Mohiuddin MW, Rihani RJ, Laine GA, Quick CM. Increasing pulse wave velocity in a realistic cardiovascular model does not increase pulse pressure with age. Am J Physiol Heart Circ Physiol 303: H116–H125, 2012. First published May 4, 2012; doi:10.1152/ajpheart.00801.2011.—The mechanism of the well-documented increase in aortic pulse pressure (PP) with age is disputed. Investigators assuming a classical windkessel model believe that increases in PP arise from decreases in total arterial compliance \((C_{\text{tot}})\) and increases in total peripheral resistance \((R_{\text{tot}})\) with age. Investigators assuming a more sophisticated pulse transmission model believe PP rises because increases in pulse wave velocity \((c_{\text{ph}})\) make the reflected pressure wave arrive earlier, augmenting systolic pressure. It has recently been shown, however, that increases in \(c_{\text{ph}}\) do not have a commensurate effect on the timing of the reflected wave. We therefore used a validated, large-scale, human arterial system model that includes realistic pulse wave transmission to determine whether increases in \(c_{\text{ph}}\) cause increased PP with age. First, we made the realistic arterial system model age dependent by altering cardiac output \((\text{CO})\), \(R_{\text{tot}}, C_{\text{tot}},\) and \(c_{\text{ph}}\) to mimic the reported changes in these parameters from age 30 to 70. Then, \(c_{\text{ph}}\) was theoretically maintained constant, while \(C_{\text{tot}}, R_{\text{tot}},\) and \(\text{CO}\) were altered. The predicted increase in PP with age was similar to the observed increase in PP. In a complementary approach, \(C_{\text{tot}}, R_{\text{tot}},\) and \(\text{CO}\) were theoretically maintained constant, and \(c_{\text{ph}}\) was increased. The predicted increase in PP in PP was negligible. We found that increases in \(c_{\text{ph}}\) have a limited effect on the timing of the reflected wave but cause the system to degenerate into a windkessel. Changes in PP can therefore be attributed to a decrease in \(C_{\text{tot}}\).

DECREASES IN TOTAL ARTERIAL compliance are implicated in the observed increase in pulse pressure with age. Otto Frank (51) originally used the principle of conservation of mass and momentum to quantify the windkessel model of the arterial system (16). According to this description, the large conductance arteries distend to accommodate blood ejected from the heart during systole and recoil to propel blood through the small resistance vessels in diastole (34, 51). Total arterial compliance \((C_{\text{tot}})\), the sum of all arterial compliances in the system, determines the ability of the arterial system to store blood, whereas the total peripheral resistance \((R_{\text{tot}})\), the average input pressure divided by the average flow, determines the ability of the arterial system to resist blood flow. According to this description, \(C_{\text{tot}}\) is high in young subjects, allowing the arterial system to accommodate an entire stroke volume without generating much pulse pressure (i.e., difference between systolic and diastolic pressures). However, with an increase in arterial stiffness with age, \(C_{\text{tot}}\) decreases and ejection creates a larger pulse pressure (10, 28, 47). This intuitive story seems to explain the observed correlation between decreases in \(C_{\text{tot}}\) and increases in pulse pressure with age (7, 8) and has been an integral part of the standard hemodynamic literature (8, 28, 44, 47).

Increases in pulse wave velocity are implicated in the observed increase in pulse pressure with age. The implicit assumption of infinite pulse wave velocity has led some to claim that the classical windkessel is fatally flawed (2). With the advent of modern transmission theory derived from the Navier-Stokes equations, however, a much more complete description of the arterial system arose (69, 70). Based on both conservation of mass and conservation of momentum, the arterial system began to be described primarily as a structure that transmits pressure pulses to and from the periphery. According to this more complete characterization, pulses travel from the heart at a finite velocity and are reflected back to the heart from various locations (21, 65). Although pulse wave velocity can be measured directly, analysis of an aortic pressure pulse into a forward and reflected traveling pressure wave must be indirectly calculated from measured pulsatile pressure and flow, a requirement that has made it difficult to apply to human data (31, 52, 63). To deal with the difficulty of measuring pulsatile flow, investigators attempted to characterize pulse wave reflection from pressure pulse waveform analysis (31, 41, 42). The observation that older patients exhibit a distinct shoulder in the systolic phase of the pressure pulse led some investigators to use it as a marker for the arrival of the reflected wave (31, 42). The subsequent rise in pressure after this shoulder is ascribed to augmentation due to the reflected pressure wave (31, 33). The observations that with age this shoulder appears to arrive earlier in the cardiac cycle (31, 40, 42) and that the apparent augmentation appears to increase pulse pressure (23, 33, 37) led to a new narrative. In young subjects, the reflected pressure wave arrives in diastole. With an increase in arterial stiffness with age, pulse wave velocity increases (17, 31, 39, 67), causing the reflected pressure pulse to arrive sooner in the cardiac cycle, augmenting peak systolic pressure (31, 33). This intuitive story seems to explain the observed correlation between observed increases in \(c_{\text{ph}}\) and increases in pulse pressure with age (23, 33, 37) and has also become an integral part of the standard hemodynamic literature (17, 31, 41, 67).

Recently, the purported effect of increased pulse wave velocity has been challenged. Although pulse transmission theory has been embraced, its use to interpret data has often been oversimplified in practice. A common underlying assumption among investigators analyzing data is that the time it takes for a reflected wave to return from the periphery is inversely proportional to the pulse wave velocity (1, 31, 37, 38, 41, 42, 67). That is, the time delay between a forward traveling wave and a reflected wave depends on the distance to the reflection...
site divided by pulse wave velocity. This assumption has been shown to be false from both empirical and theoretical perspectives. First, Segers et al. (52, 53) separated the forward and reflected pressure pulses to compare the changes in the timing of the reflected waves and changes in pulse wave velocity, and found only nominal agreement. In an equally large study, Baksı et al. (6) found that the shift in timing of the arrival of the reflected pulse wave with age is minor (0.7 ms/yr) and thus changes in pulse wave velocity may not significantly contribute to the increase in pulse pressure. Furthermore, their meta-analysis (6) suggested that a decrease in aortic compliance might be more important than \( c_{ph} \) in the development of systolic hypertension. Sharman et al. (55) also concluded that timing of the reflected pressure pulse may not be the primary cause of pressure augmentation with age. Although some of these findings were criticized because they did not reproduce an association of an early systolic shoulder with age (1, 38), they were consistent with theoretical modeling approaches. For instance, Berger et al. (9) used a simple model to show that the forward and reflected waves are composed of many reflected and re-reflected waves, so that increases in pulse wave velocity change the composite shape of the forward and reflected waves, rather than simply making the composite reflected wave arrive sooner in the cardiac cycle. This result was recapitulated by Westerhof et al. (64), who used a realistic, large-scale arterial system model to illustrate that as vessels get stiffer, pulse wave velocity increases, but the timing of the composite reflected wave changes little. Although their model reproduced the increase in pulse pressure with age, they did not specifically identify whether changes in total arterial compliance or pulse wave velocity was primarily responsible.

Experimental methods cannot be used to determine effects of increased pulse wave velocity. Both windkessel and transmission models of thought believe that it is primarily increased arterial stiffness that leads to increased pulse pressure with age. However, investigators assuming a transmission description believe that increasing arterial stiffness increases \( c_{ph} \), which in turn increases pulse pressure (17, 31, 67), and investigators assuming a windkessel description believe that increasing arterial stiffness decreases \( C_{tot} \), which in turn increases pulse pressure (7, 8, 28, 47). Both of these explanations for the development of increased pulse pressure with age have numerous adherents, and yet there are two fundamental limitations preventing investigators from determining which explanation is correct. From a theoretical perspective, windkessel models do not have \( c_{ph} \) as an explicit parameter, and transmission models have not been formulated with \( C_{tot} \) as an explicit parameter. From an empirical perspective, arterial stiffness affects both \( c_{ph} \) and \( C_{tot} \) (31, 41, 67), and there is no known means to experimentally alter \( C_{tot} \) and \( c_{ph} \) independently.

Mathematical models can be used to determine effect of pulse wave velocity. To overcome such experimental obstacles, a previously validated, realistic, large-scale, spatially distributed model of the human systemic arterial system was utilized (65). Briefly, this model consists of 121 major arterial segments, each of which is characterized by its lengths, radii, and compliances. When provided with an assumed input flow, pressure can be predicted as a function of time. This model was recently used by Mohiuddin et al. (28) to illustrate that the pulse wave velocity is normally so fast that the human arterial system acts very much like a classical (two-element) windkessel. Perhaps more importantly, this model provides the means to independently alter \( c_{ph} \) and \( C_{tot} \). We therefore used the large-scale human systemic arterial system model to test the hypothesis that increases in \( c_{ph} \) do not increase pulse pressure with age, but rather, increased pulse pressure can result directly from decreases in \( C_{tot} \).

**THEORY**

Transmission description of the systemic arterial system. In the mid-twentieth century, a mathematical description was developed to characterize the human arterial system as a spatially distributed branching tree consisting of arterial vessel segments (65). In this transmission description, the relationship between blood pressure and flow through a compliant arterial segment is expressed by an equation of motion and an equation of continuity. The pressure gradient \( \frac{\partial \mathbf{P}}{\partial z} \) depends on inerterance \( (L') \) and resistance \( (R') \) per unit length \( (l) \) of vessel segments,

\[
-\frac{\partial \mathbf{P}}{\partial z} = R' \frac{Q}{l} + \frac{L'}{l} \frac{\partial Q}{\partial t}, \quad R' = \frac{8\mu}{\pi r^4}, \quad L' = \frac{\rho}{\pi r^2}
\]

which in turn depend on vessel radius \( (r) \), blood viscosity \( (\mu) \), and blood density \( (\rho) \). The flow gradient \( \frac{\partial Q}{\partial z} \) depends on the compliance per unit length \( (C') \) of vessel segments (26, 34),

\[
\frac{\partial Q}{\partial z} = C \frac{\partial P}{\partial t}
\]

\( C' \) is also known as the “area compliance” (3, 34, 65) and has been related to the vessel’s modulus of elasticity \( (E) \), radius \( (r) \), and wall thickness \( (h) \) by the equation,

\[
C' = \frac{d}{(\pi r^2)} = \frac{3\pi r^2(r/h + 1)^2}{E(2r/h + 1)}
\]

Combining Eqs. 1 and 2 results in the Wave Equation (26, 34),

\[
L'C' \frac{\partial^2 P}{\partial t^2} + R'C \frac{\partial P}{\partial t} = \frac{\partial^2 P}{\partial z^2}
\]

For large vessels where \( R' \) is negligible, Eq. 4 yields an approximation for pulse wave velocity \( (c_{ph}) \), which is well-characterized by the Bramwell-Hill approximation (26, 34),

\[
C_{ph} = \sqrt{\frac{\pi r^2}{\rho E}}
\]

The value of \( C' \) can be calculated from mechanical properties of a vessel using Eq. 3. Equation 5 indicates that pulse wave velocity can increase if vessel compliances decrease or vessel radii increase. Total arterial compliance of the systemic arterial system can be calculated by adding all the segmental compliances,

\[
c_{tot} = \sum_{i=1}^{n} C_i/l_i
\]

where \( n \) is the number of vessel segments in the systemic arterial system.

Wave separation analysis. With wave separation analysis, the measured pressure \( (P) \) is typically analyzed into forward \( (P_f) \) and reflected \( (P_r) \) pressures using simple algorithms,
radius, wall thickness, and elastic modulus using the original Westerhof model were calculated from reported values of peripheral resistances. The values of arterial segment compliances in the model, the proximal end starts from the ascending aorta and ends with the distal runoff (34). The value of characteristic impedance, the input impedance in the absence of reflection (34). The mean values of pressure and flow (P and Q) must be subtracted from measured pressure and flow because mean values do not affect forward and reflected pulse waves (46, 52, 53).

METHODS

Human arterial system model construction. To capture the phenomena of pulse wave propagation and reflection, we implemented a realistic, large-scale model consisting of 121 major vessel segments representing the large conductance vessels of the systemic arterial system (Fig. 1). The parameters describing the vessel segments (i.e., lengths, radii, and compliances) were reported by Westerhof et al. (65). Parameter symbols are listed in Table 1. The equations governing fluid flow in arterial segments were based on Eqs. 1 and 2. In this model, the proximal end starts from the ascending aorta and ends with peripheral resistances. The values of arterial segment compliances in the original Westerhof model were calculated from reported values of radius, wall thickness, and elastic modulus using Eq. 3. Based on later measurements of systemic arterial system compliances, Stergiopulos et al. (56) suggested that the original compliances were much too low to represent normal human values. To correct this, it has become common practice (including our laboratory) to increase the calculated segmental compliances of the Westerhof model by 50% (28, 44, 48, 56, 57). To be consistent with these corrected implementations of the original Westerhof model, we also represented the normal case with a 50% increase in all of the original arterial segment compliances. A typical root aortic flow, originally reported by Stergiopulos et al. (56), was utilized as the input to this model. The period, peak flow, and the cardiac output (CO; the average input flow) were 1 s, 450 ml/s, and 5 l/min, respectively. This model was previously implemented as in Mohiuddin et al. (28) and yielded a realistic pulse pressure (Fig. 1) consistent with previously reported model implementations (56, 58).

Quantifying relative changes in hemodynamic parameters with age. Changes in critical hemodynamic parameters with the progression of age, ranging from 8 to 73 yr, have been previously reported by several investigators (15, 22, 31, 32). In particular, $c_{ph}$ increases (15), $C_{tot}$ decreases (22), $R_{tot}$ increases (32), and CO decreases (32). We digitized these reported data and performed linear regression to determine the rate each parameter changes per year, as well as the variation in rate (within 95% confidence interval). Results are illustrated in Fig. 2. Because these data arose from population studies, rather than longitudinal studies of individuals, there was a great deal of variation. Reported data for CO with age in particular showed a great deal of variation. To characterize CO consistent with values expected for resting conditions (3.8 to 8.6 l/min) (12, 14, 24), CO $>10$ l/min was not included when performing the linear regression of resting CO with age.

Modifying the realistic human systemic arterial system to predict hemodynamic changes with age. To simulate changes in the systemic arterial system with age, we first had to decide what age was best represented by the standard parameters of the realistic human arterial system model described above. We found that the accepted values of $C_{tot}$ and $c_{ph}$ of the model best matched that of a 30 yr old. To ensure that mean pressure was $\sim100$ mmHg, we increased $R_{tot}$ by 10%. Then, we assumed parameters of the model changed the same percentage per year as depicted in Fig. 2. This approach implicitly

![Diagram](https://example.com/diagram.png)

Table 1. Parameters used in the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total arterial compliance</td>
<td>$C_{tot}$</td>
</tr>
<tr>
<td>Total arterial resistance</td>
<td>$R_{tot}$</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>$c_{ph}$</td>
</tr>
<tr>
<td>Compliance per unit length</td>
<td>$C'$</td>
</tr>
<tr>
<td>Inertance per unit length</td>
<td>$L'$</td>
</tr>
<tr>
<td>Resistance per unit length</td>
<td>$R'$</td>
</tr>
<tr>
<td>Radius</td>
<td>$R$</td>
</tr>
<tr>
<td>Viscosity</td>
<td>$\mu$</td>
</tr>
</tbody>
</table>

Fig. 2. Reported changes in key hemodynamic parameters used to simulate aging in the realistic arterial system model in Fig. 1. With age, total arterial compliance ($C_{tot}$) decreases (22) (A), total peripheral resistance ($R_{tot}$) increases (32) (B), cardiac output (CO) decreases (32) (C), and pulse wave velocity ($c_{ph}$) increases (15) (D). Data were digitized from Liang et al. (22), Nichols et al. (32), and Gozna et al. (15), respectively, and replotted (●). Solid lines represent linear regression lines of the reported data.

AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00801.2011 • www.ajpheart.org
assumes that the realistic human arterial model, representing a single human, changes with age in a manner similar to the population as a whole. Specifically, we assumed that CO decreased from 30 to 70 yr old, by scaling the assumed input cardiac flow illustrated in Fig. 1 by the same percent decrease per year as CO depicted in Fig. 2C. We then assumed that all terminal resistances of the arterial system model increased from 30 to 70 yr old by scaling the model terminal resistances the same percent increase per year as \( R_{\text{tot}} \) depicted in Fig. 2B. For simplicity, we did not scale the segmental resistances in the arterial system model, because they were very low and did not significantly contribute to \( R_{\text{tot}} \). We then assumed all arterial segmental compliances decreased from 30 to 70 yr old by assuming that compliance of each vessel segment decreased the same percentage per year as \( C_{\text{tot}} \) depicted in Fig. 2A. Finally, we assumed \( c_{\text{ph}} \) increased from 30 to 70 yr old by assuming that each vessel segment pulse wave velocity increased the same percentage per year as aortic \( c_{\text{ph}} \) depicted in Fig. 2D. Due to a lack of information about how \( c_{\text{ph}} \) in most arteries changes with progression of age, we chose to use published changes in aortic \( c_{\text{ph}} \) (Fig. 2D) to represent changes in \( c_{\text{ph}} \) in all arteries. The reported increases in \( c_{\text{ph}} \) with age, however, are similar to increases reported for a number of peripheral arteries such as brachial, radial, and femoral arteries (4). The Westerhof arterial system model, which forms the basis of our analysis, typically is not formulated in terms of segmental \( c_{\text{ph}} \) as an explicit parameter. We therefore simulated changes with age by altering segmental arterial radii using the approximation for \( c_{\text{ph}} \) in Eq. 5. This caused radii in each arterial segment to increase with age and is consistent with changes in radii with age reported by Nichols et al. (32). The resulting pressure pulse was predicted as a function of age and compared with reported changes in pulse pressure with age.

Determining effects of increasing pulse wave velocity on pulse pressure. To determine whether changes in \( c_{\text{ph}} \) with age cause the observed increase in pulse pressure, two modeling approaches were taken. In each approach, changes in the hemodynamic parameters were consistent with the reported relative changes as illustrated in the Fig. 2. In the first approach, a decrease in \( C_{\text{tot}} \), increase in \( R_{\text{tot}} \), and decrease in CO were assumed with the progression of age (Fig. 2, A–C). However, the values of \( c_{\text{ph}} \) were maintained at baseline values (i.e., for a 30 yr old). The value of \( c_{\text{ph}} \) was maintained constant by balancing decreases in arterial compliance with increases in radii according to Eq. 5. The resulting pulse pressure was predicted as a function of age. In the second approach, only \( c_{\text{ph}} \) was assumed to increase with age (Fig. 2D). This was accomplished by adjusting radii according to Eq. 5. The values of \( C_{\text{tot}} \), \( R_{\text{tot}} \), and CO were maintained at baseline values (i.e., for a 30 yr old). The resulting pulse pressure was predicted as a function of age.

Calculating the time delay between forward and reflected pressure pulses with progression of age. Forward (\( P_f \)) and reflected (\( P_r \)) pressure pulses of the large-scale model were calculated for 30-, 50-, and 70-yr-old subjects utilizing Eq. 7 and plotted. The time delay (\( \Delta T_{f-r} \)) between the forward and reflected waves was calculated using their zero cross-overs as reference points as in Segers et al. (53). The time delay was then calculated for ages 30–70, for the case that either the windkessel parameters (\( C_{\text{tot}} \), \( R_{\text{tot}} \), and CO) or \( c_{\text{ph}} \) was kept constant.

Comparing pressure pulses in the large-scale arterial system model with those in a corresponding classical two-element windkessel. It has been previously shown that the systemic arterial system degenerates into a classical two-element windkessel when vessel compliances decrease (28). Following the methodology established by Mohiuddin et al. (28), pressure pulses predicted from the large-scale human arterial system model were compared with those predicted from an equivalent classical two-element windkessel. Three representative cases representing 30-, 50-, and 70-yr-old subjects were chosen for comparison. Briefly, the total arterial compliance and total peripheral resistance of the classical two-element windkessel were given values equal to the total arterial compliance (Eq. 6) and total peripheral resistance of the large-scale model. The same input aortic flow was input into both the large-scale human arterial system model and the windkessel model. Windkesslessness of the arterial system for each age was determined by quantifying the correlation coefficient (28) of the resulting pressure pulses.

Identifying hemodynamic parameters that have the greatest impact on aortic pulse pressure. Age-related changes in the hemodynamic parameters presented in this work (\( C_{\text{tot}} \), \( R_{\text{tot}} \), CO, and \( c_{\text{ph}} \)) may alter pulse pressure. To quantify their individual contributions, a simple parameter sensitivity analysis was performed. Briefly, pulse pressure was predicted for four special cases. In each case, the pulse pressure was predicted for a 70 yr old, when one of the four parameters (mentioned above) was set to that of a 30 yr old. In a complementary approach, pressure was predicted for a subject when only one of the four parameters (mentioned above) was set to that of a 70 yr old. To estimate how variation in parameters measured for a population (illustrated in Fig. 2) affects the predicted pulse pressure of the model, the pulse pressure resulting from the ranges of parameters were also determined.

RESULTS

Representative predicted pressures for ages 30, 50, and 70. Figure 3 illustrates the pressure predicted by the realistic, large-scale arterial system model. Pressure at the age of 30 yr is considered the baseline (Fig. 3A). Predicted pulse pressures when only windkessel parameters (\( C_{\text{tot}} \), \( R_{\text{tot}} \), and CO) were altered (dashed lines, Fig. 3, B and C) were very similar to

![Fig. 3](https://via.placeholder.com/150)

Fig. 3. Pulse pressures of 3 representative cases (30-, 50-, and 70-yr-old subjects) predicted from a large-scale human arterial system model. Pulsatile pressure of a 30-yr-old subject was considered the baseline (A). Pulsatile pressure of a 50-yr-old subject when either \( C_{\text{tot}} \), \( R_{\text{tot}} \), and CO were altered (dashed line) or only \( c_{\text{ph}} \) was altered (dotted line; B). Pulsatile pressures of a 70-yr-old subject when either \( C_{\text{tot}} \), \( R_{\text{tot}} \), or CO were altered (dashed line) or \( c_{\text{ph}} \) was altered (dotted line; C). Solid line represents normal aging (i.e., all parameters change consistent with Fig. 2). Pulse pressure was best reproduced when windkessel parameters (\( C_{\text{tot}} \), \( R_{\text{tot}} \), and CO were altered). Altering \( c_{\text{ph}} \) had minimal impact on pulse pressure.
pulse pressures predicted for normal aging (solid lines). Predicted pulse pressures for 50- and 70-yr-old subjects when only $c_{ph}$ was altered (dotted lines) were not significantly higher.

**Increase in aortic pulse pressure with age.** Figure 4 illustrates that with a physiological decrease in total arterial compliance, increase in total peripheral resistance, decrease in CO, and increase in pulse wave velocity, the realistic, large-scale, distributed human arterial system model predicted that pulse pressure increased with age (solid line). The slope found from linear regression is 0.54 mmHg/yr and is very similar to trends reported in the literature that varies from 0.48 to 0.68 mmHg/yr (13, 20, 25, 68). Also depicted in Fig. 4 is the pulse pressure data previously reported by Franklin et al. (13), along with the 95% confidence interval. The predicted pulse pressure falls within this confidence interval.

**Effect on aortic pulse pressure when pulse wave velocity is increased.** When pulse wave velocity was increased with age consistent with reported values (15), but CO, total peripheral resistance, and total arterial compliance were maintained at their baseline values (i.e., for a 30 yr old), predicted pulse pressure increased by 32% from 30 to 70 yr old (Fig. 5A). This increase in pulse pressure is similar to the increase (37%) predicted for normal aging. The increase in $c_{ph}$ is not necessary to explain increase in pulse pressure with age.

**Effect on aortic pulse pressure when only pulse wave velocity is increased.** When pulse wave velocity was increased with age, the predicted pulse pressure increased by >32% from 30 to 70 yr old (Fig. 5A). This increase in pulse pressure is similar to the increase (37%) predicted for normal aging. The increase in $c_{ph}$ is not necessary to explain increase in pulse pressure with age.

**Changes in forms of the composite forward and reflected pressure pulses with age.** Figure 6 illustrates the changes in the forward and reflected pulse waves predicted for 30-, 50-, and 70-yr-old subjects. Changes in $C_{tot}$, $R_{tot}$, CO, and $c_{ph}$ affect both the magnitude and shapes of forward and reflected waves.

**Effect on time-delay between the composite forward and reflected pressure pulses.** Although the value of $c_{ph}$ increased by >50% from ages 30 to 70, the time-delay between the forward and reflected wave ($\Delta T_{fr}$) decreased by <27%, mostly between the ages of 40 and 60 (Fig. 7A). When the windkessel parameters ($C_{tot}$, $R_{tot}$, and CO) were altered and pulse wave velocity ($c_{ph}$) was maintained at the baseline, $\Delta T_{fr}$ decreased only by 1% (Fig. 7B). On the other hand, when the pulse wave velocity ($c_{ph}$) was altered while the windkessel parameters ($C_{tot}$, $R_{tot}$, and CO) were maintained at baseline, $\Delta T_{fr}$ decreased in a similar fashion to normal aging (i.e., a 24% decrease; Fig. 7C).

**Degeneration of systemic arterial system into the classical two-element windkessel.** Three cases from large-scale human arterial system model (corresponding to 30-, 50-, and 70-yr-old subjects) were compared with their equivalent classical two-element windkessel. The arterial system behaved progressively more like a classical two-element windkessel with age. The index of windkesselness was found to be 0.97, 0.98, and 0.99 for the age of 30, 50, and 70 (Fig. 8, A, B, and C respectively). Because the complex, realistic human arterial system model acts so much like a windkessel whose behavior is determined solely by CO, $C_{tot}$, and $R_{tot}$, the particular value of $c_{ph}$ has little effect on pulse pressure.

**Identifying the parameter of greatest impact on aortic pulse pressure.** Table 2 illustrates the contribution of each hemodynamic parameter of interest to changes in pulse pressure from 30 to 70 yr of age. $C_{tot}$ had the most influence on the increase in pulse pressure with the progression of age, whereas $R_{tot}$ had the least. Other than $C_{tot}$ CO had substantial influence on pulse pressure. Although $c_{ph}$ had more influence on pulse pressure than $R_{tot}$, it was minor compared with that of either $C_{tot}$ or CO. This analysis focused on the effect of “knocking out” change in a single parameter by assuming it did not change with age. In a complementary approach, Table 3 illustrates how altering only one parameter at a time affects pulse pressure. Decreases in $C_{tot}$ typical for a 70-yr-old subject again had the greatest...
effect on pulse pressure. Similarly, although $c_{ph}$ had more influence on pulse pressure than $R_{tot}$, it was slight compared with that of either $C_{tot}$ or CO. The ranges of pressure resulting from the variability in possible values of $C_{tot}$ in 70-yr-old subjects is quite high, which is expected from the scatter in the $C_{tot}$ data illustrated in Fig. 2.

**DISCUSSION**

The present work provides a novel method for quantifying the effect of increasing arterial pulse wave velocity with age on aortic pulse pressure and found that it is limited. Forming a basis of a novel methodology, a realistic, distributed arterial system model was used to theoretically alter hemodynamic parameters ($C_{tot}$, $R_{tot}$, CO, and $c_{ph}$) and quantify their individual contribution to an increase in pulse pressure. Theoretically changing classical windkessel parameters with age (i.e., $C_{tot}$, $R_{tot}$, and CO) without a concomitant increase in $c_{ph}$ predicted increases in pulse pressure consistent with observed values (Fig. 5A). On the other hand, theoretically increasing $c_{ph}$ with age without a concomitant change in the other parameters (i.e., constant $C_{tot}$, $R_{tot}$, and CO) predicted negligible increases in pulse pressure (Fig. 5B). Increases in $c_{ph}$ were neither necessary nor sufficient to explain the observed increase in pulse pressure with age. Furthermore, increases in $c_{ph}$ did not have a commensurate effect on the timing of the reflected wave (Fig. 7), consistent with recent reports (6, 27, 53).

Problems with experimental approaches to determine the effect of increased pulse wave velocity. To understand these results, it is first informative to consider the difference between the present technique and a purely empirical approach. Conventionally, pulse wave velocity is observed to increase in certain conditions (e.g., aging). However, there are simultaneous changes in other parameters, the most conspicuous of which are arterial compliance and peripheral resistance. Of course, experimental correlation is not strong evidence of causality. For this reason, Berger et al. (10) developed a simple model consisting of a compliant tube and a terminal resistance to evaluate the role of changing pulse wave velocity. They similarly reported that pulse wave velocity had little impact on pulse pressure. However, the modeled changes in $c_{ph}$ lacked physiological relevance to the aging process, and the implications of an arterial system degenerating into a windkessel were yet to be fully appreciated (28). Our physiologically relevant expansion of the pioneering work of Berger et al. (10) illustrates that the common inference that $c_{ph}$ increases pulse pressure apparently arises from a correlation and that this correlation may be spurious.

**Limitations to altering $c_{ph}$ theoretically by adjusting arterial radii.** To model the normal aging process in the systemic arterial system, we assumed the normal reported changes in $c_{ph}$ and $C_{tot}$ with age and predicted increases in pulse pressure (Fig. 4) that were surprisingly similar to reported values (13, 20, 25). These are not the typical parameters used to characterize the large-scale, realistic, human arterial system model originally described by Westerhof et al. (65). Although arterial...
parameters are conventionally expressed in terms of segment radii and compliances per unit length (65) or alternatively, radii, elastances, and wall thickness (3), we simply parameterized the system using Eq. 5, noting that the sum of all segmental compliances was equal to $C_{tot}$ (Eq. 6). Independently altering $C_{tot}$ and $C_{ph}$, however, cannot be accomplished experimentally, and it was necessary to choose a model parameter that can affect $C_{ph}$ without changing $C_{tot}$. Two possibilities presented themselves. First, lengths of vessel segments could have been altered to adjust $C_{tot}$ without altering $C_{ph}$ (Eq. 6). Second, radii of the vessel segments could have been altered to adjust $C_{ph}$ without altering $C_{tot}$ (Eq. 5). Either choice would have accomplished the goal of separating changes in $C_{ph}$ from changes in $C_{tot}$. However, each possibility comes at a cost. If we had changed segmental lengths, for instance, we could have been altered to adjust $C_{tot}$ but also have altered the

length to reflection sites, which has been claimed to be an important modulator of pulse pressure (42, 53). Instead, altering radii to cause changes in $C_{ph}$ had the fewer confounding effects on pulse pressure. First, altering radii of the vessel segments can affect the resistance of the large arteries of the human model. However, because these arterial segments are relatively large, the normal resistances are exceedingly small. Altering radii to increase $C_{ph}$ only changed total arterial resistance by 0.31%. Also, altering radii of all vessel segments an equal amount has minimal effect on local pulse wave reflection at bifurcations (34). The largest effect on the arterial system of altering arterial radii may be on the characteristic impedance of the aortic root, which is known to affect pulse pressure (66). To quantify the unintended consequences of altering aortic characteristic impedance, we simulated the system with an aortic root characteristic impedance that was kept constant as $C_{ph}$ was altered by adjusting radii. The resulting pulse pressure changed by $<0.27\%$. This indicates that altering radius, which had a major effect on $C_{ph}$, had minimal effects on other hemodynamic properties believed to effect pulse pressure and thus is a valid method to independently alter $C_{ph}$ without effecting $C_{tot}$.

Using variation in measured parameters in a population to characterize changes in an individual. The data set that we used to adjust $C_{tot}$, $R_{tot}$, CO, and $C_{ph}$ with age was chosen for convenience, although it had two limitations. First, it did not include data for the oldest subjects (therefore we had to perform a small extrapolation to 70-yr-old subjects). Nonetheless, the changes in parameters per year (6.31 cm·s$^{-1}$·yr$^{-1}$, $-0.03$ l·min$^{-1}$·yr$^{-1}$, 0.0074 mmHg·s·ml$^{-1}$·yr$^{-1}$, and $-0.0074$ ml·mmHg$^{-1}$·yr$^{-1}$, for $C_{ph}$, CO, $R_{tot}$, and $C_{tot}$, respectively) are similar to reported ranges by other investigators (5, 11, 19, 50). Second, the degree of variation of parameters with age was large (Fig. 2), although not unusual for data derived from population studies. The range of parameters for a 70-yr-old subject resulted in somewhat large ranges of predicted pulse pressures (Table 3). If it were possible to measure each parameter from a single subject year after year, it is expected that the variation would be smaller. Such a data set would be most appropriate for our large-scale human arterial system model that predicts pulse pressure of one subject as he ages. However, such longitudinal measurements are not possible, given the difficulty and invasiveness of the measurements. Instead of using our model to predict the variation in pulse pressures of a population (31), we took the vastly more modest approach of assuming that a single subject adapts with age in a way that mimics the average changes in a population per year.

Validity of assumed model properties. Although it is common practice to adjust assumed properties to make mathematical model predictions match observed behavior (a process

<table>
<thead>
<tr>
<th>Parameter Changed</th>
<th>Pulse Pressure, mmHg</th>
<th>Range of Pulse Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal case</td>
<td>42.6</td>
<td>—</td>
</tr>
<tr>
<td>$C_{tot}$</td>
<td>70.5</td>
<td>43.8–178.0</td>
</tr>
<tr>
<td>$R_{tot}$</td>
<td>42.4</td>
<td>42.3–42.6</td>
</tr>
<tr>
<td>CO</td>
<td>34.9</td>
<td>21.5–49.6</td>
</tr>
<tr>
<td>$C_{ph}$</td>
<td>44.7</td>
<td>43.4–45.1</td>
</tr>
</tbody>
</table>

Each parameter was altered to reflect the changes for a 70-yr-old subject. Range of parameter values found from linear regression of data in Fig. 2 used to estimate resulting range of pulse pressures.

Fig. 8. Pulse pressures of 3 representative cases [30- (A), 50- (B), and 70 (C)-yr-old subjects] predicted from a large-scale human arterial system model (dotted line) were compared with those predicted from their equivalent classical two-element windkessel (solid line). With the progression of age, the arterial system acted more like windkessel, i.e., the windkesselness (28) increased with age. However, even a 30-yr-old simulation behaves remarkably like a windkessel with behavior dominated by $C_{tot}, R_{tot}$, and CO.
typically described as “model development”), this practice was pointedly not applied in the present work. The mathematical model used in the present work was mostly developed over a four-decade period and utilized well-established fundamental hemodynamics equations and accepted parameter values (18, 35, 36, 65). Stergiopulos et al. (59) made the last major change to the model by increasing total arterial compliance by 50%, since the model $C_{\text{tot}}$ was found very low compared with $C_{\text{tot}}$ derived from human data reported in the literature (49). Since then, it became a common practice to increase $C_{\text{tot}}$ by 50% in studies using a large-scale arterial system model (28, 44, 45, 56, 57). As noted by Mohiuddin et al. (28), increasing $C_{\text{tot}}$ actually increases the relative impact of $c_{\text{ph}}$ on pulsatile hemodynamics. We did have the option of adjusting assumed properties even further to force the mathematical model to better reproduce observed data but decided to keep model manipulation to a minimum. For instance, we decided to keep the shape of the input blood flow waveform constant for the sake of simplicity and only scale it to represent changes in mean value (i.e., CO) with age. However, the shape of the input flow waveform has been reported to change with the progression of age (30). In fact, when we replaced the input flow from (Fig. 1) with aortic flow waveforms measured from 28-, 52-, and 68-yr-old subjects (30), the change in our predicted pressures were minor. This particular case illustrates how the model assumptions can be made more accurate. However, given the central importance of a modeling approach to test a hypothesis, we chose not to engage in “model development.” Model development, taken to its logical conclusion, would preclude hypothesis testing, because the goal of model development is to iteratively adjust assumptions to reproduce observed behavior. Instead, we tested whether commonly accepted assumptions do indeed reproduce observed behavior (i.e., does increasing $c_{\text{ph}}$ increase pulse pressure with age?). The only adjustments in the standard realistic human arterial system mathematical model was a 10% increase in $R_{\text{tot}}$ for baseline conditions to ensure a mean pressure of $\sim 100$ mmHg and a change in model parameters with age, because we have not been able to find a reported model that has previously attempted this.

Experimental and clinical evidence for model predictions.

The large-scale, realistic arterial system model reproduced four fundamental behaviors previously reported in the literature. First, the model reproduced the increase in pulse pressure with age (Fig. 4). The increase was consistent with the rate and magnitude of increase in pulse pressure with age reported by Franklin et al. (13) and Wilson and Merrett (68). Second, the model reproduced the time-delay between the forward and reflected wave (Δ$T_{\text{c}}$) with progression of age (Fig. 7A) reported by Segers et al. (53). Third, pressure waveforms generated by the model mimicked observed changes in pressure waveforms with age. The pressure predicted for the 30-yr-old subject exhibited a peak in late systole (Fig. 3A), characterized as a “Type C” waveform by Murgo et al. (29). The pressure predicted for the 50-yr-old subject exhibited an inflection point in late systole (Fig. 3B), characterized as a “Type B” waveform (29). The pressure waveform for a 70 yr old subject also had a well-defined inflection point in late systole (Fig. 3C), similar to a “Type A” waveform (29). Fourth, the model reproduced the degeneration of the arterial system into classical two-element windkessel with progression of age, which was similar to previous reports (28, 44, 60, 62). Taken together, reproduction of such diverse observations with a single mathematical model provides a degree of confidence that the predictions of the realistic arterial system model used in the present work reflect reality. Given the number of assumptions that were necessary, however, it may seem prudent to introduce a level of epistemological modesty when drawing conclusions from a large-scale mathematical model that necessarily included a large number of assumptions, especially when it is impossible to test model results experimentally. However, our studious avoidance of “cherry-picking” assumptions is bolstered by a fundamental principle ultimately making most model assumptions irrelevant to the results: the arterial system degenerates into a simple windkessel with age (Fig. 8), and therefore, $c_{\text{ph}}$ is irrelevant to pulse pressure (28, 43, 60, 62).

The arterial system acts like a windkessel. Whereas Fig. 5B illustrates that increasing $c_{\text{ph}}$ does not itself increase pulse pressure, we were able to identify the fundamental cause of an increase in pulse pressure with age. By changing the classical windkessel parameters (i.e., $\Delta C_{\text{tot}}$, $\Delta R_{\text{tot}}$, and $\Delta$ CO) with age while maintaining $c_{\text{ph}}$ at its baseline, the observed increase in pulse pressure was reproduced (Fig. 5A). This result is consistent with results from windkessel models (13, 58), which do not have $c_{\text{ph}}$ as an explicit parameter. The use of some version of the classical windkessel model has been criticized, because it makes the implicit assumption that pressures rise and fall everywhere in the arterial system simultaneously (2). This assumption is equivalent to assuming an infinite wave velocity (51). Pulse wave velocity in adults, however, is finite. Typically reported to be $\sim 5$ m/s in young, healthy subjects (31), aortic pulse wave velocity is fast enough to traverse the distance of the aorta approximately seven times in a single heartbeat (9). Recently, Mohiuddin et al. (28) reported that pulse wave velocity in the human arterial system is so high that the normal human arterial system is already very much like a windkessel. If the pulse wave velocity in an arterial system already is fast enough for it to act like a windkessel, it should not be surprising that increasing pulse wave velocity has little effect on pulse pressure. The concept that an arterial system degenerates into a windkessel is not in itself new. In 1973, Westerhof et al. (66) presented a three-element windkessel, which was said to incorporate both windkessel and transmission characteristics. Quick et al. (45) generalized this characterization with the concept of “Apparent Compliance,” which was later applied to show that a large-scale human arterial system (also used in the present work) degenerates into a classical windkessel at low frequencies (44). Furthermore, direct analysis of data also illustrated how arterial systems degenerate into a windkessel at high mean pressures (45). Similar concepts were presented by Parker (43), Tyberg and colleagues (60, 61), and Wang et al. (62), who analyzed measured pressure into “reservoir” and “transmission” components, concluding that pulse pressure is predominantly due to windkessel properties. Recent large-scale simulation by Westerhof et al. (64) and direct analysis of data by Segers et al. (54) led both groups to conclude the system is acting more like a windkessel with age. However, Fig. 5 is nonetheless the first reported evidence that increasing pulse wave velocity with age has negligible effects on pulse pressure. We identify that the decrease in total arterial compliance is the primary cause of increased pulse pressure with age.
AUTHOR CONTRIBUTIONS

104476-01A1 (to M. W. Mohiuddin and G. A. Laine) and American Heart

GRANTS

Portions of this work were supported by National Heart, Lung, and Blood

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES