Aortic Pulse Pressure Homeostasis Emerges
From Physiologic Adaptation of Systemic Arteries
To Local Mechanical Stresses

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Aortic pulse pressure arises from the interaction of the heart, the systemic arterial system and peripheral microcirculations. The complex interaction between hemodynamics and arterial remodeling precludes the ability to experimentally ascribe changes in aortic pulse pressure to particular adaptive responses. Therefore, the purpose of the present work was to use a human systemic arterial system model to test the hypothesis that pulse pressure homeostasis can emerge from physiologic adaptation of systemic arteries to local mechanical stresses. First we assumed a systemic arterial system that had a realistic topology consisting of 121 arterial segments. Then the relationships of pulsatile blood pressures and flows in arterial segments were characterized by standard pulse transmission equations. Finally, each arterial segment was assumed to remodel to local stresses following three simple rules: 1) increases in endothelial shear stress increases radius, 2) increases in wall circumferential stress increases wall thickness, and 3) increases in wall circumferential stress decreases wall stiffness. Simulation of adaptation by iteratively calculating pulsatile hemodynamics, mechanical stresses and vascular remodeling led to a general behavior in response to mechanical perturbations: initial increases in pulse pressure led to increased arterial compliances, and decreases in pulse pressure led to decreased compliances. Consequently, vascular adaptation returned pulse pressures back towards baseline conditions. This behavior manifested when modeling physiologic adaptive responses to changes in cardiac output, changes in peripheral resistances, and changes in local arterial radii. The present work thus revealed that pulse pressure homeostasis emerges from physiologic adaptation of systemic arteries to local mechanical stresses.

**Keywords:** Vascular adaptation, compliance resetting, pulsatile hemodynamics, multiscale modeling
INTRODUCTION

Aortic pulse pressure appears to be homeostatic despite the lack of global regulatory mechanisms affecting elastic arteries. Cardiac output, peripheral resistances, and arterial compliances are the primary mechanical determinants of aortic pressures (40, 47). Whereas mean pressure is predominantly determined by cardiac output and peripheral resistance, pulse pressure (systolic – diastolic) is also affected by compliance (the change in volume per change in transmural pressure) of the large elastic arteries (69).

As arterial compliances decrease, pulse pressures tend to increase (40, 41, 47, 48). Acutely, mean pressure and pulse pressure are physiologically coupled by feedback mechanisms: when pulse pressure rises, stretch-induced baroreceptors lower peripheral resistance, i.e., the baroreflex, which in turn lowers mean pressure. Furthermore, mean pressure and pulse pressure are mechanically coupled: when mean pressure rises acutely, stretch-induced stiffening of the arterial walls lowers arterial compliances, i.e., pressure-dependent compliance (35). Both the baroreflex and stretch-induced stiffening of elastic arteries thus are synergistic and couple acute changes in mean and pulse pressure. However, mean and pulse pressures are chronically regulated independently of one another. Over time, the effect of the baroreflex dissipates as mean pressure becomes primarily regulated by renal control of blood volume. Yet the initial changes in pulse pressure due to sustained changes in peripheral resistance (25, 76), cardiac output (21, 26, 32, 44, 72, 81), or aortic stenosis (2, 8, 15, 27, 29, 70, 71, 74) tend to ameliorate with time. In each case, pulse pressure appears to be chronically regulated independently of mean pressure by modulation of a key mechanical property: arterial compliance. The high pulse pressure of isolated systolic hypertension has long been attributed to decreased
compliance of the large elastic arteries (47). However, no mechanism yet has been identified that attributes chronic regulation of aortic pulse pressure to feedback mechanisms that control arterial compliance.

*Aortic pulse pressure is affected by the specific distribution of mechanical properties of elastic arteries throughout the systemic arterial system.* Arterial pressures vary from artery to artery and generally do not rise and fall simultaneously throughout the healthy systemic arterial system (40, 47, 48). As the ventricle ejects a bolus of blood into the arterial system, a pressure pulse propagates toward the periphery and is reflected back from multiple locations, particularly at bifurcations or where arterial geometry or stiffness changes (6, 40, 47, 48). To capture the complex hemodynamics arising from pulse wave propagation and reflection, investigators have developed realistic, large-scale arterial system models characterized by the standard “transmission line equations” (50, 54, 70, 79). Such models have reproduced not only the observed increase in pulse pressure toward the periphery (50, 62, 70, 79), but also the changes in pulse pressure with increased peripheral resistance (63, 78), decreased arterial compliance (41, 42, 70), and aortic coarctation (70). These modeling efforts have established that regional pulsatile pressures and flows arise from complex interaction among vessels in a network—any changes in the mechanical properties of one artery significantly affect the pulsatile pressures and flows in all other arteries.

*Arteries adapt in response to changes in local mechanical stresses.* Chronic changes in blood pressure and flow have been correlated with structural remodeling of the arterial wall both in the young and elderly, involving changes in lumen radius, wall thickness, and stiffness of the arterial wall within weeks (7, 13, 20, 36, 38, 55, 64, 74,
Most mechanistic studies of adaptive behaviors, however, have only employed acute, in vitro experiments performed on cultured cells or isolated muscular arteries. Such studies have revealed that vessels respond to mechanical stresses, particularly endothelial shear stress and wall circumferential stress (7, 20, 65). Due to the inherent difficulty associated with chronically culturing vessels in vitro (16), the insight that mechanical stresses are fundamental adaptive stimuli has been difficult to apply to the study of chronic growth and remodeling of large elastic arteries in vivo. It is exceedingly difficult to control endothelial shear stress and wall circumferential stress in vivo. Adaptation-induced changes in radius, wall thickness or stiffness affect mechanical stresses (9, 17, 37, 39, 75), even when luminal pressure and flow can be maintained (3, 38, 43, 66). The inability to make mechanical stresses controlled, independent variables in vivo is an inescapable consequence of arterial growth and remodeling (22, 55). Nonetheless, consensus is emerging that endothelial shear stress is the primary stimulus affecting arterial radius (20, 55, 60, 82), and wall circumferential stress is the primary stimulus affecting wall thickness and stiffness (4, 20, 24).

Mathematical models have revealed that the complex distribution of systemic arterial system mechanical properties, pulsatile hemodynamics, and mechanical stresses can emerge from three simple adaptive rules. To overcome the inherent difficulty characterizing adaptive responses in vivo, Nguyen et al. (46) employed a classical systemic arterial system model with 121 arterial segments, and removed all parameter values except vessel lengths and peripheral resistances (79). They then employed the standard assumptions that vessel radius is determined by endothelial shear stress, and that wall thickness and stiffness are determined by wall circumferential stress. Iteratively
predicting local pulsatile hemodynamics, mechanical stresses, and vascular properties (46) reproduced five trends in arterial system properties from aortic root to peripheral arteries: decreases in lumen radii, wall thicknesses and pulsatile flows, and increases in elastic moduli and pulsatile pressures (40, 46, 47). Furthermore, propagation pressure and flow waves along the arterial tree were consistent with physiologic values, including specific pulsatile pressures and flows. This simple approach, however, has not yet been employed to study the chronic adaptation of the arterial system to mechanical perturbations and the implications to aortic pulse pressure. Therefore, the purpose of the present work was to use a human systemic arterial system model to test the hypothesis that pulse pressure homeostasis can emerge from physiologic adaptation of systemic arteries to local mechanical stresses.

**METHODS**

*Architecture of the systemic arterial system model and its assumed input flow.* As in Nguyen et al. (46), the present work utilizes a classical model of a realistic human systemic arterial system originally reported by Westerhof et al. (79), illustrated in Fig. 1. Briefly, mechanical properties for each of the 121 vessel segments were characterized by a luminal radius \( r \), wall thickness \( h \), elastic modulus (i.e., a measure of material stiffness) \( E \) and length \( l \). Baseline blood flow from the heart into the ascending aorta (solid line, Fig. 2) was assumed to have the same morphology as that reported by Stergiopulos et al. (68), but scaled to obtain a pulse pressure of 40 mmHg in the first segment the ascending aorta. Normal peripheral resistances were assumed to be equal to the terminal resistances reported Westerhof et al. (79).
Overview of iterative process to determine equilibrium values of all model variables. As in Nguyen et al. (46), the systemic arterial system model (Fig. 1) was altered to make its arterial segments grow and remodel in response to local mechanical stresses. The iterative process to determine hemodynamics variables, arterial mechanical properties, and mechanical stresses is illustrated in Fig. 3. It consisted of three distinct steps, described below in more detail. First, pressures and flows ($P$ and $Q$) were calculated from values of mechanical properties ($r$, $h$, and $E$). Next, wall circumferential stresses and endothelial shear stresses ($\sigma$ and $\tau$) were calculated from pressures, flows, and mechanical properties. Next, new values of mechanical properties were calculated from the values of endothelial shear stresses and wall circumferential stresses, assuming the parameters (Table 1) originally reported by Nguyen et al. (46). These three steps were iterated until equilibrium was established. Equilibrium was assumed when the values of the mechanical properties were within 0.001% of the values obtained from the previous iteration. Unlike Nguyen et al. (46), systemic responses to perturbations were then studied. Three distinct perturbations were employed, described below in more detail: reduced cardiac output, increased peripheral resistances, and aortic coarctation.

Calculating blood pressures and flows. The pulsatile blood pressures and flows in each arterial segment were calculated from the standard “transmission line equations” (40, 48) that incorporate the effects of blood inertia, blood viscosity and arterial compliance (change in volume per change in pressure). Based on simplifications of the Navier-Stokes equations (48), the transmission line equations capture the complex propagation and reflection of pressure pulses throughout the arterial network (40, 48, 70, 79). To relate pulsatile pressure to pulsatile flow in each arterial segment, the vessel
resistance, compliance, and inertance were calculated from \( r, h, E \), and \( l \). From these mechanical properties, the vessel longitudinal impedance, transverse impedance, and characteristic impedance were calculated \((40, 47, 48)\). The ratio of pulsatile pressure to pulsatile flow in any given vessel is characterized by the input impedance, which is unique to each vessel, and is dependent on both the vessel characteristic impedance and properties of the downstream network. The transmission line approach thus can be used to calculate pressures and flows everywhere in a network of arteries with known boundary conditions: 1) input flow, 2) terminal resistances, and 2) network structure and topology. We used the standard transmission line equations of Westerhof et al. \((79)\), which only predict blood pressures and flows, and do not characterize mechanical stresses or indicate how vessels may grow and adapt to in response to mechanical stresses.

Calculating endothelial shear stresses and wall circumferential stresses. Since blood pressures and flows vary with time, endothelial shear stresses and wall circumferential stresses also vary with time. To be consistent with Nguyen et al. \((46)\), the root mean squared values of endothelial shear stress \((\tau_{rms})\) and wall circumferential stress \((\sigma_{rms})\), calculated over the cardiac period \((T)\), were assumed as stimuli for adaptation. They effectively incorporate both pulsatile and steady components of these time-varying shear and circumferential stresses.

\[
\tau_{rms} = \frac{1}{\sqrt{T}} \int_{0}^{T} \tau(t)^2 \, dt \quad (1a)
\]

\[
\sigma_{rms} = \frac{1}{\sqrt{T}} \int_{0}^{T} \sigma(t)^2 \, dt \quad (1b)
\]
The time-varying endothelial shear stress, $\tau(t)$, was approximated from the time-varying axial flow, $Q(t)$ by assuming a time-varying parabolic velocity profile (48).

$$\tau(t) = \frac{4\mu}{\pi r^3} Q(t) \quad (2a)$$

The time-varying wall stress $\sigma(t)$, averaged over the thickness of the arterial wall in the radial direction, was calculated using the time-varying pressure $P(t)$ at the entrance of each arterial segment according to Laplace’s law.

$$\sigma(t) = \frac{r}{h} P(t) \quad (2b)$$

Calculating radii, wall thicknesses, and elastic moduli. Following the approach of Nguyen et al. (46), 363 parameters for radii, wall thicknesses, and elastic moduli of 121 vessel segments were transformed into variables using three adaptive rules with six parameters characterizing equilibrium radii, wall thicknesses, and elastic moduli. Briefly, vessel lengths and terminal resistances were kept constant at values reported by Westerhof et al. (79). The model predicted new values of radii ($r$), wall thicknesses ($h$), and elastic moduli ($E$) by assuming that radius adapts to endothelial shear stress, wall thickness adapts to wall circumferential stress, and elastic modulus adapts to wall circumferential stress according to Eq. 3.

$$r = r_o + \alpha \cdot \tau_{rms} \quad (3a)$$

$$h = h_o + \beta \cdot \sigma_{rms} \quad (3b)$$

$$E = E_o - \gamma \cdot \sigma_{rms} \quad (3c)$$

The constant parameters characterizing the process of adaptation ($r_o$, $\alpha$, $h_o$, $\beta$, $E_o$ and $\gamma$) were previously established in by Nguyen et al. (46) and are reproduced in Table 1. These “adaptive rules” were developed to characterize the steady-state values of $r$, $h$, and $E$, and therefore do not assume a particular rate of vascular growth and remodeling. The
timescale of chronic adaptation is weeks to months, when normal growth and remodeling reaches steady state (20), rather than the timescale of years and decades, when age-related pathologies lead to isolated systolic hypertension (47). Furthermore, Eq. 3 represents linear approximations of what may be more complex (e.g., sigmoidal) relationships. Therefore, the values of $r$, $h$, and $E$ have no explicit maximum or minimum values, and could adapt to very large or small values if mechanical stresses were to become very low or very high. Perhaps as critical, the adaptive responses were assumed to apply to all arteries of the model in Fig. 1. Taken together, Eqs. 1-3 characterize the adaptive responses of each artery to mechanical stresses.

Adaptation to reduced pulsatility of input flow. Adaptation to reduced pulsatility from the heart was simulated by reducing the peak input aortic flow by 50% from the baseline value of 424 ml/s (Fig. 2, dashed line). This magnitude of reduction in aortic pulsatile flow is consistent with the reported reduction of ejection fraction in patients with congestive heart failure (21) and in patients and experimental animals with implanted left-ventricular assist devices (26, 32, 44, 72, 73, 81). To maintain mean pressure, peripheral resistances were increased. Pulse pressures and arterial compliances before and after adaptation were calculated.

Adaptation to increased peripheral resistances. Adaptation to increased systemic vascular resistance was simulated by increasing the total peripheral resistance by 20% from baseline values of 0.85 mmHg·s/ml, increasing mean pressure to approximately 120 mmHg. Pulse pressures and arterial compliances before and after adaptation were calculated.
Adaptation to aortic coarctation. A segment of the descending aorta (Fig. 1, CA) was made narrow to explore arterial adaptation to an abrupt change in local mechanical properties. The radius of the entire vessel segment was reduced by 75% from the baseline value of 0.68 cm. The wall thickness and elastic modulus of this segment were held constant while the rest of the arterial segments of the model were allowed to adapt according to the process illustrated in Fig. 3. Such narrowing causes the creation of a significant site of pulse wave reflection (70). Pulse pressures and arterial compliances before and after adaptation were calculated. For clarity, only adaptive changes in aortic segments upstream of the coarctation are reported.

Calculation of acute and chronic arterial compliances. The compliance of each arterial segment in the model was calculated assuming thick-walled vessels. Characterized elsewhere (48), it is a function of vessel $r$, $h$, $E$ and $l$.

$$C = \frac{3\pi r^2 (r+h)^2 l}{E h (2r+h)} \quad (4)$$

When mean pressure increases acutely, vessel compliance decreases due to stretch-induced stiffening of the arterial wall (40, 47). To illustrate transient changes (i.e., within minutes) in compliances after an initial perturbation, the compliances per unit length ($C'$) for all vessels were assumed to be a function of mean arterial pressure ($P$)

$$C' = ae^{bp}. \quad (5)$$

The empirical constants $a$ and $b$, reported by Liu et al. (35), were assumed for all vessel segments. This calculation was adopted merely to establish values of compliance after an acute perturbation that increases mean pressure.

Graphical analysis of adaptation of vessels upstream of an aortic coarctation. To illustrate the adaptation induced by altering local pulse wave reflection, three balance
point graphs were constructed for a segment upstream (Fig. 1, DeA) of a coarctation site (Fig. 1, CA). The structural variables \((r, h, \text{ and } E)\) were varied while their corresponding mechanical stimuli \((\tau_{\text{rms}} \text{ and } \sigma_{\text{rms}})\) were calculated according to Eqs. 1 and 2 to establish biomechanics curves before (baseline) and after coarctation. The adaptation curves (Eq. 3) were then calculated for the relevant range of \(\tau_{\text{rms}} \text{ and } \sigma_{\text{rms}}\). Balance point graphs were then created by simultaneously plotting the biomechanics curves and adaptation curves.

**RESULTS**

Partial restoration of pulse pressures and shear stresses in response to sustained reduction in pulsatility of input flow. A 50% reduction in inlet pulsatile flow had no acute impact on arterial compliances (Fig. 4A, grey bars), because resistances were adjusted to maintain mean pressure (Eq. 5). However, acute values of pulse pressures decreased in all arteries (Fig. 4B, grey bars), as well as values of \(\tau_{\text{rms}} \text{ and } \sigma_{\text{rms}}\) (not shown). Arterial adaptation caused radii and thicknesses to decrease, and arterial elastic moduli to increase (not shown). Taken together, these adaptations caused all arterial compliances to decrease (Fig. 4A, solid bars), which in turn increased pulse pressures back toward baseline values (Fig. 4B, solid bars). The most significant restoration in pulse pressure occurred in the ascending and descending aorta (\(~50\% \text{ compared to acute values}\) ), and less significant restoration occurred in the iliac and femoral arteries. Arterial adaptation also increased \(\tau_{\text{rms}}\) towards baseline values in all vessels.

Partial restoration of pulse pressure and mechanical stresses in response to sustained increase in peripheral resistances. A 20% increase in peripheral resistances
increased mean pressure, and thus acutely decreased arterial compliances (Fig. 4C, grey bars) according to Eq. 5. Decreased arterial compliances caused an acute increase in pulse pressure in all arteries (Fig. 4D, grey bars). Acute values of $\tau_{rms}$ decreased in all arteries compared to baseline, and values of $\sigma_{rms}$ increased (not shown). Arterial adaptation increased radii, increased wall thicknesses, and decreased elastic moduli in all vessels (not shown). Taken together, these adaptations caused all arterial compliances to increase (Fig. 4C, solid bars), which in turn returned pulse pressures back toward baseline values (Fig. 4D, solid bars). Restoration of pulse pressure was more pronounced in the largest arterial segments. Arterial adaptation also increased $\tau_{rms}$ and decreased $\sigma_{rms}$ back towards baseline values in all arterial segments.

Partial restoration of pulse pressure in aortic segments upstream of an aortic coarctation. A 75% reduction in lumen radius of a segment of the descending aorta (Fig. 1, CA) slightly increased mean pressure upstream, and thus slightly decreased upstream arterial compliances (Fig. 5A, grey bars) according to Eq. 5. Increased pulse wave reflection, however, had caused a very large acute increase in pulse pressure (Fig. 5B grey bars). Acute values of $\tau_{rms}$ decreased compared to baseline, and values of $\sigma_{rms}$ increased (not shown). Adaptation reduced radii, increased wall thicknesses and decreased elastic moduli (not shown). Taken together, these adaptations caused all arterial compliances to increase significantly (Fig. 5A, solid bars), which in turn returned pulse pressures back toward baseline values (Fig. 5B, solid bars). Arterial adaptation also increased $\tau_{rms}$ and decreased $\sigma_{rms}$ back towards baseline values in all arterial segments.

Graphical illustration for adaptation of an arterial segment upstream of an aortic coarctation. Figure 6 graphically illustrates the changes in equilibrium values of $\tau_{rms}$ and
\( \sigma_{\text{rms}} \) as well as \( r, h \) and \( E \) in an aortic segment upstream of an aortic coarctation.

Equilibrium balance points are indicated by intersections of curves representing biomechanics (solid curves, Eq. 2) and the adaptive processes (dashed lines, Eq. 3). The increased local pulse wave reflection due to coarctation shifts the equilibrium of the illustrated upstream segment to smaller radius and lower shear stress (Fig. 6A), higher wall thickness and wall stress (Fig 6B), and lower elastic modulus and higher wall stress (Fig. 6C). Because \( \alpha, \beta, \) and \( \gamma \) had finite values, changes in mechanical stresses induced by sustained coarctation were only partially restored by arterial adaptation.

\[\text{DISCUSSION}\]

\textit{Aortic pulse pressure homeostasis emerged from simple adaptive rules applied to a realistic human systemic arterial network.} The present work reveals that a seemingly coordinated regulation of pulse pressure emerges from independent adaptation of arteries. In each of the perturbations explored in the present work, stress-induced adaptation of radii, wall thicknesses and elastic moduli acted in concert to alter arterial compliances. First, a reduction in pulse pressures due to reduced pulsatility of input flow elicited an adaptive response that decreased arterial compliances, thus increasing pulse pressures back towards baseline (Figs. 4A and 4B). Second, an increase in pulse pressures due to increased peripheral resistances elicited an adaptive response that increased arterial compliances, thus decreasing pulse pressures back towards baseline (Figs. 4C and 4D). Third, an increase in upstream pulse pressures due to reduction in radius of segment of the aorta elicited an adaptive response that increased compliances, thus decreasing pulse
pressures back towards baseline (Fig. 5). A fundamental principle has thus been revealed: aortic pulse pressure homeostasis emerges from physiologic adaptation of the large conductance arteries stimulated by to local mechanical stresses.

Connecting local stress-induced arterial adaptation to pulse pressure homeostasis. In the present work, we have assumed that radii, wall thicknesses, and elastic moduli adapt to local stresses (Eq. 1). Although each response provides negative feedback to partially restore vascular stresses, they also act in concert to alter arterial segment compliances. In general, increases in arterial compliances reduce pulse pressures (34, 40, 48). When pulsatile pressures increase, pulsatile wall stresses increase. The resulting increases in wall thicknesses and decrease in elastic moduli act antagonistically, increasing and decreasing arterial compliances, respectively (Eq. 4). The balance of the two opposing adaptive responses, however, favors an increase in compliance, a requirement to provide negative feedback and maintain stability of the arterial network. The fact that the larger arteries have far more compliance than smaller arteries may explain why adaptation had a greater impact on pulse pressure in the ascending aorta (Figs. 4B, 4D, 5B). As a result, pulse pressure homeostasis was more pronounced in the larger arteries proximal to the heart. However, additional complexities in our results arose from the hemodynamics in networks: 1) pressures in all vessels are affected by the sum of arterial compliances (34, 57, 59, 61), 2) pulse pressure in each vessel segment is affected by pulse wave reflection, which depends on compliances, cross-sectional areas, and network architecture (48, 58), and 3) equilibrium pulse pressure and compliance of any one arterial segment results from the simultaneous adaptation of all arterial segments in the network. Our work thus clarified a critical concept—information transfer by
hemodynamic signals in a complex arterial network is sufficient to coordinate the local adaptive responses and yield aortic pulse pressure homeostasis.

Judicious use of simplifying assumptions allowed identification of homeostatic mechanisms. A number of simplifying assumptions were made to characterize hemodynamic regulation by stress-induced arterial adaptation. First, we assumed linearity in the mathematical descriptions of pulsatile hemodynamics (40, 48, 50) and arterial adaptation (46), limiting the number of model parameters to only those describing fundamental behaviors. Second, the root mean square values of mechanical stresses were used to incorporate both mean and pulsatile stresses. Third, we assumed only adaptation to average wall circumferential stress (46), minimizing unnecessary complications in the results by second-order effects such as longitudinal extension and torsion. Fourth, we assumed that the same adaptive responses to mechanical stresses (i.e., same parameter values in Table 1) in all vessels. Together, the assumptions retained the tractability of our numerical simulations and allowed us to attribute complex, emergent behaviors of large conductance vessels to simple adaptive rules. Many clinically-relevant perturbations to the systemic atrial system can be recognized as combination of the three simple perturbations reported here: changes in input pulsatile flow, changes in total peripheral resistance and changes in specific radii. It is expected that the present model also could be used to predict complex adaptations resulting from pathologies of vascular growth and remodeling. Our goal, however, was to illustrate a central principle underlying physiologic adaptation of the systemic vasculature.

Justification for assumed adaptive responses to mechanical stresses. The adaptive rules of the present work (Eq. 3) were first developed by Nguyen et al. (46), who
assumed that chronic adaptation is functionally similar to the acute shear stress-induced vasodilation and wall stress-induced vasoconstriction of muscular arteries (3, 17, 20, 24, 60) and microvessels (28, 55, 56, 66). These adaptive rules were consistent with reported mechanisms of endothelial mechanotransduction (7) and observations from human clinical studies (9, 37, 39). Although most studies have focused on pathological changes in wall stiffness (34, 47), simulations by Nguyen et al. (46) supported the hypothesis that the elastic modulus must decrease with wall circumferential stress to yield physiologic remodeling. The assumption of chronic linear responses to stresses (Eq. 3), however, notably differs from the acute sigmoidal responses observed for small muscular arteries (20, 47, 64). Although it is generally agreed that chronic adaptation in vivo allows radii and wall thicknesses to grow beyond limits imposed by contraction and relaxation of smooth muscle (20, 47, 60), more realistic adaptive rules might include maximum and minimum values of mechanical properties at very high and low stresses. The present work, like that of Nguyen et al. (46), however, found that the range of equilibrium mechanical stresses were relatively narrow, and thus nonlinearities manifesting at more extreme stresses may not be relevant. Perhaps more striking is that all vessels represented in Fig. 1 were assumed to have the same responses to local mechanical stresses (Eq. 3), as well as the same sensitivity parameters (α, β, and γ; Table 1). Size-specific sensitivity in acute response to endothelial shear stress has been documented for the porcine coronary microvessels (28) and assumed in a model to predict the architecture the rat mesenteric microvasculature (56). Similar differences in chronic adaptive responses likely exist in the human systemic vasculature, especially within networks of small muscular arteries perfusing different organs. The vessels represented in Fig. 1 are
relatively large conductance arteries that are typically characterized as elastic, which may
explain why assumption of common adaptive responses were able to predict reported
radii, wall thicknesses, and elastic moduli (46). Altering the values of \( \alpha \), \( \beta \), and \( \gamma \) or
making them explicit functions of the radius, wall thickness, or the \( r/h \) ratio may be a
logical extension to characterize smaller arteries. Although homogenous adaptive
responses were assumed, it is notable that differences in local mechanical stresses led to
heterogeneous mechanical properties and an increase in pulse pressure towards the
periphery. Adjusting parameters so that smaller arteries have lower values of \( \alpha \), higher
values of \( \beta \), or lower values of \( \gamma \) (not shown) lead to even greater increase in pulse
pressures towards the periphery.

*Balance point approach is more physiological than assuming equilibrium stress set points.* Consistent with in vivo experiments (9, 39), our model predicted that
adaptation to perturbations would not return the local mechanical stresses and pulse
pressures back to baseline values (Fig. 4 and 5). The adaptive processes only ameliorate
acute deviations. The basis for this incomplete restoration of stresses can be illustrated
with the balance point graph in Fig. 6. The use of *finite* values for \( \alpha \), \( \beta \), and \( \gamma \) prevents
the adaptive process to return to *point a*, the baseline equilibrium point. Rather, a new
equilibrium is achieved at *point c*. Increasing the gain of the adaptive processes by
increasing all three sensitivity parameters \( (\alpha, \beta, \text{and } \gamma) \) to infinity results in vertical lines
for the adaptation curves. An infinite gain reduces the system into one in which
perturbations affect mechanical variables \( (r, h, \text{and } E) \) but perfectly maintains equilibrium
stresses. In this case, the two parameters characterizing each adaptive response can be
replaced with one: a target stress set point. As discussed earlier (46), assuming a set point
stress removes from the model a role of sensitivity of arterial radii, wall thickness, and
stiffness ($\alpha$, $\beta$, and $\gamma$) to mechanical stresses. These parameters relate to
mechanobiology, with $\alpha$ being the chronic analog of the acute shear-induced dilation
sensitivity measured in vitro (28). Instead of assuming mechanical stress set points (7, 17,
20, 55, 60, 66), the present balance point approach provides a means to integrate research
focused on vascular biomechanics with research focused on vascular mechanobiology.

Validation of baseline predictions of and responses to mechanical perturbations.
Our previous work established the ability of the model to predict a large number of
mechanical properties, pulsatile pressures and flows, and mechanical stresses in the large
conductance arteries of the human systemic arterial system (46). In particular, by
assuming the six adaptive parameters in Table 1, the values of radii, wall thicknesses, and
estatic moduli of 121 arterial segments compiled by Westerhof et al. (79) were
reproduced. Furthermore, the morphology of pressure waveforms along the aorta were
consistent data reported in the literature, and the salient observation that pulse pressure
increases towards the periphery (79) was reproduced (47). The predicted values of pulse
pressure and pulse flows in baseline were within the normal human values reported by 14
studies in the literature (46). Similarly, predicted values of endothelial shear stresses and
wall circumferential stresses were comparable to reported values (51, 53). In the present
work, the predicted changes in arterial compliances with three very disparate
perturbations were also consistent with reported changes. First, decreases in vessel
compliances were predicted with decreases in mean and pulsatile flow (Fig. 4A). Similar
decreases in arterial compliances have been documented in patients with reduced cardiac
output after myocardial infarction (1). Similarly, increased pulse wave velocity (an
indicator of decreased arterial compliance) is highly correlated to incidence of heart failure (40, 47). Restoration of cardiac output by implantation of continuous-flow left ventricular assist devices reduces input flow pulsatility (26, 32, 44, 72, 81), and results in a decrease in carotid and aortic compliance (72, 73). Second, increases in arterial compliances were predicted in response to chronic increases in peripheral resistance (Fig. 4C). In the current study, we kept mean flow while simulating increases in peripheral resistance to clearly relate increases in compliances (Fig. 4B, solid bars) to changes in pulse pressures (Fig. 4D, solid bars). As mean pressures increase acutely, arterial compliances immediately decrease (Fig. 4C, grey bars). However, the concomitant increase in pulse pressure acts to induce growth and remodeling that increases arterial compliance (i.e., Fig. 4C, solid bars). Increases in peripheral resistance are typically accompanied by a reduction in flow. With a reduction in input flow, we expect a combination of the effects of reduced input flow (Fig. 4A) and increased peripheral resistances (Fig. 4B), which would ameliorate the increase in chronic compliance. Taken together, chronic adaptation acts to increase compliance, which has been described as “compliance resetting” (12), which was first observed in rat carotid arteries (14, 19). Furthermore, numerous studies of hypertensive humans have reported that conductance artery compliance is similar to (31) or even higher (12, 18, 30) than normotensive subjects when measured at similar pressures. Third, increases in compliances were predicted upstream of an aortic coarctation (Fig. 5). Successful repair of aortic coarctation in children and normotensive adults results in decreased aortic compliance upstream of the coarctation site (5, 33, 52, 74). The documented changes in aortic compliance due to surgery are the inverse of our result illustrated in Fig. 5. Baseline (Fig.
5A, white bars, before coarctation) corresponds to the post-surgical measurements (i.e.,
after coarctation repair), and adapted (Fig. 5A, black bars, after coarctation) corresponds
to pre-surgical measurements. That is, we predicted that addition of coarctation increases
upstream compliance, and it was observed that removal of coarctation decreases upstream
compliances. Taken together, reported changes in arterial compliance in response to three
disparate perturbations were reproduced by the model. In each case, reported
observations now can be attributed to the interaction of three well-documented adaptive
responses (7, 17, 20, 24, 43, 47, 60, 82) approximated by Eq. 3.

Arterial adaptation to mechanical stress simultaneously can meet many demands.

Not only are human pulse pressures and mechanical stresses found within relatively
narrow ranges in response to significant perturbations, they are relatively constant across
mammalian species (11, 49). Previous attempts to predict the mechanical properties of
the mammalian arterial system have relied on teleological principles (23, 45, 77, 80). The
most popular explanations for mammalian cardiovascular similarity is that the systemic
arterial system minimizes energy dissipation (23, 45, 77, 80) or maintains optimal
mechanical stresses (7, 20, 56, 82). Murray (45) predicted vascular branching patterns
based on the assumption that the arterial system minimizes energy dissipation. Zamir (82)
arrived at the same predicted geometries assuming that endothelial shear stresses in all
vessels of a branch are constant. In the present work, we depart from convention and take
a mechanistic approach to predict arterial behaviors from simple adaptive mechanisms
(i.e., Eq. 3). The resulting structure tends to minimize energy dissipation and maintain
stresses within narrow ranges. Furthermore, the use of identical adaptive responses
eliminates the need for genetically encoding a large amount of information to achieve and
maintain optimality throughout the arterial network. Whether the adaptive responses in the present work are conserved and provide a mechanistic basis for mammalian similarity and numerous reported allometric relationships (10, 11, 67) remains an intriguing question.

_Perspectives and significance._ Although knowledge of the role of mechanical stress in vascular remodeling is expanding rapidly, its application to regulatory, integrative and comparative physiology has been limited. On one hand, the field of mechanobiology focuses on the effects of mechanical stresses on vascular structure. On the other hand, the field of biomechanics focuses on the effects of vascular structure on mechanical stresses. The present work does little to advance current understanding of either mechanobiology or biomechanics. Instead, it represents a significant departure from convention by using mathematical modeling to integrate these disparate fields. The main contribution of the present work is to illustrate that simultaneous physiologic adaptation of arteries to local mechanical stresses in the systemic arterial network leads to systemic regulation of hemodynamic variables. In each of the perturbations explored in the present work, physiologic adaptations of radii, wall thicknesses and elastic moduli in response to local mechanical stresses act in concert to alter arterial compliances, and thus pulse pressures. The simplicity of our assumptions made it possible to illustrate a novel homeostatic mechanism: pulse pressure homeostasis emerges from physiologic adaptation of the large conductance arteries to local mechanical stresses. The scope of the present work was limited to physiologic adaptation of arteries to changes in mechanical stresses. However, this innovative modification to a classic transmission line model provides a new framework for future studies in hemodynamic regulation and comparative
physiology. Furthermore, this framework provides a means to explore the clinical ramifications of pathophysiologic remodeling of vessels.
ACKNOWLEDGEMENTS

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REFERENCES


**FIGURE LEGENDS**

**Table 1:** Values of parameters quantifying adaptation of radius, wall thickness and the modulus of elasticity to mechanical stresses in Eq. 3. Parameters were previously reported in Nguyen et al. (41).

**Figure 1:** Illustration of the distributed systemic arterial model reported by Westerhof et al. (75) consisting of 121 arterial segments. Original values of lengths and terminal resistances were maintained as constant parameters. Values of radius, wall thickness and material stiffness were converted into variables that respond to mechanical stresses. To simulate coarctation, \( CA \) was narrowed. Figure modified from Nguyen et al. (41).

**Figure 2:** Prescribed aortic input flow into the ascending aorta. To simulate baseline conditions, the inlet aortic flow was digitized from Stergiopulos et al. (63), modified by altering peak flow, and replotted (solid line). To simulate reduced cardiac output, the peak value of the flow wave was reduced by 50%.

**Figure 3:** Iterative process to calculate equilibrium hemodynamic variables, mechanical stresses, and vascular structure after adaptation to three perturbations. Changes in pressures and flows in all arterial segments caused by sustained external perturbations were calculated using the model developed by Nguyen et al. (41). The corresponding changes in wall circumferential and endothelial shear stresses were calculated using Eqs. 1 and 2. Finally, the adapted values of radii, wall thicknesses, and elastic moduli for each vessel were calculated using the adaptive rules prescribed by Eq. 3. This iterative process was terminated when equilibrium was reached. Iterative process was identical to that employed by Nguyen et al. (41).

**Figure 4:** Evidence of pulse pressure homeostasis in vessels along the aortic-femoral pathway (labeled in Fig. 1) in response to changes in input flow (A and B).
and downstream peripheral resistances (C and D). A) A 50% decrease in in peak and mean input flow had no acute effect on arterial compliance. Adaptation decreased arterial compliance in all vessels. B) Decreased inlet pulsatile flow caused an acute decrease in pulse pressure, but the decrease in arterial compliance with adaptation caused pulse pressure to increase back towards baseline values. C) A 20% increase in peripheral resistances caused an acute decrease in arterial compliances. Arterial adaptation caused compliances to increase. D) Increased peripheral resistance caused an acute increase in pulse pressure in most arterial segments, but increases in arterial compliances with adaptation caused most pulse pressures to return towards baseline values.

Figure 5: Evidence of pulse pressure homeostasis in arterial segments upstream (Fig. 1, DeA) of a 75% narrowing of a segment of the descending aorta (Fig. 1, CA). A). Coarctation acutely decreases arterial compliance (grey bars), and adaptation increases compliance (solid bars). B) Coarctation acutely increases pulse pressure, but the increase in arterial compliance with adaptation decreases pulse pressure toward baseline values.

Figure 6: Graphical balance point approach to illustrate effect of an aortic coarctation (Fig. 1, CA) on equilibrium in an upstream arterial segment (Fig. 1, DeA). Dashed lines characterize adaptive responses (Eq. 3). Solid curves characterize the relationships of mechanical stresses to mechanical properties (Eq. 2). A) Coarctation shifts the shear stress-radius relationship, acutely shifting equilibrium from point \(a\) to point \(b\). The intersection at point \(c\) represents the chronic equilibrium, indicating a decrease in both radius and shear stress. B) Coarctation shifts the wall stress-wall thickness relationship, acutely shifting equilibrium from point \(d\) to point \(e\). The chronic equilibrium (point \(f\)) indicates an increase in both wall thickness and wall stress. C) Coarctation acutely shifts the equilibrium from point \(g\) to \(h\). The chronic equilibrium (point \(i\)) indicates a decrease in material stiffness and an increase in wall stress.
Calculate changes in pulsatile pressures and flow rates in each vessel using network model.

Calculate wall circumferential and endothelial shear stresses \((Eqs. \ 1 \ and \ 2)\).

Calculate values of vessel radii, wall thicknesses, and elastic moduli \((Eq. \ 3)\).

Increased peripheral resistances

Reduced cardiac output

Aortic coarctation
Adaptation to Reduced Pulsatility

Adaptation to Increased Peripheral Resistances

**Compliance (ml/mmHg)**

- **A**
- **B**

**Pulse Pressure (mmHg)**

- **C**
- **D**

Legend:
- baseline
- acute
- adapted
Compliance (ml/mmHg)

Pulse Pressure (mmHg)

A

B

ascending aorta

aortic arch

descending aorta

baseline

acute

adapted

75% coarctation
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