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Determinant factors for arterial hemodynamics in hypertension: theoretical insights from a computational model-based study

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Abstract

Hypertension is a well-documented predictive factor for cardiovascular events. Clinical studies have extensively demonstrated the differential hemodynamic consequences of various anti-hypertensive drugs, but failed to clearly elucidate the underlying mechanisms due to the difficulty in performing a quantitative deterministic analysis based on clinical data that carry confounding information stemming from inter-patient differences and the nonlinearity of cardiovascular hemodynamics. In the present study, a multi-scale model of the cardiovascular system was developed to quantitatively investigate the relationships between hemodynamic variables and cardiovascular properties under hypertensive conditions, aiming to establish a theoretical basis for assisting in the interpretation of clinical observations and the optimization of therapy. Results demonstrated that heart period, central arterial stiffness and arteriolar radius were the major determinant factors for blood pressures and flow pulsatility indices both in large arteries and in the microcirculation. These factors differed in the degree and the way in which they affect hemodynamic variables due to their differential effects on wave reflections in the vascular system. In particular, it was found that the hemodynamic effects of varying arteriolar radius were considerably influenced by the state of central arterial stiffness, and vice versa, which implied the potential of optimizing anti-hypertensive treatment by selecting proper drugs based on patient-specific cardiovascular conditions. When analyzed in relation to clinical observations, the simulated results provided mechanistic explanations for the beneficial pressure-lowering effects of vasodilators as compared to β -blockers, and highlighted the significance of monitoring and normalizing arterial stiffness in the treatment of hypertension.

Keywords: Computational model of the cardiovascular system; Hypertension; Hemodynamic variables; Cardiovascular properties; Arterial stiffness; Blood pressure

1. Introduction

Hypertension is a well-documented predictor for cardiovascular risk and mortality, affecting over 25% of the adult population [30]. The beneficial roles of antihypertensive medication in the prevention of major cardiovascular events have been extensively demonstrated [15,55]. In the past decades, various drugs have been used to treat hypertension, and, accordingly, there has been a long-standing question about how to achieve optimal pressure-lowering effects by proper medications. Relevant clinical studies have demonstrated that various classes of anti-hypertensive drugs have differential effects on arterial systolic and pulse pressures despite similar effects on mean pressure [4,56]. Moreover, the pressure-lowering effects of some drugs have been found to differ between central and peripheral arteries [10,31,32,61]. In the meantime, some studies have been devoted to assessing the changes in cardiovascular properties following anti-hypertensive therapy, with an aim to uncover the mechanisms underlying the differential pressure-lowering effects of various drugs. Major findings in this direction include the decrease of pulse wave velocity (PWV) in large arteries [5,31] and microvascular ameliorations characterized by increased lumen area, reduced media-to-lumen ratio, and improved vascular reactivity [19,33]. The degree of PWV decrease has been found to be comparable among different drug regimens, whereas beneficial microvascular alterations are more likely to be achieved by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) rather than by β -blockers [9,46]. Such clinical findings have offered important insights into drug selection and patient management. However, population-based clinical studies have not been able to clarify the relationships between hemodynamic variables and cardiovascular properties due to the presence of confounding inter-patient differences, the nonlinear nature of cardiovascular hemodynamics, and the interplays among multiple cardiovascular factors under in vivo conditions. Moreover, although there have been increasing studies suggesting that central blood pressure may be more valuable than peripheral blood pressure in predicting target organ damage or guiding the treatment of hypertension

[1,42,47,58,60], the reliability and clinical utility of noninvasively measuring aortic blood pressures remain debatable. Several studies have demonstrated that the accuracy of noninvasive central arterial pressure measurement is device-dependent, not exchangeable among devices, and susceptible to the influence of pathophysiological conditions [8,41,50], which may compromise the validity of or the comparability among the conclusions drawn by studies that employ different measurement methods. These limitations of clinical studies may lead to misinterpretations of the pressure-lowering mechanisms or improper drug evaluation. In addition to hemodynamic variables in large arteries, the pulsatile component of blood pressure in the microvasculature has been speculated to play potential roles in vascular biology and remodeling in the context of hypertension [11]. However, little is known about how microvascular blood pressure responds to anti-hypertensive treatment due to the lack of practical means for measuring microvascular blood pressure in general clinical settings [25].

In comparison with clinical measurements, computational modeling is a more practical approach to quantifying the hemodynamic effects of cardiovascular properties. In particular, a model-based computational study can provide insights into hemodynamic variables not accessible with general clinical methods and eliminate experimental errors associated with noninvasive measurement of blood pressure. One-dimensional (1-D) models of the arterial system have been widely employed to study arterial hemodynamics under various pathophysiological conditions [3,7,28,29,36,37,38,45,48]. Traditional 1-D models have mainly focused on simulating wave propagation phenomena in the arterial system while introducing significant simplifications when modeling distal arteries/arterioles. Such sorts of models may not be well suited for studying hemodynamic phenomena under hypertensive conditions since significant mechanical, structural and functional changes may occur in the entire cardiovascular system as a cause or consequence of hypertension [52].

In the present study, a multi-scale modeling method was developed to integrate the main cardiovascular

components prone to alterations in hypertension (such as the heart, large arteries, distal arteries and arterioles) into a unique computational framework that enables us to explore the determinant cardiovascular factors for hemodynamic variables of concern in the treatment of hypertension. With the model, a series of numerical experiments were carried out to provide fundamental knowledge for guiding the interpretation of clinical data and inferring the mechanisms underlying hemodynamic changes monitored during the treatment of hypertension.

2. Methods

A geometrical multi-scale modeling approach was adopted to construct a heterogeneous model capable of representing the major cardiovascular properties involved in the pathogenesis of hypertension, such as cardiac function, mechanical properties of large arteries, and structural properties of distal arteries/arterioles (see Fig.1). Herein, large arteries were represented by a 1-D model coupled with structured-tree (ST) models of distal arteries/arterioles. The 1D-ST model was further closed by a lumped-parameter (0-D) model of the left heart, pulmonary circulation, right heart, capillaries and veins to yield a closed-loop representation of the entire cardiovascular system. The resulting model enables the tracing of hemodynamic variations from the heart down to the capillary bed along the arterial system, thus furnishing a practical tool for quantifying the hemodynamic effects of various cardiovascular properties under hypertensive conditions.

2.1 1-D modeling of the arterial tree

1-D modeling was applied to an arterial tree constituted by fifty-five large arteries [28,29,51]. The governing equations consisted of the mass and momentum conservation equations of blood flow and a constitutive equation that accounts for the viscoelastic deformation of arterial wall [14].

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial s} = 0, \quad (1)$$

$$\frac{\partial Q}{\partial t} + \frac{\partial}{\partial s} \left(\alpha \frac{Q^2}{A} \right) + \frac{A}{\rho} \frac{\partial P}{\partial s} + f \frac{Q}{A} = 0, \quad (2)$$

$$P + \tau_\sigma \frac{\partial P}{\partial t} = \phi(A) + \tau_\epsilon \frac{\partial \phi(A)}{\partial t}, \text{ with } \phi(A) = \frac{Eh}{r_0(1-\sigma^2)} \left(\sqrt{\frac{A}{A_0}} - 1 \right) + P_0. \quad (3)$$

Here, t is the time and s the axial coordinate; A , Q and P refer to the cross-sectional area, volume flux and pressure, respectively; α is the momentum-flux correction coefficient and f the friction force per unit length, which were taken to be, respectively, $4/3$ and $-8\pi\nu$ (ν is the kinematic viscosity of blood) by assuming a Poiseuille cross-sectional velocity profile. τ_σ and τ_ϵ represent, respectively, the relaxation times for constant stress and strain; P_0 is the reference pressure; E is the Young's modulus; h is the wall thickness; σ is the Poisson's ratio, here taken to be 0.5; A_0 and r_0 are the arterial cross-sectional area and radius, respectively, at the reference pressure. It is noted that modeling the arterial wall as a viscoelastic rather than purely elastic material may help to inhibit nonphysiological high-frequency oscillations in simulated pressure waves, thereby improving the reliability of model-based simulations of arterial systolic and pulse pressures [2].

Continuity of mass flux and total pressure was imposed at the bifurcating points to link hemodynamic variables in adjacent arteries [28,37]. The proximal and distal ends of the arterial tree model were coupled to models of other cardiovascular portions as described below.

2.2 Modeling of distal arteries and arterioles

Each peripheral artery represented by the 1-D model was terminated at a given distance from the proximal bifurcation, leaving a complex distal vascular system consisting of numerous small arteries, arterioles, capillaries and veins whose geometrical and mechanical parameters cannot be fully determined by in vivo measurements. In particular, small arteries and arterioles are prone to structural changes under hypertensive conditions, such as the reduction in lumen area and the increase in media-to-lumen ratio [19,33], which may not only increase the viscous resistance to blood flow but also alter the characteristics of wave reflection. Herein, the structured-tree (ST) modeling method was adopted to represent distal arteries/arterioles, in which the complex vascular anatomy is mimicked by a simplified tree-like structure [39]. ST modeling has been shown to be more sophisticated than traditional lumped-parameter modeling in

representing the wave reflection properties of distal arteries/arterioles [14]. More importantly, ST modeling allows an explicit parametric definition of the geometrical and mechanical properties of distal arteries/arterioles, thereby providing a practical means to account for microvascular alternations under hypertensive conditions.

The original solution of the ST model was expressed in the frequency domain in form of input impedance derived by solving the linearized equation system of the 1-D model [39]. The impedance expression was later reformulated in form of an admittance matrix to facilitate relating hemodynamic variables at the proximal and distal ends of a structured tree [44]. For a vessel contained in a structured tree, we have

$$\begin{pmatrix} Q_p \\ Q_d \end{pmatrix} = \mathbf{Y} \begin{pmatrix} P_p \\ P_d \end{pmatrix}, \quad (4)$$

where Q_p , Q_d , P_p and P_d refer to the volumetric flow rates and pressures (corresponding to a harmonic in the frequency domain) at the proximal and distal ends of the vessel, respectively. The admittance matrix, $\mathbf{Y}$, is a function of the geometrical and mechanical parameters of the vessel [44]

$$\mathbf{Y} = \begin{pmatrix} Y_{11} & Y_{12} \\ Y_{21} & Y_{22} \end{pmatrix} = \frac{ig_\omega}{\sin(\omega L / c)} \begin{pmatrix} -\cos(\omega L / c) & 1 \\ 1 & -\cos(\omega L / c) \end{pmatrix}, \quad (5)$$

where L is the length of the vessel; ω is the angular velocity and g_ω is a coefficient. c represents the pulse wave velocity. g_ω and c are both determined by the physical properties of the vessel.

$$c = \sqrt{\beta A_0 (1 - F_J) / \rho}, \quad g_\omega = \sqrt{A_0 (1 - F_J) / \beta \rho}, \quad (6)$$

where A_0 is the the cross-sectional area of the vessel at the reference pressure; ρ is the density of blood; and F_J is a function of the zero-order and first-order Bessel functions of the first kind. β ($=2Eh/(3A_0r_0)$) is the coefficient of the pressure-area relationship, where E and h represent respectively the Young's modulus and thickness of vessel wall, and r_0 is the radius of the vessel at the reference pressure. For more details on the derivation of Eqs. (5) and (6) and the definitions of the parameters therein, readers are referred to [44,57].

The overall admittance of a structured tree can be deduced through continuously combining the admittances of branch vessels from the distal ends up to the root along the tree. Details on the principles and mathematical operations for admittance combination can be found in [14,44].

2.3 Modeling of the heart and the remaining vasculatures

The remaining cardiovascular portions included the heart, the pulmonary circulation and systemic capillaries, venules and veins, which were herein represented by a lumped-parameter (0-D) model. The heart was modeled by representing the contraction/relaxation function of each cardiac chamber with a time-varying elastance [53]. Taking the left ventricle as an example, the elastance (E_{lv}) was defined as [28,29]

$$E_{lv}(t) = E_{lva} e_{lv}(t) + E_{lvp}, \quad (7)$$

where E_{lva} describes the maximal contractility of the ventricular myocardium in systole; E_{lvp} represents the baseline stiffness of the ventricular chamber; and $e_{lv}(t)$ is a normalized elastance which varies with time over a heart period (T_0).

Vasculatures distal to arterioles (represented by ST models) are featured by complex anatomy and organ-specific hemodynamic conditions. To limit the complexity of the modeling work, we assumed that the distal ends of all ST models converged respectively to two capillary beds (namely, upper-body and lower-body capillary beds) (see Fig.1). The simplification made the model unable to simulate organ-specific hemodynamics in capillaries and veins, but preserved its ability to account for the behaviors of systemic hemodynamics. The upper-and lower-body vascular systems and the pulmonary circulation were respectively compartmentalized and represented by lumped parameters following the methods proposed in [29]. Governing equations of blood flows through the vascular systems were formulated based on the mass and momentum conservation principle [18,26,27,28], which together with the governing equations of the heart formed a nonlinear ordinary differential equation system.

2.4 Model coupling and numerical algorithms

The 1-D equation system and the 0-D equation system were solved with the two-step Lax-Wendroff method and the fourth-order Runge-Kutta method, respectively. At the proximal end (i.e., aortic root) of the arterial tree, solutions of the 1-D model were coupled to those of the 0-D model of the left ventricle via an iterative method (details of the numerical algorithm have been given in [29]). In the present study, emphasis was placed on developing methods to couple the ST models of distal arteries/arterioles with the upstream 1-D model and downstream 0-D model. Taking a ST model (labeled with 'j') as an example, the flow rates and pressures at its inlet ($Q_{j, \text{in}}^{\text{ST}}, P_{j, \text{in}}^{\text{ST}}$) and outlet ($Q_{j, \text{ou}}^{\text{ST}}, P_{j, \text{ou}}^{\text{ST}}$) were related by

$$\begin{pmatrix} Q_{j, \text{in}}^{\text{ST}} \\ Q_{j, \text{ou}}^{\text{ST}} \end{pmatrix} = \mathbf{Y}_j^{\text{ST}} \begin{pmatrix} P_{j, \text{in}}^{\text{ST}} \\ P_{j, \text{ou}}^{\text{ST}} \end{pmatrix}, \quad (8)$$

where $\mathbf{Y}_j^{\text{ST}}$ is the admittance of the whole ST model.

Equation (8) was rewritten in algebraic form to obtain

$$\begin{cases} P_{j, \text{in}}^{\text{ST}} = A Q_{j, \text{in}}^{\text{ST}} + B P_{j, \text{ou}}^{\text{ST}} \\ Q_{j, \text{ou}}^{\text{ST}} = C P_{j, \text{in}}^{\text{ST}} + D P_{j, \text{ou}}^{\text{ST}} \end{cases}, \text{ with } A = \frac{1}{Y_{j,11}^{\text{ST}}}, B = -\frac{Y_{j,12}^{\text{ST}}}{Y_{j,11}^{\text{ST}}}, C = Y_{j,21}^{\text{ST}}, D = Y_{j,22}^{\text{ST}}. \quad (9)$$

Since both the 1-D and 0-D models were solved in the time domain, equation (9) was further transformed to the time domain using convolution

$$\begin{cases} p_{j, \text{in}}^{\text{ST}}(t) = \int_0^T a(\tau) q_{j, \text{in}}^{\text{ST}}(t - \tau) d\tau + \int_0^T b(\tau) p_{j, \text{ou}}^{\text{ST}}(t - \tau) d\tau \\ q_{j, \text{ou}}^{\text{ST}}(t) = \int_0^T c(\tau) p_{j, \text{in}}^{\text{ST}}(t - \tau) d\tau + \int_0^T d(\tau) p_{j, \text{ou}}^{\text{ST}}(t - \tau) d\tau \end{cases}. \quad (10)$$

From Eq.(10), $p_{j, \text{in}}^{\text{ST}}$ and $q_{j, \text{ou}}^{\text{ST}}$ are determinable given $q_{j, \text{in}}^{\text{ST}}$ and $p_{j, \text{ou}}^{\text{ST}}$.

Further imposing continuity of hemodynamic variables at model interfaces, we have

$$\begin{cases} q_{j, \text{in}}^{\text{ST}} = q_{j, \text{ds}}^{\text{1D}}, p_{j, \text{in}}^{\text{ST}} = p_{j, \text{ds}}^{\text{1D}} \\ \sum_{j=1}^{J_{\text{up}}} q_{j, \text{ou}}^{\text{ST}} = q_{\text{up}, \text{in}}^{\text{0D}}, p_{j, \text{ou}}^{\text{ST}} = p_{\text{up}, \text{in}}^{\text{0D}} \end{cases}, \quad (11)$$

where $q_{j, \text{ds}}^{\text{1D}}, p_{j, \text{ds}}^{\text{1D}}$ are the flow rate and blood pressure at the distal end of the j th peripheral artery, and $q_{\text{up}, \text{in}}^{\text{0D}}, p_{\text{up}, \text{in}}^{\text{0D}}$ are the flow rate and blood pressure at the entrance of the 0-D model of the upper body. Note that the outflows of the ST models (with a total number of J_{up}) in the upper body converge to the entrance of

the 0-D model of the upper body, and that the interface hemodynamic conditions described by Eq. (11) are applicable to the lower-body vascular system as well.

Using Eqs. (10) and (11) we were able to interactively update hemodynamic variables at the boundaries of the 1-D, ST and 0-D models. Herein, an iterative algorithm was employed to solve Eqs. (10) and (11). At a numerical time step ($t = n\Delta t$), $q_{j,ds}^{1D}(=q_{j,in}^{ST})$ and $p_{up,in}^{0D}(=p_{j,ou}^{ST})$ were firstly guessed as a precondition of Eq.(10), the computed $p_{j,in}^{ST}(=p_{j,ds}^{1D})$ and $q_{j,ou}^{ST}(\sum_{j=1}^{J_{up}} q_{j,ou}^{ST} = q_{up,in}^{0D})$ were subsequently used as boundary conditions to solve the 1-D and 0-D models to update $q_{j,ds}^{1D}, p_{up,in}^{0D}$. In consideration of the closed-loop nature of the present model system, model couplings were simultaneously implemented at all model interfaces (a schematic description of the numerical procedure is given in Fig. 2), and, accordingly, convergence was judged based on a synthesized iterative error for flow rates (E_T) at the proximal and distal ends of the 1-D model,

$$E_T = \frac{1}{2} \left(\left| \frac{q_{pr}^{1D(k)} - q_{pr}^{1D(k-1)}}{\bar{q}} \right| + \frac{1}{J} \sum_{j=1}^J \left| \frac{q_{j,ds}^{1D(k)} - q_{j,ds}^{1D(k-1)}}{\bar{q}} \right| \right) < \varepsilon. \quad (12)$$

Here, j is the label number of a peripheral artery with J indicating the total number of peripheral arteries; k represents the current iteration step and $k-1$ the previous iteration step; subscripts ‘pr’ and ‘ds’ denote the proximal and distal ends of the arterial tree, respectively. The iterative error was normalized by the mean distal flow rate ($\bar{q} = \frac{1}{J} \sum_{j=1}^J q_{j,ds}^{1D}$) computed at the previous time step. ε was herein set to be 0.0001.

2.5 Parameter assignment

2.5.1 Baseline model parameters

The geometrical and mechanical parameters of arteries represented by the 1-D model and the parameters used in the 0-D model were initially assigned based on the data reported in previous studies [28,29]. Values of τ_σ and τ_ϵ in Eq.(3) and the parameters of the ST models were derived from [14]. Heart period was set to be 0.8s [10]. The parameter assignment enabled the model to reproduce the general

hemodynamic profile of a healthy young subject of 25 years old. The simulated subject was assumed to have a weight of 75kg and height of 175cm, with a body surface area (BSA) of 1.92m².

2.5.2 Parameter adjustments based on population-specific in vivo data

Severe hypertension is more prevalent in middle-aged to old subjects [30], and, in particular, middle-aged subjects with hypertension represent a subpopulation of special concern in studies related to hypertension. Therefore, the values of model parameters were further adjusted to fit model simulations to in vivo data measured in middle-aged subjects. Herein, two sets of in vivo data were used, with one set being acquired from normotensive subjects and the other set from hypertensive patients. The parameters selected for adjustment were those representing the major cardiovascular properties prone to the influence of aging or hypertension, such as the Young's moduli of the aorta and elastic arteries (E in Eq. (3)), the radii of distal arteries/arterioles (r_0 in Eq. (6)), the resistance of the capillary bed and the peak systolic elastance of the left ventricle (E_{lva} in Eq.(7)). Parameter adjustments for the middle-aged normotensive case were implemented mainly by incorporating the aging effects (such as the increases in aortic stiffness, diameter and peripheral vascular resistance with age) using the methods employed in previous studies [14,28], with the resulting parameter values being set as the control values. Parameter adjustments for hypertension were performed either based directly on available in vivo measurements or through data fitting. For instance, the increase of capillary resistance in hypertension was estimated to be 20% according to in vivo measurements [43]. The Young's moduli of the aorta and elastic arteries were increased by 52.9% relative to their control values to match the carotid-femoral pulse wave velocity (cfPWV) measured in hypertensive patients [4,6]. It is noted that when tuning E to fit model simulations to the measured cfPWV in hypertensive patients, the wall thicknesses of large arteries were fixed at their reference values, although arterial alterations associated with hypertension may involve both the structural and mechanical properties of arterial wall under in vivo conditions. The diameters of small arteries/arterioles in hypertensive patients have been found to be 7%-26%

smaller than those in normotensive subjects [11,17,22]. They were herein reduced by 8.23% to calibrate the model-simulated mean arterial pressure to in vivo measurements [24,31]. The Young's modulus of small arteries/arterioles was held at the control state according to the clinical finding that the mechanical properties of small arteries/arterioles do not differ significantly between hypertensive patients and normotensive subjects [20,54]. The contractility of the left ventricle may slightly increase as a consequence of adaptive response to increased arterial load in hypertension [23]. In the present study, E_{lva} was elevated by 29.2% relative to the control value so that the simulated cardiac index (cardiac output divided by BSA) was comparable to available in vivo data [13].

Model-simulated hemodynamic variables are compared with population-averaged in vivo measurements in Table 1. Our model reasonably captured the hemodynamic characteristics both in normotensive subjects and in patients with hypertension. Figure 3 shows the model-simulated pressure wave variations from the left ventricle towards the capillary bed along the vascular system of the left arm. An elevation of blood pressure was observed in all the vascular regions under the hypertensive condition. The degree of hypertension-associated blood pressure elevation was significantly diminished across the distal microvascular system, making the post-capillary blood pressure comparable between the hypertensive and normotensive cases, which is consistent with clinical observations [21].

2.6 Parameter sensitivity analysis

The model parameters selected for sensitivity analysis were those representing the major cardiovascular properties involved in the development of hypertension or as potential targets of antihypertensive treatment, such as cardiac function, stiffness of large arteries and structural properties of distal arteries/arterioles [11]. The selected parameters were categorized into three groups (i.e., cardiac, macrovascular and microvascular groups) according to the districts where they are defined. The cardiac parameters consisted of heart period (T_0) and the peak systolic elastance of the left ventricle (E_{lva} in Eq.(7), which represents the contractility of

the left ventricle), the macrovascular parameters were the Young's moduli (E in Eq.(3), which represents the effective arterial stiffness given that the wall thickness is fixed) of elastic arteries (including the aorta and the first-generation branching arteries of the aorta) and peripheral arteries, and the microvascular parameters included the radius and media-to-lumen ratio of distal arteries/arterioles (r_0 and h/r_0 in Eq.(6)) (for purpose of simplicity, the radius and media-to-lumen ratio of distal arteries/arterioles will be termed as arteriolar radius and arteriolar media-to-lumen ratio in the following text). The selected model parameters were respectively varied in certain ranges (see Table 2) that cover the bounds of cardiovascular states reported in clinical studies [4,5,11,23]. Herein, in view of the fact that the parameters differ in both physical unit and order of magnitude, parameter variations were expressed as percentage changes relative to the reference values (those assigned to simulate the baseline hypertensive conditions reported in Table 1) to facilitate inter-parameter comparisons. It is noted that the microvascular parameters were varied uniformly for all distal arteries/arterioles to simplify the sensitivity analysis, although the degrees of their changes under hypertensive conditions might vary along the vascular system and differ among organs/tissues [11].

Sensitivity analysis was initially implemented in a univariate manner (i.e., when a parameter was varied, other parameters were fixed at their reference states). Then, the hemodynamic effects of simultaneously varying multiple parameters were also studied where necessary. All parameter sensitivity analyses were performed using a computer program (written in FORTRAN language) of the model calibrated to the in vivo data of hypertensive patients. Each set of computer simulation started from fixed initial conditions and converged to a periodic solution after running for about 15 cardiac cycles. The results simulated in the last cardiac cycle were used for data analysis.

2.7 Data analysis

Our data analysis focused on hemodynamic variables of concern in the management of hypertension, such as aortic pressures (systolic, pulse and mean pressures at location 'B' in Fig.3), pre-capillary pressures

(pulse and mean pressures at location 'E' in Fig.3), flow pulsatility indices (defined as the amplitude of a flow wave divided by the mean flow rate) in different vascular regions, cardiac index, and the amplification ratio of pulse pressure from the ascending aorta (location 'B' in Fig.3) to the left brachial artery (location 'C' in Fig.3). The simulated hemodynamic variables (except for pre-capillary pressures) were expressed in form of percentage changes relative to the reference values, so that their sensitivities to model parameters can be intercompared. Moreover, hemodynamic variables in the ascending aorta (location 'B' in Fig.3) were analyzed to derive indices that characterize the conditions of wave reflection, such as the forward-traveling and backward-traveling components of pressure wave, input impedance and wave reflection coefficient.

3. Results

3.1 Hemodynamic effects of varying cardiac function

Figure 4 shows the simulated changes in hemodynamic variables when heart period and cardiac contractility were varied respectively in certain ranges. When heart period was prolonged, aortic pulse pressure (PP) was significantly increased despite remarkable decreases in aortic mean pressure (MP), and, in the meantime, moderate decreases in aortic systolic pressure (SP) and aortic-to-brachial pulse pressure amplification ratio (AR) were observed. The degrees of hemodynamic changes elicited by varying cardiac contractility were only mild to moderate, although all hemodynamic variables were related positively to the contractility of the heart.

3.2 Hemodynamic effects of varying macrovascular properties

Large arteries (herein termed macro-vasculatures) were divided into two subgroups, namely, the central elastic arterial subgroup and the peripheral muscular arterial subgroup. The effective stiffness of these arteries was varied by changing the Young's modulus of arterial wall while maintaining the wall thickness at the reference value. The results of numerical simulations showed that varying central arterial stiffness had remarkable influence on PP and moderate influence on SP and AR, but had negligible influence on MP and CI (see Fig.5(a)). Stiffening of central arteries tended to increase PP and SP but reduce AR. In comparison, varying the stiffness of peripheral arteries only induced mild hemodynamic changes (see Fig.5(b)), although the patterns of hemodynamic changes were similar to those resulting from varying central arterial stiffness.

3.3 Hemodynamic effects of varying microvascular properties

Reduced lumen area and increased media-to-lumen ratio represent the major microvascular alterations observed in hypertensive patients. Our results showed that reducing arteriolar radius significantly elevated MP and SP, considerably increased AR and slightly reduced CI, but with little influence on PP (see Fig.6(a)). Increasing arteriolar media-to-lumen ratio induced little hemodynamic changes except for a slight increase in PP (see Fig.6(b)).

3.4 Inter-parameter comparisons with respect to hemodynamic effects

Hemodynamic changes corresponding to $\pm 20\%$ variations in the model parameters are compared in Fig.7. MP was determined primarily by arteriolar radius, followed by heart period and cardiac contractility. SP was significantly affected by arteriolar radius and moderately affected by heart period and central arterial stiffness. PP was determined mainly by central arterial stiffness and heart period. AR was sensitive to arteriolar radius, heart period and central arterial stiffness. CI was dominated by heart period and moderately influenced by arteriolar radius and cardiac contractility. As expected, the trends of hemodynamic changes induced by a 20% increase in model parameters (Fig.7(a)) were opposite to those resulting from reducing the model parameters by 20% (Fig.7(b)), although the magnitudes of hemodynamic changes were different due to the nonlinear nature of the model. Corresponding to the hemodynamic changes presented in Fig.7, the results of wave analysis performed in the ascending aorta are illustrated in Fig.8. The variations of heart period, central arterial stiffness and arteriolar radius were observed to induce greatest changes in wave reflection conditions. In particular, varying heart period or central arterial stiffness - though having little influence on the static component of vascular load - significantly altered the spectrums of wave reflection coefficient and aortic input impedance, leading to marked changes in the timing and magnitude of reflected pressure wave.

Figure 9 further shows the changes in flow pulsatility indices along the vascular system (in the aorta, brachial artery, distal artery and capillary bed) in response to $\pm 20\%$ parameter variations. It was observed that heart period, central arterial stiffness and arteriolar radius were the factors with the greatest influence on flow pulsatility index (PI). Shortening heart period or decreasing central arterial stiffness induced an overall decrease in PI throughout the vascular system. Interestingly, when increasing arteriolar radius, PI was reduced in large arteries, but increased in distal artery and capillary bed.

3.5 Hemodynamic effects of simultaneously varying central arterial stiffness and arteriolar radius

In consideration of the nonlinear relationships between hemodynamic variables and cardiovascular properties, single-factor sensitivity analyses performed under a fixed cardiovascular condition carry a risk of

missing important phenomena that may occur under other conditions. Herein, central arterial stiffness and arteriolar radius, which have been found to have remarkable hemodynamic effects, were varied in an intercrossing way to virtually generate various cardiovascular conditions. Obtained results showed that hemodynamic changes induced by varying one factor were considerably influenced by the state of the other (see Fig.10). For instance, with higher central arterial stiffness, increasing arteriolar radius resulted in greater decrease in SP but less decrease in AR. The effects on PP of varying arteriolar radius exhibited a more complicated association with arterial stiffness. With low central arterial stiffness, increasing arteriolar radius tended to elevate PP, but the trend was gradually changed into reducing PP following the increase of central arterial stiffness. Similarly, the state of arteriolar radius considerably influenced the degrees of hemodynamic changes induced by varying central arterial stiffness. Specifically, reducing central arterial stiffness led to a more evident decrease in PP and increase in AR in the presence of smaller arteriolar radius.

3.6 Sensitivity of microvascular blood pressure to cardiovascular properties

Figure 11 shows the changes in the pulsatile and static components of pre-capillary blood pressure (at location 'E' in Fig.3) with the variations of model parameters. Increasing central arterial stiffness and arteriolar radius was observed to significantly enhance the pulsatility (i.e., the magnitude of pulse pressure) of pre-capillary pressure. As for the static component, a considerable pressure elevation was observed following the decrease in heart period or increase in arteriolar radius.

4. Discussion

4.1 Methodological novelty

In the present study, a multi-scale model of the cardiovascular system was developed to quantitatively address hemodynamic problems related to hypertension, aiming to establish a theoretical basis for interpreting clinical data and exploring new clues to treating hypertension. In comparison with traditional clinical studies, model-based numerical experiments enable quantitative assessment of the inherent relationships between hemodynamic variables and cardiovascular properties, without suffering from the limitations of traditional clinical studies, which are often restricted by available in vivo measurements and complicated by inter-patient differences. In the literature, a large number of computational models have been employed to address various aspects of cardiovascular hemodynamics, spanning from lumped-parameter (0-D) formulations focusing on simulating systemic hemodynamics and the dynamic behaviors of hemodynamic regulation [16,18,26] to one-dimensional (1-D) frameworks dedicated to describing flow distribution and pulse wave propagation in the arterial or venous system [3,7,28,29,36,37,38,45,48]. 0-D

models cannot simulate pulse wave propagation phenomena [12,49], and most 1-D models adopted a highly simplified windkessel representation of distal vascular systems, which not only discard the structural information of distal arteries/arterioles but also are defective in simulating wave propagation/reflection phenomena at the microvascular level [14]. Our study was the first to integrate the main cardiovascular components (e.g., the heart, large arteries and distal arteries/arterioles) prone to alterations in hypertension into a unique model system for the study of hypertension. The resulting model enabled a simultaneous simulation of pulse wave propagation in the arterial tree, wave reflections in distal arteries/arterioles and systemic hemodynamic interaction, thus furnishing a practical tool for quantifying the hemodynamic effects of various cardiovascular properties under hypertensive conditions.

4.2 Determinant cardiovascular factors for hemodynamic variables and associated clinical implications

Our numerical experiments demonstrated that heart period, the stiffness of central (elastic) arteries and the radius of distal arteries/arterioles are the determinant cardiovascular factors for arterial blood pressures. Although the results of our factor identification study are basically a confirmation of the well-documented knowledge of cardiovascular physiology, the model-based study for the first time systemically compared various cardiovascular factors with respect to the degree and the way in which they affect arterial pressures under hypertensive conditions. In particular, our study revealed the considerable interplay between central arterial stiffness and arteriolar radius in the regulation of arterial pressures. From the results presented in Fig.10, the decreases in SP and PP accompanying the MP lowering effect of dilating distal arteries/arterioles are more evident when the stiffness of central arteries is high, which implies that patients with stiffer arteries might benefit specially from vasodilation agents. On the other hand, the beneficial hemodynamic consequences (characterized by the decrease in PP and increase in AR) of reducing central arterial stiffness are more pronounced in the presence of smaller arteriolar radius, implying that patients with severe concentric remodeling of distal arteries/arterioles would benefit specially from drugs capable of improving the mechanical properties of large arteries. These model-based findings highlight the importance of comprehensively considering patient-specific cardiovascular conditions when selecting anti-hypertensive drugs or exploring the mechanisms underlying hemodynamic changes associated with anti-hypertensive treatment.

In addition to the findings regarding the sensitivity of blood pressures to cardiovascular factors, our study demonstrated that flow pulsatility indices in the peripheral and distal arteries correlated positively with central arterial stiffness and heart period, which is basically concordant with the results reported in previous

clinical studies [34,59]. A new finding is that arteriolar dilation (i.e., increase in arteriolar diameter) - though having an effect of reducing flow pulsatility in large arteries - enhances flow pulsatility in distal small vessels (see Fig. 9). The phenomenon is related to the dependence of wave reflections in the arteriolar tree (represented by the ST model) on arteriolar dimension. An increase in arteriolar diameter will reduce the impedance of the arteriolar tree, allowing more pulsatile power in upstream large arteries to be transmitted down to the capillary bed. Given the clinical consensus that exposure of small vessels to highly pulsatile flow and pressure exacerbates microvascular damage and organic dysfunction (e.g., renal insufficiency, intellectual deterioration) [34,40], beyond the pressure-lowering and flow pulsation-inhibiting effects in large arteries, the biological impact of hemodynamic changes associated with microvascular dilation might deserve further study.

Although hemodynamic variables in large arteries have been extensively investigated, blood pressure in the microcirculation remains rarely addressed in the context of anti-hypertensive treatment. Our study provided some preliminary insights into the dependence of pre-capillary (or post-arteriolar) pressure on cardiovascular properties. Main findings are twofold (see Fig. 11): (1) arteriolar radius is an important determinant of both the pulsatile and static components of pre-capillary pressure; (2) central arterial stiffness and heart period significantly affect the pulsatile and static components, respectively. Notably, because distal arteries/arterioles are located in-between large arteries and the capillary bed, dilating distal arteries/arterioles remarkably increases pre-capillary mean and pulse pressures, as opposed to its effects on aortic pressure, which is similar to the phenomenon observed for flow pulsatility index. The clinical relevance of these findings remains unclear. In particular, there might be changes in the viscous resistance of the capillary bed (having been held constant in the sensitivity analyses) secondary to the normalization of upstream arterioles, which would further complicate microvascular hemodynamic changes associated with anti-hypertensive treatment. To clarify the issue, clinical studies capable of simultaneously monitoring the responses of macrovascular and microvascular hemodynamic variables to anti-hypertensive treatment would be warranted.

4.3 Insights into the differential hemodynamic consequences of various anti-hypertensive drugs

Administration of β -blockers in hypertensive patients has been found to induce less decrease in arterial pulse pressure despite its obvious efficacy in normalizing mean blood pressure [5,32,35]. That is to say, β -blockers have differential effects on the static and pulsatile components of arterial blood pressure. Clinically observed cardiovascular changes associated with β -blockers were featured mainly by a pronounced reduction of heart rate (amount to prolongation of heart period) and a moderate decrease of

aortic pulse wave velocity [10,32]. Our numerical results showed that prolonging heart period significantly reduced aortic mean pressure, but at the expense of increasing aortic pulse pressure and diminishing aortic-to-brachial pulse pressure amplification ratio (see Fig.4 and Fig.7), which are basically consistent with previous clinical observations [5]. In contrast, reducing the stiffness of central arteries (amount to reducing aortic pulse wave velocity) evidently reduced aortic pulse pressure, although its effect on mean blood pressure was negligible (see Fig.5 and Fig.7). Pulse wave analysis revealed that the differential hemodynamic consequences of prolonging heart period and reducing central arterial stiffness were attributable to their opposite effects on aortic input impedance and wave reflection coefficient (see Fig.8). These model-based findings indicate that prolongation of heart period and decrease of central arterial stiffness play counteractive roles in regulating arterial pulse pressure in the context of anti-hypertensive treatment with β -blockers and, hence, simultaneously monitoring the two factors would favor a better understanding of clinical observations.

In comparison with β -blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) were found to have more favorable hemodynamic consequences, as characterized by a marked decrease in both aortic systolic pressure and pulse pressure, and a considerable increase in aortic-to-brachial pulse pressure amplification ratio (AR) [5,10,31,61]. The pressure-lowering effects of ACEIs and ARBs are generally considered to be mediated mainly by the relaxation and dilatation of distal resistant vessels [9,19,46]. Our numerical results showed that dilating distal arteries/arterioles resulted in a significant decrease in both aortic systolic pressure and mean pressure, but with mild influence on aortic pulse pressure (see Fig.6 and Fig.7). Interestingly, it was found that dilating distal arteries/arterioles tended to reduce the aortic-to-brachial pulse pressure amplification ratio (AR), which seems contrary to the clinical observation that AR slightly increased (by approximately 2%~9%) following anti-hypertensive therapy with ACEIs or ARBs [5,10,32]. Our wave analysis revealed that the reduction in AR with arteriolar dilation was related to the attenuation of wave superposition effects in large arteries during systole due to reduced wave reflections originating from dilated distal vessels. Normalization of the media-to-lumen ratio of distal vessels is another typical vascular consequence of ACEIs and ARBs that differs from β -blockers [9,46]. In view of the fact that the media-to-lumen ratio of distal vessels can increase by up to 100% in hypertensive patients compared to normotensive subjects [11], normalization of this factor may be expected to decrease aortic pulse pressure according to the results presented in Fig.6, but plays little role in increasing AR. Taken all together, it seems that structural ameliorations of distal arteries/arterioles alone cannot fully account for the selected pressure-lowering effects of ACEIs and ARBs in the aorta. In consideration of the remarkable

effects of central arterial stiffness on aortic pulse pressure and AR (see Fig.5 and Fig.7), the decrease of arterial stiffness should be another coexisting mechanism behind the clinically observed hemodynamic changes associated with ACEIs or ARBs.

According to clinical data reported in the literature, the decrease of central arterial stiffness seems to be a common phenomenon associated with anti-hypertensive treatment, without significant differences being observed among traditional anti-hypertensive agents (e.g., β -blockers versus ACEIs) [5,10,32], which implies that the decrease of arterial stiffness might be a consequence of reduced mechanical load of arterial wall secondary to the pressure lowering effect. Nevertheless, allowing for potential inter-patient differences in baseline cardiovascular conditions and the model-based findings regarding the hemodynamic effects of central arterial stiffness and its interaction with other cardiovascular factors in hemodynamic regulation, the stiffness of central arteries should be a nonnegligible factor when interpreting patient-specific hemodynamic data, no matter what type of anti-hypertensive agent is used.

4.4 Limitations and future work

The present study focuses on quantifying the hemodynamic impacts of various cardiovascular properties by means of single-factor sensitivity analysis based on a hemodynamic model calibrated to population-averaged data. As a matter of fact, hemodynamic conditions differ among patients and cardiovascular factors are interrelated under in vivo conditions due to the existence of various short-term regulatory and long-term adaptive mechanisms. That is to say, when one cardiovascular factor is altered, the associated hemodynamic changes would induce changes in other cardiovascular factors. This is especially true in the context of anti-hypertensive treatment. Therefore, the model-based findings would rather serve as a theoretical reference for interpreting clinical data than predict the hemodynamic consequence of anti-hypertensive treatment for a specific patient. Moreover, while the present study focuses on investigating the hemodynamic effects of cardiac function and the structural/mechanical properties of blood vessels, it should be stressed that the total blood volume contained in the cardiovascular system (which has been kept constant in this study) is an important determinant factor for cardiac stroke volume and may have influence on arterial pulse and mean pressures, which may be of especial importance to the treatment of hypertension of renal origin. With regard to the modeling of distal arteries/arterioles, the adopted ST modeling method has been established based on a linearization of the 1-D momentum equation and the pressure-area state equation [39], which makes the ST model unable to precisely account for the effect of pressure-dependent change in vascular cross-sectional area along the axis on pulse wave propagation. However, the influence of the defect is believed to be small given the fact that distal arteries/arterioles are much stiffer than proximal large

arteries. Nevertheless, performing a deliberate validation work by, for example, comparing a ST model with a 1D model, would provide more direct and authentic evidence for clarifying the influence. In addition, connecting the distal ends of the ST models in the upper-or lower-body to a unique capillary bed amounts to assuming that all pressure waves leaving the ST models are in phase, although they may differ among tissues/organs under in vivo conditions. The assumption may compromise the fidelity of hemodynamic simulation in post-arteriolar vessels and make the effective impedance of distal vessels dependent on the phase-matching state of pressure waves. The influence is expected to be especially evident upon variations in heart period when the frequency spectrums of pressure waves and patterns of wave superimposition are significantly altered. This may partly explain the model-simulated mild change in aortic input impedance with heart period and the asymmetric sensitivities of capillary pulse pressure and flow pulsatility index to heart period. To solve the problem, connecting the distal end of each ST model to a specific capillary bed would be necessary, although the complexity of model and associated computational cost will increase considerably. Specifically to the issues addressed in the present study, structural alterations associated with hypertension have been assumed to be uniform across the structured tree and among different organs/tissues. In fact, it remains poorly understood whether microvascular changes in hypertension differ significantly among organs/tissues, since in vivo plethysmographic studies are usually limited to small subcutaneous or omental arteries [11]. Furthermore, structural changes of distal arteries/arterioles are usually accompanied by changes in vascular reactivity which will become important for hemodynamic regulation under stress [9,11,46]. Such mechanisms were not incorporated in the present model since we focused on hemodynamic phenomena under resting conditions. Models capable of overcoming the limitations related to model construction or accounting for hemodynamic regulatory mechanisms would be expected to deepen the understanding of hemodynamic characteristics under hypertensive conditions, although improvements of modeling methods and sufficient data support from in vivo studies would be required.

5. Conclusions

A multi-scale model of the cardiovascular system has been constructed to quantitatively investigate the hemodynamic impacts of various cardiovascular factors under hypertensive conditions. Numerical experiments demonstrated that heart period, central arterial stiffness and arteriolar radius were the major determinant factors for hemodynamic variables of concern in the treatment of hypertension. In particular, our study revealed that structural normalization of distal vessels alone could not fully account for the selected pressure-lowering effects in the aorta unless the stiffness of central arteries was reduced simultaneously,

which highlighted the importance of normalizing central arterial stiffness in the management of hypertension. Moreover, the model-based findings regarding the interactional roles of central arterial stiffness and arteriolar radius in hemodynamic regulation implied the potential clinical significance of selecting anti-hypertensive drugs based on patient-specific cardiovascular conditions.

Conflic of interest statement

There are no conflicts of interest in this study from any of the authors.

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Reference

- [1] Agabiti-Rosei, E., Mancia, G., O'Rourke, M. F., Roman, M. J., Safar, M. E., Smulyan, H., Wang, J. G., Wilkinson, I. B., Williams, B., Vlachopoulos, C., 2007, "Central blood pressure measurements and antihypertensive therapy: a consensus document," *Hypertension*, 50(1), pp. 154-160.
- [2] Alastruey J., Khir A. W., Matthys K. S., Segers P., Sherwin S. J., Verdonck P. R., Parker K. H., Peiró J., 2011, "Pulse wave propagation in a model human arterial network: Assessment of 1-D visco-elastic simulations against in vitro measurements," *J. Biomech*, 44(12), pp. 2250-2258.
- [3] Alastruey, J., Parker, K. H., Sherwin, S. J., 2012, "Arterial pulse wave haemodynamics," In Anderson S (Ed.), 11th International Conference on Pressure Surges, Virtual PiE Led t/a BHR Group, Chapter 7, 401–442, (ISBN: 978-1-85598-133-1).
- [4] Asmar, R., Benetos, A., London, G., Hugue, C., Weiss, Y., Topouchian, J., Laloux, B., Safar, M., 1995, "Aortic distensibility in normotensive, untreated and treated hypertensive patients," *Blood Press*, 4(1), pp. 48-54.
- [5] Asmar, R. G., London, G. M., O'Rourke, M. E., Safar, M. E., 2001, "Improvement in blood pressure, arterial stiffness and wave reflections with a very low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol," *Hypertension*, 38, pp. 922-926.

- [6] Benetos, A., Adamopoulos, C., Bureau, J. M., Temmar, M., Labat, C., Bean, K., Thomas, F., Pannier, B., Asmar, R., Zureik, M., Safar, M., Guize, L., 2002, "Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period," *Circulation*, 105(10), pp. 1202-1207.
- [7] Blanco, P. J., Watanabe, S. M., Dari, E. A., Passos, M. A. R. F., Feijóo, R. A., 2014, "Blood flow distribution in an anatomically detailed arterial network model: criteria and algorithms," *Biomech. Model Mechanobiol.*, 13(6), pp. 1303-1330.
- [8] Cloud, G. C., Rajkumar, C., Kooner, J., Cooke, J., Bulpitt, C. J., 2003, "Estimation of central aortic pressure by SphygmoCor requires intra-arterial peripheral pressures," *Clin. Sci. (Lond)*, 105(2), pp. 219-225.
- [9] Debbabi, H., Bonnin, P., Levy, B. I., 2010, "Effects of blood pressure control with perindopril/indapamide on the microcirculation in hypertensive patients," *Am. J. Hypertens*, 23(10), pp. 1136-1143.
- [10] Dhakam, Z., McEniery, C. M., Cockcroft, J. R., Brown, M. J., Wilkinson, I. B., 2006, "Atenolol and eprosartan: differential effects on central blood pressure and aortic pulse wave velocity," *Am. J. Hypertens*, 19(2), pp. 214-219.
- [11] Feihl, F., Liaudet, L., Levy, B. I., Waeber, B., 2008, "Hypertension and microvascular remodelling," *Cardiovasc Res.*, 78(2), pp. 274-285.
- [12] Formaggia, L., Lamponi, D., Tuveri, M., Veneziani, A., 2006, "Numerical modeling of 1D arterial networks coupled with a lumped parameters description of the heart," *Comput. Methods Biomech. Biomed. Engin.*, 9(5), pp. 273-288.
- [13] Ganau, A., Devereux, R. B., Roman, M. J., De Simone, G., Pickering, T. G., Saba, P. S., Vargiu, P., Simongini, I., Laragh, J. H., 1992, "Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension," *J. Am. Coll. Cardiol.*, 19(7), pp. 1550-1558.
- [14] Guan, D., Liang, F., Gremaud, P. A., 2016, "Comparison of the Windkessel model and structured-tree model applied to prescribe outflow boundary conditions for a one-dimensional arterial tree model," *J. Biomech.*, 49(9), pp. 1583-1592.
- [15] Gueyffier, F., Bulpitt, C., Boissel, J. P., Schron, E., Ekblom, T., Fagard, R., Casiglia, E., Kerlikowske, K., Coope, J., 1999, "Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials," *INDANA Group. Lancet*, 353(9155), pp. 793-796.
- [16] Guyton, A. C., Montani, J. P., Hall, J. E., Manning, R. D. Jr., 1988, "Computer models for designing hypertension experiments and studying concepts," *Am. J. Med. Sci.*, 295(4), pp. 320-326.
- [17] Heagerty, A. M., Aalkjaer, C., Bund, S. J., Korsgaard, N., Mulvany, M.J., 1993, "Small artery structure in hypertension. Dual processes of remodeling and growth," *Hypertension*, 21(4), pp. 391-397.
- [18] Heldt, T., Shim, E. B., Kamm, R. D., Mark, R. G., 2002, "Computational modeling of cardiovascular response to orthostatic stress," *J. Appl. Physiol.*, 92(3), pp. 1239-1254.
- [19] Hughes, A. D., Stanton, A. V., Jabbar, A. S., Chapman, N., Martinez-Perez, M. E., McG, Thom, S. A., 2008, "Effect of antihypertensive treatment on retinal microvascular changes in hypertension," *J.*

Hypertens., 26(8), pp. 1703-1707.

- [20] Intengan, H. D., Schiffrin, E. L., 2000, "Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants," *Hypertension*, 36(3), pp. 312-318.
- [21] James, M. A., Tulleit, J., Hemsley, A. G., Shore, A. C., 2006, "Effects of aging and hypertension on the microcirculation," *Hypertension*, 47(5), pp. 968-74.
- [22] Korsgaard, N., Aalkjaer, C., Heagerty, A. M., Izzard, A. S., Mulvany, M. J., 1993, "Histology of subcutaneous small arteries from patients with essential hypertension," *Hypertension*, 22, pp. 523-526.
- [23] Lam, C. S., Shah, A. M., Borlaug, B. A., Cheng, S., Verma, A., Izzo, J., Oparil, S., Aurigemma, G. P., Thomas, J. D., Pitt, B., Zile, M. R., Solomon, S. D., 2013, "Effect of antihypertensive therapy on ventricular-arterial mechanics, coupling, and efficiency," *Eur. Heart J.*, 34(9), pp. 676-683.
- [24] Laurent, S., Girerd, X., Mourad, J. J., Lacolley, P., Beck, L., Boutouyrie, P., Mignot, J. P., Safar, M., 1994, "Elastic modulus of the radial artery wall material is not increased in patients with essential hypertension," *Arterioscler Thromb*, 14(7), pp. 1223-1231.
- [25] Levy, B. I., Ambrosio, G., Pries, A. R., Struijker-Boudier, H. A., 2001, "Microcirculation in hypertension: a new target for treatment?" *Circulation*, 104(6), pp. 735-740.
- [26] Liang, F. Y., Liu, H., 2006, "Simulation of hemodynamic responses to the valsalva maneuver: an integrative computational model of the cardiovascular system and the autonomic nervous system," *J. Physiol. Sci.*, 56(1), pp. 45-65.
- [27] Liang, F. Y., Sugimoto, K., Matsuo, K., Liu, H., Takagi, S., 2014, "Patient-specific assessment of cardiovascular function by combination of clinical data and computational model with applications to patients undergoing Fontan operation," *Int. J. Numer. Method Biomed. Eng.*, 30(10), pp. 1000-1018.
- [28] Liang, F. Y., Takagi, S., Himeno, R., Liu, H., 2009, "Biomechanical characterization of ventricular-arterial coupling during aging: A multi-scale model study," *J. Biomech.*, 42(6), pp. 692-704.
- [29] Liang, F. Y., Takagi, S., Himeno, R., Liu, H., 2009, "Multi-scale modeling of the human cardiovascular system with applications to aortic valvular and arterial stenoses," *Med. Biol. Eng. Comput.*, 47(7), pp. 743-755.
- [30] Lloyd-Jones, D. M., Evans, J. C., Levy, D., 2005, "Hypertension in adults across the age spectrum: current outcomes and control in the community," *J. A. M. A.*, 294(4), pp. 466-472.
- [31] London, G. M., Asmar, R. G., O'Rourke, M. F., Safar, M. E., REASON Project Investigators, 2004, "Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol," *J. Am. Coll. Cardiol.*, 43(1), pp. 92-99.
- [32] Mackenzie, I. S., McEniery, C. M., Dhakam, Z., Brown, M. J., Cockcroft, J. R., Wilkinson, I. B., 2009, "Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension," *Hypertension*, 54(2), pp. 409-413.

- [33] Mathiassen, O. N., Buus, N. H., Larsen, M. L., Mulvany, M. J., Christensen, K. L., 2007, "Small artery structure adapts to vasodilatation rather than to blood pressure during antihypertensive treatment," *J. Hypertens.*, 25(5), pp. 1027-1034.
- [34] Mitchell G. F., van Buchem M. A., Sigurdsson S., Gotlib J. D., Jonsdottir M. K., Kjartansson Ó., Garcia M., Aspelund T., Harris T. B., Gudnason V., Launer L.J., 2011, "Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study," *Brain*, 134(Pt 11), pp. 3398-3407.
- [35] Morgan, T., Lauri, J., Bertram, D., Anderson, A., 2004, "Effect of different antihypertensive drug classes on central aortic pressure," *Am. J. Hypertens.*, 17(2), pp. 118-123.
- [36] Müller, L. O., Toro, E. F., 2014, "A global multiscale mathematical model for the human circulation with emphasis on the venous system," *Int. J. Numer. Meth. Biomed. Engng.*, 30(7), pp. 681-725.
- [37] Mynard, J. P., Nithiarasu, P., 2008, "A 1D arterial blood flow model incorporating ventricular pressure, aortic valve and regional coronary flow using the locally conservative Galerkin (LCG) method," *Commun. Numer. Meth. En.*, 24(5), pp. 367-417.
- [38] Mynard, J. P., Smolich, J.J., 2015, "One-dimensional haemodynamic modeling and wave dynamics in the entire adult circulation," *Ann. Biomed. Eng.*, 43(6), pp. 1443-1460.
- [39] Olufsen, M. S., Peskin, C. S., Kim, W. Y., Pedersen, E. M., Nadim, A., Larsen, J., 2000, "Numerical simulation and experimental validation of blood flow in arteries with structured-tree outflow conditions," *Ann. Biomed. Eng.*, 28(11), pp. 1281-1299.
- [40] O'Rourke M. F., Safar M. E., 2005, "Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy," *Hypertension*, 46(1), pp. 200-204.
- [41] Papaioannou, T. G., Protogerou, A. D., Stamatelopoulos, K. S., Vavuranakis, M., Stefanadis, C., 2009, "Non-invasive methods and techniques for central blood pressure estimation: procedures, validation, reproducibility and limitations," *Curr. Pharm. Des.*, 15(3), pp. 245-253.
- [42] Pini, R., Cavallini, M. C., Palmieri, V., Marchionni, N., Di Bari, M., Devereux, R. B., Masotti, G., Roman, M. J., 2008, "Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomano Study," *J. Am. Coll. Cardiol.*, 51(25), pp. 2432-2439.
- [43] Prasad, A., Dunnill, G. S., Mortimer, P. S., MacGregor, G. A., 1995, "Capillary rarefaction in the forearm skin in essential hypertension," *J. Hypertens.*, 13(2), pp. 265-268.
- [44] Qureshi, M. U., Vaughan, G. D. A., Sainsbury, C., Johnson, M., Peskin, C. S., 2014, "Olufsen MS, Hill NA. Numerical simulation of blood flow and pressure drop in the pulmonary arterial and venous circulation," *Biomech. Model. Mechanobiol.*, 13(5), pp. 1137-1154.
- [45] Reymond, P., Merenda, F., Perren, F., Rufenacht, D., Stergiopoulos, N., 2009, "Validation of a one-dimensional model of the systemic arterial tree," *Am. J. Physiol. Heart Circ. Physiol.*, 297(1), pp. H208-H222.
- [46] Schiffrin, E. L., Park, J. B., Pu, Q., 2002, "Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function," *J. Hypertens.*, 20(1), pp. 71-78.

- [47] Sharman, J.E., Marwick, T.H., Gilroy, D., Otahal, P., Abhayaratna, W.P., Stowasser, M., Value of Central Blood Pressure for GUIDing ManagEment of Hypertension Study Investigators, 2013, "Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study," *Hypertension*, 62(6), pp. 1138-1145.
- [48] Sherwin, S. J., Franke, V., Peiró, J., Parker, K., 2003, "One-dimensional modelling of a vascular network in space-time variables," *J. Eng. Math.*, 47(3-4), pp. 217-250.
- [49] Shi, Y., Lawford, P., Hose, R., 2011, "Review of zero-D and 1-D models of blood flow in the cardiovascular system," *Biomedical Engineering Online*, 10(1), pp. 33.
- [50] Smulyan, H., Siddiqui, D. S., Carlson, R. J., London, G. M., Safar, M. E., 2003, "Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses," *Hypertension*, 42(2), pp. 150-155.
- [51] Stergiopulos, N., Young, D. F., Rogge, T. R., 1992, "Computer simulation of arterial flow with applications to arterial and aortic stenoses," *J. Biomech.*, 25(12), pp. 1477-1488.
- [52] Struijker, Boudier, H. A., Cohuet, G. M., Baumann, M., Safar, M. E., 2003, "The heart, macrocirculation and microcirculation in hypertension: a unifying hypothesis," *J. Hypertens. Suppl.*, 21(3), pp. S19-S23.
- [53] Sun, Y., Beshara, M., Lucariello, R. J., Chiaramida, S. A., 1997, "A comprehensive model for right-left heart interaction under the influence of pericardium and baroreflex," *Am. J. Physiol.*, 272(3 Pt 2), pp. H1499-H1515.
- [54] Thybo, N. K., Mulvany, M. J., Jastrup, B., Nielsen, H., Aalkjaer, C., 1996, "Some pharmacological and elastic characteristics of isolated subcutaneous small arteries from patients with essential hypertension," *J. Hypertens.*, 14(8), pp. 993-998.
- [55] Turnbull, F., 2003, "Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials," *Lancet*, 362(9395), pp. 1527-1535.
- [56] Van, Bortel, L. M., Struijker-Boudier, H. A., Safar, M. E., 2001, "Pulse pressure, arterial stiffness, and drug treatment of hypertension," *Hypertension*, 38(4), pp. 914-921.
- [57] Vaughan, G. D. A., 2010, "Pulse propagation in the pulmonary and systemic arteries," PhD Thesis, Faculty of Information and Mathematical Sciences, University of Glasgow, UK.
- [58] Vlachopoulos, C., Aznaouridis, K., O'Rourke, M. F., Safar, M. E., Baou, K., Stefanadis, C., 2010, "Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis," *Eur. Heart J.*, 31(15), pp. 1865-1871.
- [59] Xu T. Y., Staessen J. A., Wei F. F., Xu J., Li F. H., Fan W. X., Gao P. J., Wang J. G., Li Y., 2012, "Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation," *Am. J. Hypertens.*, 25(3), pp. 319-324.
- [60] Wang, K. L., Cheng, H. M., Chuang, S. Y., Spurgeon, H. A., Ting, C. T., Lakatta, E. G., Yin, F. C., Chou, P., Chen, C. H., 2009, "Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality?" *J. Hypertens.*, 27(3), pp. 461-467.

[61] Williams, B., Lacy, P. S., Thom, S. M., Cruickshank, K., Stanton, A., Collier, D., Hughes, A. D., Thurston, H., O'Rourke, M., CAFE Investigators, Anglo-Scandinavian Cardiac Outcomes Trial Investigators, CAFE Steering Committee and Writing Committee, 2006, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study," *Circulation*, 113(9), pp. 1213-1225.

Captions

Table 1 Comparisons of model-simulated hemodynamic variables with in vivo measurements. Abbreviations: BSP, brachial systolic pressure; BDP, brachial diastolic pressure; BPP, brachial pulse pressure; BMP, brachial mean pressure; CI, cardiac index; cfPWV, carotid-femoral pulse wave velocity.

Table 2 Ranges of parameter variations applied in the sensitivity analysis study. Notations: T_0 , heart period; E_{lva} , peak ventricular elastance in systole; E_c , Young's modulus of central arteries; E_p , Young's modulus of peripheral arteries; r_d , radius of distal arteries/arterioles; W_d , media-to-lumen ratio of distal arteries/arterioles.

Fig.1 Schematic description of multi-scale modeling of the cardiovascular system. The fifty-five largest arteries are represented by a one-dimensional (1-D) model and distal arteries/arterioles are mimicked by structured-tree (ST) models. The 1-D model is coupled with the ST models at the distal ends of peripheral arteries and further integrated into a lumped-parameter (0-D) model of the remaining cardiovascular portions. It is noted that blood flows through the ST models are assumed to converge respectively to the upper-body and lower-body capillary beds to simplify the modeling work.

Fig.2 Flowchart of the numerical scheme employed to couple the 0-D, 1-D and ST models. Notations: $n\Delta t$, current time step; $(n+1)\Delta t$, next time step; k , iteration step; $w_{1,j}$, forward-traveling Riemann invariant at the distal end of the j th peripheral artery; w_2 , backward-traveling Riemann invariant at the root of the ascending aorta. See the text for further details of notations.

Fig.3 Model-simulated pressure wave variations from the heart towards the capillary bed along the vascular system of the left arm (normotensive vs hypertensive). Locations: A, left ventricle; B, middle of the ascending aorta; C, middle of the brachial artery; D, distal end of the radial artery (i.e., inlet of the ST model); E, distal end of arterioles (i.e., outlet of the ST model or inlet of the capillary bed); F, distal end of the capillary bed.

Fig.4 Changes of hemodynamic variables with variations in cardiac parameters ((a), heart period; (b), peak systolic elastance of the left ventricle). Abbreviations: MP, mean aortic pressure; SP, aortic systolic pressure; PP, aortic pulse pressure, AR, pulse pressure amplification ratio from the aorta to the branchial artery; CI, cardiac index. The reference values of MP, SP, PP, AR and CI are 123.38 mmHg, 152.33 mmHg, 58.20 mmHg, 1.23 and 2.77 l/min/m², respectively. The abbreviations and reference values will be used throughout the paper unless stated elsewhere.

Fig.5 Changes of hemodynamic variables with variations in macrovascular parameters ((a), stiffness of central arteries; (b), stiffness of peripheral arteries).

Fig.6 Changes of hemodynamic variables with variations in microvascular parameters ((a), radius of distal arteries/arterioles; (b), media-to-lumen ratio of distal arteries/arterioles).

Fig.7 Hemodynamic changes induced by $\pm 20\%$ variations in model parameters relative to the reference values ((a),

parameter value +20%; (b), parameter value -20%).

Fig.8 $\pm 20\%$ parameter variations-induced changes in the forward-traveling (P_f) and backward-traveling (P_b) components of pulse pressure, the modulus of input impedance (Z_{in}) and the modulus of wave reflection coefficient (I) in the ascending aorta (from left to right). See the caption of Table 2 for the notations of model parameters. Herein, the subscript '0' denotes the reference state of each parameter.

Fig.9 Changes in flow pulsatility indices along the vascular system induced by $\pm 20\%$ variations in model parameters relative to the reference values ((a), parameter value +20%; (b), parameter value -20%). The distal arterial flow pulsatility index is monitored in the distal segment of the left radial artery, and the capillary flow pulsatility index is calculated based on the simulated flow wave through the upper-body capillary bed. The flow pulsatility indices computed under the reference conditions are 6.11, 3.74, 2.28 and 0.13 in the aorta, brachial artery, distal artery and capillary bed, respectively.

Fig.10 Surface plots of hemodynamic changes induced by combined variations in central arterial stiffness and arteriolar radius ((a), MP; (b), SP; (c), PP; (d), AR). The numbers in the white boxes denote the amounts of hemodynamic changes when arteriolar radius is changed from the -10% state to the +20% state (relative to the reference value).

Fig.11 Changes of pre-capillary pressure with variations in model parameters ((a), pulse pressure; (b), mean pressure)

Table 1

Hemodynamic variables	Normotensive		Hypertensive	
	Simulation	In vivo measurement	Simulation	In vivo measurement
BSP (mmHg)	123	$125 \pm 9^{[4]}$, $128 \pm 2^{[24]}$, $128 \pm 0.7^{[6]}$	164	$164 \pm 13^{[4]}$, $165 \pm 25^{[24]}$
BDP (mmHg)	71	$77 \pm 8^{[4]}$, $71 \pm 13^{[24]}$, $78.4 \pm 0.5^{[6]}$	93	$102 \pm 9^{[4]}$, $96 \pm 24^{[24]}$
BPP (mmHg)	52	$49.6 \pm 0.4^{[6]}$	71	$68 \pm 16.5^{[31]}$
BMP (mmHg)	92.5	$90 \pm 15^{[24]}$, $94.9 \pm 0.5^{[6]}$	122	$121 \pm 24^{[24]}$, $120 \pm 7^{[31]}$
CI (l/min/m ²)	3.19	$2.9 \pm 0.7^{[13]}$	2.77	$2.4 \pm 0.5^{[13]}$
cfPWV (m/s)	8.6	$8.5 \pm 1.5^{[4]}$, $9.84 \pm 0.13^{[6]}$	11.5	$11.8 \pm 2.7^{[4]}$, $11.4 \pm 0.19^{[6]}$

Table 2

Model parameters		Range of variation	Interval
Cardiac	T_0	-12.5%~50%	12.5%
	E_{lva}	-50%~50%	20%
Macrovascular	E_c	-40%~60%	20%
	E_p	-40%~60%	20%
Microvascular	r_d	-10%~20%	5%
	W_d	-30%~70%	20%

Fig.1

Fig.2

Fig.3

Fig.4

Fig.5

Fig.6

Fig.7

Fig.8

Fig.9

Fig.10

Fig.11