquired Hemodynamic Data

Thirty-eight patients, ranging in age from 18 to 79 years (mean, $54 \pm 15$), were studied at the time of left heart catheterization. None had angiographic evidence for coronary or valvular heart disease. Invasive and noninvasive measurements of central arterial pressure were compared in 30 patients. Invasive and noninvasive aortic inflow data were acquired in addition to and simultaneously with pressure measurements in a further 6 patients. Total vascular resistance and arterial compliance were determined for the 8 patients in whom simultaneous pressure and flow data had been acquired.

Determination of Normal Reference Values for Arterial Compliance

Eligibility criteria comprised (1) absence of clinical and/or echocardiographic evidence of valvular heart disease, (2) normal left ventricular function assessed by two-dimensional and M-mode echocardiography (no regional wall motion abnormalities and shortening fraction $>30\%$), (3) no history of angina or previous myocardial infarction, (4) normal sinus rhythm on the resting ECG, and (5) average daytime and nighttime mean arterial blood pressures of $<105$ and $<95$ mm Hg, respectively, obtained at 15-minute intervals by 24-hour ambulatory blood pressure monitoring (Acutracker, Spacelabs Medical Inc.).

Continuous pressure and flow measurements were acquired noninvasively in 86 subjects. Of these, 16 were excluded because data did not fulfill the rigorous criteria for beat selection, which had been defined before the study and which are outlined in the section entitled "Data Analysis." The study population therefore comprised 70 normotensive subjects.

Data Acquisition

Central Arterial Pressure

Invasive arterial pressure measurements were obtained using an 8F high-fidelity micromanometer catheter (Millar Instruments, model SPC-484A) introduced into the right femoral artery and advanced under fluoroscopic guidance to the ascending aorta until the tip was situated just distal to the aortic valve.

Noninvasive arterial pressure measurements were generated from subclavian pulse tracings, obtained using a small plastic funnel positioned over the right subclavian artery at its point of maximal impulse in the supraclavicular fossa and connected by Silastic tubing to a strain-gauge transducer (model 03040170, Cambridge Instrument Co.). The subclavian artery waveform was recorded using a physiological pulse wave recording system with an amplitude/frequency bandwidth response range of 0.05 to $>50$ Hz. The subclavian pulse tracing was calibrated according to the proximal brachial artery pressure obtained using an oscillometric sphygmomanometer-based system (Dinamap vital signs monitor, model 1846 SX, Critikon Inc.).\textsuperscript{13} The maximal systolic pressure measured by the Dinamap was assigned to the peak of the tracing and the diastolic Dinamap pressure to the nadir of the tracing.\textsuperscript{14,15} Noninvasive instantaneous pressures were then derived throughout the cardiac cycle by linear interpolation. ECG, subclavian pulse, and high-fidelity central arterial pressure recordings were acquired simultaneously with the patient in the supine position. All data were fed into an echocardiographic unit (Hewlett-Packard Inc) via a custom-made multichannel physiological signal module.

Aortic Inflow

Invasive flow measurements were obtained using an 8F Millar catheter (model SVPB-684D) with high-fidelity pressure and electromagnetic velocity sensors mounted at the same catheter location 5 cm from the catheter tip. The catheter was positioned in the left ventricle such that the pressure and fluid velocity sensors were located just distal to the aortic valve. The flow probe was connected to a square-wave electromagnetic flowmeter (Carolina Medical Electronics, model FM 501). The intravascular velocity signal was calibrated with thermodilution cardiac output measurements.
using a Swan-Ganz catheter that had been advanced through the right femoral vein into the pulmonary artery. Thermodilution cardiac output was determined as the average value of three successive measurements that varied by <10%.

Noninvasive flow data were generated from continuous-wave Doppler recordings and two-dimensional echocardiographic measurements of aortic annular area. Aortic blood velocity was measured noninvasively using a 1.9-MHz continuous-wave Doppler transducer (Hewlett-Packard Inc) positioned at the cardiac apex. The aortic annular diameter (D), in centimeters was measured at the bases of the aortic valve leaflets (trailing to leading edges) from parasternal long-axis, two-dimensional echocardiographic recordings using a 2.5-MHz transducer. Diameter was assumed to be constant throughout the cardiac cycle. Annular cross-sectional area (CSA) was calculated, assuming a circular orifice, as CSA = \( \pi(D/2)^2 \). Instantaneous aortic flow was obtained as the product of the instantaneous Doppler aortic blood flow velocity and CSA. The invasively acquired flow velocity signal was fed into the echocardiographic unit to enable simultaneous recording with Doppler spectra.

Data Analysis

Beat Selection Criteria for Noninvasively Acquired Data

Analysis of noninvasive data was restricted to individual beats in which (1) the magnitude of the baseline shift in diastolic pressure of the subclavian pulse tracing was <10% of the pulse pressure; (2) the Doppler envelope was well demarcated, a visible Doppler closing click was evident, and the peak Doppler flow velocity was within 10% of the maximum velocity value recorded for any beat in that subject; and (3) the ECG showed sinus rhythm with RR interval variations of <15% for the three analyzed beats.

Central Arterial Pressure Measurements: Invasive Versus Noninvasive

Simultaneously acquired central aortic pressure and subclavian pulse tracings were traced by hand and digitized (by interpolation) at 5-millisecond intervals using a digitizing tablet (Bit Pad Two, Summagraphics Corporation). Data were stored on an Epson Equity III+ personal computer. Appropriate corrections were made for pulse transmission delay by temporally aligning the incisura of the pulse tracing with the Doppler closing click of the aortic valve. For each patient, three cycles were analyzed and results averaged. Invasive and noninvasive mean aortic pressures were calculated by integrating the area under the high-fidelity pressure tracing and calibrated right subclavian pulse waveform, respectively. Data acquired invasively and noninvasively were compared at 10% time intervals throughout ejection and nonejection phases of the cardiac cycle. This was done to facilitate analysis of grouped data from individual subjects with different heart rates.

Aortic Inflow Measurements: Invasive Versus Noninvasive

The simultaneously acquired electromagnetic aortic flow waveform signal and the outer envelope of the continuous-wave aortic Doppler velocity spectrum were traced by hand and digitized as for the pressures. Synchronization was accomplished by aligning R waves of the ECG from identical beats. Thermodilution stroke volume was used for calibration of the area under the electromagnetic flowmeter signal. Data were stored on an Epson Equity III+ personal computer. Electromagnetic flow data with stable baseline flows were selected for analysis. Velocity signals detected after end ejection (defined as a return to zero-flow voltage with the electromagnetic flowmeter and by the closing aortic click with Doppler) were not included in the analysis. For each experimental condition, three cycles were analyzed and the results averaged. Stroke volume, cardiac output, and instantaneous flow rates were determined from the electromagnetic and Doppler flow velocity data for each cycle. The instantaneous derivative of flow (dQ/dt) was computed using a five-point Lagrangian interpolation method from digitized data that were filtered with a three-point smoothing technique. Ejection time (ET), peak flow (Ques), maximum flow acceleration (dQ/dtmax), and time to Qmax were determined. To facilitate analysis of grouped data from individual subjects with different heart rates, instantaneous flow rates were compared at 10% intervals throughout left ventricular ejection.

Arterial Mechanical Properties

Models

Arterial compliance and total vascular resistance were determined from simultaneous pressure and flow data acquired invasively and noninvasively for two- and three-element windkessel-based models of the arterial system (Fig 1). Total vascular resistance was calculated as

\[
TVR = \frac{MAP}{Q_{mean}}
\]

where TVR is total vascular resistance in dyne·sec·cm⁻², MAP is mean arterial pressure in mm Hg, and Qmean is mean flow in cm³·sec⁻¹.

Arterial compliance for the two-element model was determined using the area method of Liu et al.⁶ wherein the solution of the two-element model equation (derivation in the "Appendix") is expressed as

\[
C_{2e} = \frac{A_d}{TVR \times (P_e - P_d)}
\]

where \( C_{2e} \) is arterial compliance (two-element model) in cm³/mm Hg, \( A_d \) is the area under the diastolic portion of the arterial pressure wave, \( P_e \) is the end-systolic pressure, and \( P_d \) is the diastolic pressure.

Arterial compliance for the three-element model (\( C_{3e} \)) was determined by iteration (Fig 2) using customized software to identify best-fit model parameter values for compliance and
transverse resistance elements ($C_2E$ and $r$, respectively), the two unknowns in the three-element equation (derivation in the "Appendix").

The error function for the three-element model, $e_{min}$ (mm Hg), determined by iteration as the smallest root-mean-square difference between measured and model pressures, was used as a measure of model performance.

**Statistical Analysis**

Simultaneously acquired invasive and noninvasive pressure and flow data, as well as derived hemodynamic parameters (i.e., arterial compliance and total vascular resistance), were compared using the statistical method of Bland and Altman for assessing agreement between two methods of clinical measurement.

Interobserver error and beat-to-beat variability were computed for noninvasively acquired arterial compliance data using the formula:

$$CV = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{d}{C} \times 100 \right)$$

where $CV$ is the coefficient of variation ($\%$), $n$ is the number of patients, $C$ is arterial compliance, and $d$ is the absolute difference between compliance values determined by two independent observers as the average of three analyzed beats (interobserver error) or the maximal difference between compliance values determined for individual beats in each subject by a single observer (beat-to-beat variability).

Multivariate regression was used to evaluate the impact of individual demographic characteristics on arterial compliance values. Pearson's correlation coefficient was determined for the relation between arterial compliance and age.

The significance of individual hemodynamic variables (heart rate, duration of diastole, mean arterial pressure, mean diastolic pressure, minimal diastolic pressure, end-systolic pressure, diastolic pressure difference, and mean flow) as determinants of $C_{2E}$ and $C_{3E}$ was investigated. Since multicollinearity was an important consideration, multivariate regression analysis (both a stepwise procedure and an all regression modeling using Mallows $C_p$ as a selection criterion), ridge regression, and a principal component analysis were used.

**Results**

**Validation of Noninvasive Techniques**

A representative example of simultaneously acquired high-fidelity aortic pressure, calibrated subclavian pulse tracing, electromagnetic aortic inflow velocity, and Doppler aortic inflow velocity is displayed in Fig 3.

**Calibrated Subclavian Pulse Versus High-Fidelity Micromanometer Aortic Pressure**

Invasive and noninvasive pressure measurements, compared at 10% time intervals during the ejection and nonejection phases of the cardiac cycle, were similar (Fig 4). The limits of agreement between invasively and noninvasively acquired individual patient data were narrow over a wide range of aortic pressures (Fig 5) both for discrete predetermined pressure points (peak systolic pressure, end-systolic pressure, and diastolic pressure) and for mean values during all phases of the cardiac cycle.

**Doppler Echocardiographic Versus Thermodilution-Calibrated Electromagnetic Flow**

Aortic inflow characteristics for the two techniques are summarized in Table 1. Stroke volume, cardiac output, left ventricular ejection time, and peak flow rate ($Q_{max}$) were similar, but Doppler values were higher for the three-element equation ($Q_{max}$) and lower for time to $Q_{max}$. Invasive and noninvasive flow measurements were compared at 10% time intervals throughout ejection (Fig 6). During early ejection, average values for Doppler flows were slightly higher than the corresponding electromagnetic flow rates. Analysis of individual patient data revealed a positive bias of Doppler data for the first one-tenth of the ejection period, but thereafter flow rates for the two methods were similar (Fig 7).

**Arterial Mechanical Properties: Invasive Versus Noninvasive Values**

Computations performed using the combined Doppler-subclavian pulse tracing and electromagnetic flow-Millar data yielded similar mean values for total vascular resistance (1931±295 versus 1886±282 dyne·sec·cm⁻², respectively, $r=.91$) and arterial compliance (1.09±0.44 versus $1.23±0.58$ cm³/mm Hg, respectively, for the two-element model, $r=.98$, and $0.95±0.46$ versus $1.15±0.78$ cm³/mm Hg, respectively, for the three-element model, $r=.97$). Analysis of individual patient data confirmed the narrow limits of agreement between the two methods for these parameters (Fig 8). Interobserver error for noninvasively derived compliance values was 4.2±2.5%. In contrast, mean values for transverse vascular resistance, $r$, determined from noninvasively acquired pressure and flow data, did not correlate as well with parameter estimates derived from invasively acquired hemodynamic measurements (103±29 versus $98±29$ dyne·sec·cm⁻², $r=.59$), and variance between the two methods was wide (Fig 8). The minimal pressure difference between measured and model pressures determined by iteration for the three-element model ($e_{min}$, an index of model performance) was $2.87±1.10$ mm Hg for noninvasively acquired data and $2.67±1.59$ mm Hg for invasively acquired data ($r=.85$) (Fig 9).
Demographics

Population

Flow velocity recordings from the aortic root. Ao indicates aortic; AoP, aortic pressure; EKG, electrocardiogram; EMF, electromagnetic flow; and SPT, subclavian pulse tracing.

Reference Population Values for Arterial Mechanical Properties

Population Demographics

Subjects ranged in age from 20 to 81 years (mean, 44±16). Forty-one were women and 41 were white. Body surface area was greater in men than in women (1.97±0.18 versus 1.70±0.13 m², P<.001) but was not significantly influenced by age or race.

Hemodynamic Data

Mean arterial pressure values for the 70 normotensive subjects were normally distributed, with a median value (90 mm Hg) similar to the mean (91 mm Hg). Stroke volumes, heart rates, and cardiac outputs were within normal limits. The mean values for these parameters are shown in Table 2.

Total Vascular Resistance

TVR ranged from 702 to 2559 dyne·sec·cm⁻¹ (mean±SD, 1387±342). A weak but significant direct linear correlation was found between age and TVR (r=.39, P<.001). TVR was not influenced by sex or race.

Arterial Compliance

The mean arterial compliance value for the two-element model (Cₑₑ) was 1.57±0.38 cm³/mm Hg for the entire study population, with a wide range of individual values (0.74 to 2.44 cm³/mm Hg) (Table 2) and a beat-to-beat variability of 5.2±3.9%. Arterial compliance decreased with increasing age (r=−.73, P<.001) (Fig 10). There was a trend toward higher compliance values in men (1.67±0.41 cm³/mm Hg) than in women (1.51±0.35 cm³/mm Hg, P=.07). Multivariate analysis showed both age and sex to be independent predictors of compliance (P<.01 for both). There were no racial differences in compliance values between black (1.63±0.30 cm³/mm Hg) and white (1.53±0.43 cm³/mm Hg) subjects.

Compliance values for the three-element model (Cₑₑ) were lower than but correlated well with values for the two-element model (negative bias, −21.7%, P<.001; r=.81, P<.001) (Table 2). As in the case of Cₑₑ values, Cₑₑ values were inversely related to age (r=−.56, P<.001). Beat-to-beat variability for three-element model compliance values was 7.3±4.9%. The minimal
pressure difference between measured and model pressures determined by iteration for the three-element model (\( \varepsilon_{\text{min}} \), an index of model performance) was 3.87±2.01 mm Hg (range, 1.18 to 10.55 mm Hg).

**Influence of Individual Hemodynamic Variables on Arterial Compliance**

Preliminary analysis of hemodynamic data revealed high correlations between the individual variables used to estimate compliance, suggesting multicollinearity (Table 3). This was confirmed by the high variance inflation factors and small eigenvalues of the correlation matrix when all eight variables (heart rate, duration of diastole, mean flow, mean arterial pressure, mean diastolic pressure, minimal diastolic pressure, end-systolic pressure, and diastolic pressure difference) were considered. A subset of explanatory variables was therefore selected using Mallows Cp, ridge regression, and principal component analysis. Ridge regression showed that exclusion of end-systolic pressure and mean diastolic pressure almost eliminated the problem of high-variance inflation. Two principal components comprising groups of variables associated with the smallest eigenvalues were identified: (1) minimal diastolic pressure, end-systolic pressure, and diastolic pressure difference and (2) mean diastolic pressure and mean arterial pressure. Among these, end-systolic pressure and mean diastolic pressure dominated vectors associated with small eigenvalues (0.00001 and 0.00785, respectively) and small coefficients for \( C_{3E} \) (−0.000072 and −0.001523, respectively), again reflecting their small relative contribution to variations in \( C_{3E} \). In contrast, mean flow, mean aortic

![Fig 5. Plots show limits of agreement between invasively and noninvasively acquired central arterial pressures for discrete predetermined pressure points (peak, diastolic, and end-systolic pressures) and for mean values during all phases of the cardiac cycle over a wide range of systolic and diastolic pressures. The dashed central horizontal line is the mean difference between invasive and noninvasive measurements; upward or downward displacement of this line from the zero difference level (solid horizontal line) reflects positive or negative bias of noninvasive versus invasive measurements. Upper and lower dashed horizontal lines represent ±2 SD about this mean value. SPT indicates subclavian pulse tracing.](image)

**Table 1. Aortic Inflow Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Doppler</th>
<th>EMF</th>
<th>Doppler vs EMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per minute</td>
<td>79±15</td>
<td>79±15</td>
<td>...</td>
</tr>
<tr>
<td>Stroke volume, cm³</td>
<td>62±12</td>
<td>61±12</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.81±0.86</td>
<td>4.68±0.75</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection time, ms</td>
<td>257±28</td>
<td>256±29</td>
<td>NS</td>
</tr>
<tr>
<td>( Q_{\text{max}}, \text{cm}³ \cdot \text{sec}^{-1} )</td>
<td>329±47</td>
<td>326±44</td>
<td>NS</td>
</tr>
<tr>
<td>( \text{dQ/dt}_{\text{max}}, \text{cm}³ \cdot \text{sec}^{-2} )</td>
<td>6988±1153</td>
<td>5787±751</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Time to ( Q_{\text{max}}, \text{ms} )</td>
<td>77±16</td>
<td>84±15</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

EMF indicates electromagnetic flowmeter; \( Q_{\text{max}} \), peak flow rate; and \( \text{dQ/dt}_{\text{max}} \), maximal flow acceleration.

![Fig 6. Plot shows comparison of instantaneous aortic inflows acquired invasively using thermodilution-calibrated electromagnetic flowmeters (EMF) and noninvasively using echo-Doppler at 10 equal time intervals during ejection. Each data point represents the average flow (±SD) obtained from 8 patients at each recording interval. \( P < .05 \), Doppler vs EMF.](image)
pressure, minimal diastolic pressure, and end-systolic pressure were associated with the highest eigenvalues and largest coefficients for \( C_{3E} \). The Mallows \( C_p \) analysis revealed that most of the variation in \( C_{3E} \) could be explained by a five-variable model incorporating the four variables selected by the principal component method (mean flow, mean aortic pressure, minimal diastolic pressure, and end-systolic pressure) along with heart rate (\( C[p] = 3.4541, R^2 = .7716 \)).

**Discussion**

The heart discharges mechanical energy into the arterial system in pulses of arterial pressure and flow\(^{4,10}\). If aortic inflow was entirely unimpeded, no aortic pressure would be generated and no external cardiac work would be necessary for tissue perfusion. Since external work is entirely expressed as aortic pressure and flow, characterization of the mechanical properties impeding forward flow might provide a framework for analysis of the factors controlling energy transfer between the heart and the periphery. The full impedance spectrum can be determined directly from Fourier-analyzed pressures and flows in the frequency domain, but incorporation of these data into conventional time-based clinical cardiologic paradigms is conceptually complex. An alternative approach is the use of arterial models that characterize arterial pressure-flow relations.

Traditionally, clinicians have modeled the arterial system according to Poiseille’s equation as a simple hydraulic circuit with a single resistive element (equivalent to vascular resistance) impeding continuous (non-pulsatile) forward flow. The physiological mechanisms that govern the phasic transfer of energy from the heart to the arterial system are not well explained by this “single-element model” of the circulation that is universally applied in clinical medicine\(^2,23\). More physiological albeit complex models of the circulation are needed to explain the arterial mechanical properties that transform the pulses of energy discharged by the heart during systole into a persistent arterial pressure that is maintained during diastole even after cessation of arterial inflow\(^2,5,11\). Clinical application of these concepts has been limited by the relative inaccessibility of the continuous pressure and flow data that would allow improved characterization of ventriculoarterial energy transfer. In this study, noninvasive methodology for acquisition of continuous pressure and flow measurements is validated, then applied clinically to define normal reference values for arterial compliance.

**Central Arterial Pressure**

Central arterial pressure was determined noninvasively using calibrated subclavian pulse tracings. Noninvasively acquired data were compared with continuous-pressure waveforms obtained invasively using high-fidelity micromanometers placed in the central aorta. Subclavian pulse tracings were morphologically similar to manometric ascending aortic pressure recordings despite their different sites of origin. The relatively large caliber of the subclavian artery and its close proximity to the central aorta presumably account for the observed similarities and may explain the apparent attenuation of the effects of wave reflections that frequently
result in marked differences between pressure waveforms of proximal and more distal arteries.18,19

Noninvasively acquired subclavian pulse tracings were calibrated according to upper arm blood pressure measurements obtained using an oscillometric sphygmomanometer (Dinamap, Critikon Inc). This method of calibration was validated by the close correlation between peak systolic and diastolic Dinamap blood pressure readings and corresponding central aortic pressures documented in this study. Similar results have been reported by other investigators in children and in normotensive and hypertensive adults.13-15,20,21 It is noteworthy that in none of these studies did the effects of peripheral distortion and pulse wave amplification appear to affect the oscillometrically determined pressure values significantly. One possible contributory explanation for this observation is the fact that the algorithms used to determine arterial systolic and diastolic pressures in the Dinamap system were derived by calibration against central aortic pressure rather than radial artery or cuff pressures.13

Aortic Inflow

Our data indicate that instantaneous aortic blood flow characteristics can be accurately assessed using continuous-wave Doppler echocardiography. Many previous investigations have demonstrated that the transaortic, continuous-wave, Doppler-derived spectral velocity envelope in conjunction with two-dimensional echocardiographic estimation of cross-sectional area at the level of the aortic valve annulus provides a reasonable noninvasive estimate of stroke volume.22-26 Comparisons of instantaneous Doppler and electromagnetic aortic inflow data have largely been restricted to analyses of peak flow velocities and maximal flow acceleration using pulsed-wave Doppler rather than continuous assessment of instantaneous flow throughout ejection.27-29 The use of continuous-wave Doppler in this study obviates the aliasing that occurs when aortic flow velocities exceed the Nyquist limits of the pulsed Doppler technique but introduces another potential source of error, namely, that the measured velocity is a composite of all velocities within the interrogation beam rather than simply the point velocity at the site of the electromagnetic flow sensor. Despite this limitation, a close correlation between electromagnetic and continuous-wave Doppler-derived instantaneous aortic inflow characteristics has been demonstrated in open-chest monkeys with the Doppler transducer positioned directly over the proximal aorta to ensure alignment of the interrogating Doppler beam with the direction of blood flow.16 The current investigation, in which instantaneous aortic blood flow velocity data were obtained with a Pedof transducer positioned in the region of the cardiac apex, demonstrates for the first time the accuracy of continuous-wave transthoracic Doppler for instantaneous aortic inflow assessment in the clinical environment in selected patients with normal aortic valves. Presumably, in the absence of aortic valve disease, the spectrum of velocity gradients in the proximal aorta immediately downstream from the valve is narrow, with the result that the component velocities that contribute to the net continuous-wave value are relatively similar.

Doppler flows were slightly higher than their electromagnetic counterparts during early ejection—Doppler flows accelerated faster than corresponding electromagnetic data. Similar findings were reported in the primate study quoted above.16 Possible explanations for these minor differences include overestimation by Doppler due to low sensitivity of the Doppler frequency shift signal at velocities nearing zero or underestimation by the electromagnetic system due to an inadequate frequency response of the electromagnetic flowmeter,
TABLE 2. Hemodynamic Profile of Normal Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Measured parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±13</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83±10</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>91±11</td>
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<tr>
<td>Stroke volume, cm³</td>
<td>84±15</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>68±10</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.68±1.11</td>
</tr>
<tr>
<td><strong>Model (derived) parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Total vascular resistance, dyne·sec·cm⁻⁵</td>
<td>1387±342</td>
</tr>
<tr>
<td>Arterial compliance, cm²/mm Hg</td>
<td></td>
</tr>
<tr>
<td>Cₑₑ</td>
<td>1.57±0.38</td>
</tr>
<tr>
<td>Cₑₑ</td>
<td>1.23±0.30</td>
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Fig 9. Representative measured and best-fit model pressure data generated from the three-element model equation by iteration. The root mean square of the difference between the two pressure-time curves represents the model error, eₑₑ. Top curve shows a relatively poor fit of model to measured pressures, highlighting the model error (shaded area). Lower curve shows a series of better-fit model pressures, generated during iteration and superimposed on the measured (actual) pressure profile.

which was set at 100 Hz to minimize high-frequency noise. Whatever the reason, these minor differences in morphology did not impact significantly on the derived hemodynamic parameters of interest, arterial compliance and total vascular resistance.

**Arterial Mechanical Properties**

The complex relation between pressure and flow in the vascular system cannot be described in terms of vascular resistance alone.²,⁴,¹⁰ Other mechanical properties of the arterial system must be considered in order to explain how pulsatile aortic inflow is converted into the sustained diastolic pressure wave that is essential for normal organ perfusion.³,⁴,¹⁰ Perhaps the most important of these is arterial compliance, a parameter of arterial elasticity and a major determinant of arterial blood pressure.² The compliance of the arterial system constitutes a pressure-flow buffer that stores a portion of the mechanical energy discharged by the heart during systole for delivery to the tissues during diastole.³,⁴,¹⁰ Whereas resistance can be determined as the ratio of mean pressure (estimated from systolic and diastolic pressure measurements) to mean flow (obtained from cardiac output calculations), continuous data throughout the cardiac cycle are needed for determination of arterial compliance.⁵ As a result, compliance and related arterial mechanical properties that might enhance our understanding of ventriculoarterial physiology have not been widely applied in the clinical setting.³,⁴,¹⁰

In this study, we have validated noninvasive methods for acquisition of the instantaneous pressure and flow data necessary for estimation of arterial compliance. Since this parameter can be determined for any model using the same pressure and flow data, the scope for application of these noninvasive imaging techniques in physiological studies of the arterial system is virtually unlimited. Whereas the accuracy of noninvasively generated compliance estimates was confirmed, the two
methods yielded different values for the transverse resistance element, \( r \). The estimates for this parameter are largely driven by the high-frequency components of the input (flow) signal, reflected in the time domain by the most rapidly changing portions of the flow velocity envelope. Insofar as values for maximal flow acceleration and time to peak flow rate were dissimilar for the two methods, the observed incongruity between values for \( r \) was therefore predictable. The reason for these differences is less obvious. A possible explanation is that the electromagnetic and Doppler flow velocity measurement systems have different maximal frequency responses, the limits of which are exceeded during the initial phases of ejection. In view of the discordance between \( r \) estimates obtained from invasive and noninvasive data, this parameter was not evaluated among the reference population of 70 subjects.

In that they explain the genesis of an aortic pressure waveform that is sustained during diastole, both arterial models presented in this report are clearly more physiological than the single-element model that is currently used in the clinical arena. However, until the additional hemodynamic information provided by these models is shown to be clinically useful, arterial viscoelasticity will not be incorporated in clinical paradigms for evaluation and management of cardiovascular disease. To this end, normal reference values for arterial compliance were determined in a healthy, normotensive, sample population. Among individual subjects, the range of values for arterial compliance was extremely wide. Several studies have shown that demographic factors (among which age appears to be the most important) significantly influence arterial wall stiffness.32-35 Accordingly, to obtain more meaningful population confidence limits for arterial compliance, we examined the influence of age, sex, and race on this parameter. A highly significant inverse linear correlation was found between arterial compliance and age. The profound changes in indexes of arterial wall stiffness with increasing age reflect the sensitivity of these parameters to subtle changes in the pressure-flow relation that are not detected as well by traditional hemodynamic parameters such as pressure, flow, and vascular resistance. Avolio and coworkers described a similar relation between pulse wave velocity and age in normal subjects, which they attributed to an age-related increase in arterial wall stiffness.32,36,37 Pulse wave velocity is a more indirect and multifactorial parameter of arterial viscoelasticity than arterial compliance, and some authors have suggested that the change in pulse wave velocity with age is largely pressure driven.38 The age-compliance relation should be integrated into any framework for clinical evaluation of arterial viscoelasticity.

Comprehensive statistical analysis of the individual hemodynamic determinants of compliance values indicated that compliance estimates are a composite func-

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<th>TABLE 3. Correlations Between Hemodynamic Variables</th>
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<td>Avg HR</td>
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tion of multiple variables. Although intrinsically dependent on more conventional parameters such as heart rate, flow, and various components of blood pressure, variations in the compliance estimate cannot be predicted without simultaneous consideration of multiple hemodynamic determinants. C_m values correlated closely with but were consistently higher than the corresponding values for C_m. The significant difference between compliance values for the two models highlights the fact that the derived impedance parameter values do not represent absolute physical properties but are model-dependent numerical tools that may be used to describe systemic pressure-flow relations more accurately. Applied appropriately, however, these descriptors could provide quantitative information on ventriculovascular energy transfer heretofore relatively inaccessible to the clinician. They are influenced not only by the physical properties that they represent but also by the constraints of the specific model for which they have been estimated. Accordingly, compliance values for more complex models that account for additional impedance properties would undoubtedly differ from those determined for the three-element model. In this study, the three-element model performed well, with a small average error (3.87±2.01 mm Hg). On the other hand, the simpler two-element model, although by definition less accurate, nonetheless identified the relation between age and compliance and could be applied without the customized software that was used to generate values for the aortic viscoelastic properties incorporated in the three-element model. Only by applying and clinically testing a variety of models will the optimal compromise between model performance and clinical utility be identified.

Methodological Limitations

Our failure to acquire useful data in a significant subset of subjects (16 of 86) represents the current rate-limiting factor for these methods. The relatively high data attrition rate was a compound function of the requirement for simultaneous satisfactory transaortic spectral Doppler envelopes plus high-quality noninvasive pressure data. Development of more sensitive external pressure sensors that incorporate low-frequency filters to stabilize the baseline of the subclavian pulse tracing might improve the success rate for data acquisition.

The tracing by hand of analog pressure and flow signals is time consuming and constitutes a source for random errors. Both these limitations might be obviated by introduction of technology for automated detection of the outer Doppler envelope and analog-to-digital conversion of pressure and flow velocity data.

Compliance estimates for both the two- and three-element models are based on separate sets of assumptions. In the case of the two-element model, the major assumption implicit in the method used to estimate compliance is that the diastolic pressure decays asymptotically to zero. The iterative method used to solve the three-element model equation yields parameter values for model rather than measured pressures. The validity of these values is therefore entirely dependent on the accuracy of the model. Since the mean error of the three-element model used in this study was small (3.8±2.0 mm Hg), it can be assumed that the parameter values for model and measured pressure waveforms would be very similar for this model.

Wave reflections, which result from oscillation of the blood column between the proximal and distal portions of the viscoelastic arterial system, are not accounted for by the nondistributed (single-chamber), lumped parameter models used in this study. Despite this limitation, the models presented are conceptually more physiological than that currently applied in clinical medicine. We believe that the clinical potential of these models should be thoroughly investigated before the introduction of more complex distributed parameter models that take into account the contribution of wave reflections to arterial pressure-flow relations.

Clinical Implications

The demonstration that more physiological models of the circulation are easily accessible by noninvasive methods should stimulate the application of such models in the clinical setting. Incorporation of arterial mechanical properties in conceptual models of the circulation will enable development of more accurate paradigms to explain energy transfer from heart to periphery in health and disease. Thorough evaluation of these and other vascular models under a variety of physiological and pathophysiological conditions will clarify their collective role in clinical cardiovascular physiology.

Appendix

Model Equations

For the two-element model, flow through the compliance branch of the circuit (f_t) is

\[ f_t = f_t - \left( \frac{1}{R} \right) P_t \]

where \( f_t \) and \( P_t \) are instantaneously measured aortic inflow and pressure at time \( t \), and \( R \) is total vascular resistance. Since

\[ f_c = -(C)P_t \frac{dP_t}{dt} \]

where \( C \) is arterial compliance

\[ \frac{dP_t}{dt} = \left( \frac{-1}{RC} \right) P_t + \left( \frac{1}{C} \right) f_t \] during systole,

\[ \frac{dP_t}{dt} = \left( \frac{-1}{RC} \right) P_t \] during diastole (\( f_t = 0 \))

These are the differential equations of motion for the two-element model. Similarly, for the three-element model, the differential equation of motion is

\[ \frac{dP_t}{dt} = \left( \frac{-1}{C(R+r)} \right) P_t + \left( \frac{1}{C} \right) \left( \frac{R}{R+r} \right) f_t + \left( \frac{R_r}{R+r} \right) \frac{df_t}{dt} \] during systole,

\[ \frac{dP_t}{dt} = \left( \frac{-1}{C(R+r)} \right) P_t \] during diastole (\( f_t = 0 \))

where \( r \) is the transverse resistance of the arterial wall.

It is evident from these model equations that determination of values for arterial viscoelastic properties requires simultaneous continuous measurements of aortic pressure and flow.

Acknowledgments

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