Published in final edited form as:

IEEE Trans Biomed Eng. 2008 February ; 55(2): 407–418.

A Large-Scale, Energetic Model of Cardiovascular Homeostasis Predicts Dynamics of Arterial Pressure in Humans

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Abstract

The energetic balance of forces in the cardiovascular system is vital to the stability of blood flow to all physiological systems in mammals. Yet, a large-scale, theoretical model, summarizing the energetic balance of major forces in a single, mathematically closed system has not been described. Although a number of computer simulations have been successfully performed with the use of analog models, the analysis of energetic balance of forces in such models is obscured by a big number of interacting elements. Hence, the goal of our study was to develop a theoretical model that represents large-scale, energetic balance in the cardiovascular system, including the energies of arterial pressure wave, blood flow, and the smooth muscle tone of arterial walls. Because the emphasis of our study was on tracking beat-to-beat changes in the balance of forces, we used a simplified representation of the blood pressure wave as a trapezoidal pressure-pulse with a strong-discontinuity leading front. This allowed significant reduction in the number of required parameters. Our approach has been validated using theoretical analysis, and its accuracy has been confirmed experimentally. The model predicted the dynamics of arterial pressure in human subjects undergoing physiological tests and provided insights into the relationships between arterial pressure and pressure wave velocity.

Keywords

Cardiovascular homeostasis; energetic model; strong-discontinuity

I. Introduction

CARDIOVASCULAR homeostasis, an equilibrium state of activity determined by the balance of participating forces, is vital to the stability of blood flow to all physiological systems in mammals. Hence, its theoretical analysis constitutes an important, albeit non-trivial problem, which includes a large number of variables and physiological mechanisms. Valuable insights into the relationships between some participating forces have been gained from seminal experimental studies, most notably Starling's law, linking myocardial stretch to the contraction force, and the Suga-Sagawa pressure-volume areas, describing the total work of the ventricular pump [1]–[3]. Still, a large-scale, theoretical model, summarizing the energetic balance of major forces in a single, mathematically-closed (thus, theoretically tractable) system has not been described. Although a number of computer simulations have been successfully performed with the use of analog models, the analysis of energetic balance of forces in such models is obscured by a big number of interacting elements that create a combinatorial “information explosion” [4]–[7]. A more appropriate modeling approach is suggested by the classical works in theoretical hydrodynamics, which explicitly described the large-scale, energetic balance of forces in the system {fluid + vessel} [8]–[10]. The need for a theoretical model of the cardiovascular homeostasis has been also stimulated by recent advances in device technologies

[11]. Development of optimal monitoring and therapeutic systems, including resynchronization pacing and ventricular assist devices, requires understanding of the force-energy dynamics in the system [12].

Thus, the goal of our study was to develop a theoretical model that represents large-scale, energetic balance in the cardiovascular system, including the energies of arterial pressure wave, blood flow, and the smooth muscle tone of the arterial wall. Furthermore, because the emphasis of our study was on tracking beat-to-beat changes in the balance of forces, we used a simplified representation of the blood pressure wave as a trapezoidal pressure-pulse with a strong-discontinuity leading front. This allowed significant reduction in the number of required parameters. Although this approach has been successfully used in hydrodynamics in the past, the classical hydrodynamic theory of a strong discontinuity (SD) applies only to compressible fluids. Here, for the first time, we show how this theory can be extended to make it applicable to incompressible fluids flowing in pipes with elastic walls. Our approach has been validated using theoretical analysis and its accuracy has been confirmed experimentally; the model predicted the dynamics of arterial pressure in human subjects undergoing physiological tests.

II. Methods

A. The Model Design

In this section, we summarize the assumptions and define the model pressure waves (the mathematical description is provided in the subsequent sections). The model parameters are described in Table I. The pressure waves are the solutions of the governing system of equations, herein referred to as the SD pressure waves (Section II-B). The systolic and diastolic pressures are defined as the pressure values after and before the SD-front, respectively (Fig. 1). This simplification allows us to make the model mathematically complete. On the short time scales (within a single cardiac cycle), the SD-description of the pressure waveform would not be sufficiently accurate. However, the primary focus of our model is on beat-to-beat changes in the large-scale, energetic balance over time intervals of ≥ 2 and, preferably, hundreds of cardiac cycles since large-scale physiological changes usually occur over longer time scales. Therefore, intra-beat variations in the pressure waveform could be omitted without loss of theoretical completeness or significant reduction in experimental accuracy. An SD has approximately the same propagation velocity as the traditional pressure wave (see Section III-A) and has been previously used for the description of blood pressure waves [13].

Application of the SD solutions reduces the source integral equations of the final system (Section II-B) to the algebraic equations of Rankine–Hugoniot type (Sections II-C and II-D) [9]. These equations bind together core parameters on both sides of the SD front using fundamental principles of fluid dynamics in elastic reservoirs as described below.

The instantaneous, SD wavefront is considered lying on a radial cross-section of the vessel at any fixed moment of time (Fig. 1). The core parameters $\delta \mathbf{R}_i$, $\mathbf{u}_i$, $\mathbf{p}_i \rho_i$, ($i = 1, 2$), $\mathbf{E}$ (the effective Young modulus), and $\mathbf{c}$ (velocity of the wave propagation in a stationary coordinate system) are constant within a cardiac cycle but may change from beat to beat [Fig. 1(c)]. Thus, the deformation-related increment of the vessel's radius, $\delta \mathbf{R}$, the axial flow velocity $\mathbf{u}$, pressure $\mathbf{p}$, and density ρ may change abruptly on the SD front similar to the Heaviside τ -function. The wall thickness, $\mathbf{h}$, is assumed to be constant and substantially smaller than the radius $\mathbf{R}$ of the cylinder, $\mathbf{h} \ll \mathbf{R}$. Indeed, the ratio $\mathbf{h}/\mathbf{R}$ is relatively constant in systemic arteries, having a value of approximately 0.14 in the large arteries [13] and 0.25 in the medium-size arteries [7], [14]. In our model, the terms of order $O((\mathbf{h}/\mathbf{R})^2)$ and higher are neglected, because the relative error of this simplification is $\lesssim 0.25^2 = 0.0625$. $\mathbf{R}$ represents an approximate or “averaged” radius of the arteries over the path of the traveling pressure wave. This value is considered constant and can be determined using calibration measurements (see Section II-F) [15].

Following previous studies, we used a compact representation of variable elastic properties, referred to as the effective Young modulus; previously, this descriptor also has been called the incremental elastic modulus [13], [16]–[18]. Vibrations of the walls are disregarded, and the corresponding terms are omitted in the elasticity equation. Hence, changes in the kinetic energy caused by the vibrations are also disregarded.

Because the focus of our study is on large-scale dynamics, the slight differences in the flow velocity across the arterial lumen caused by viscosity of blood could be neglected, and the axial flow velocity could be considered constant across the lumen. Therefore, the explicit description of blood viscosity could be neglected, as in some previous large-scale, theoretical studies [19], [20]. However, because our model uses approximate (averaged) values of axial velocity, blood viscosity is still implicitly taken into account. Similarly, the geometry of the vascular tree is also relatively constant and could be neglected as well. For computational simplicity, an artery is considered as a round cylindrical pipe, and the flow motion is accepted as axially symmetric. The errors introduced by these simplifications do not change over time, and thus would not affect the beat-to-beat changes in the large-scale energy balance of forces.

To simplify the computations, we accepted the flow velocity before the pressure wavefront to be equal to zero ($\mathbf{u}_1 = 0$). Thus, we are considering a single cardiac beat without memory of previous beats. Since the modeling approach presented here is sufficiently general, in the future it can be extended to incorporate realistic values of $\mathbf{u}_1 > 0$.

The density of blood in our model is different before and behind the wavefront of the pressure wave (ρ_1 and ρ_2). Indeed, Schneditz *et al.* demonstrated beat-to-beat variations in blood density and have suggested the existence of even faster periodicities that could not be quantified due to the long time-constant of their measurement device [21]. These may include pressure-related density variations due to the re-distribution of the lower-density plasma and higher-density erythrocytes inside the lumen of the vessel [21], as well as deformation of the erythrocytes by the passing pressure wave [14]. The density of blood also varies within the vascular tree, since the density distribution depends on the vessel size [14]. Thus, the pressure wave propagating from larger towards smaller arteries would encounter subtle differences between the density behind and before the wavefront. However, the differences between ρ_1 and ρ_2 for most practical applications are insignificant and their impact on the model predictions is negligible (see Section II-E).

B. The Governing System of Equations

Below we deduce the governing system of equations with the use of conservation laws and two boundary conditions that are applied to balance the fluid and wall motions.

The Boundary Condition #1: The fluid pressure on the wall must be equal to the wall stress (by Newton's third law);

The boundary condition #2: A radial component of the flow velocity must be equal to the velocity of the radial wall deformation.

The stress and strain of the wall are linked together by the elasticity equation (Hooke's law) [10], [14]

$$\mathbf{p} = \mathbf{E} \cdot \mathbf{h} \cdot \delta \mathbf{R} / \mathbf{R}^2 \quad (1)$$

where $\mathbf{p}$ is the pressure on the wall, $\mathbf{E}$ is the effective Young modulus, $\mathbf{R}$ is the constant radius of a non-deformed vessel, $\delta \mathbf{R}$ is the deformation-related increment, and $\mathbf{h}$ is the vessel's wall thickness (which is also considered constant). The incompressibility equation binds together the radial and the axial flow velocities for the rotary symmetric flow [9]

$$\partial \mathbf{u} / \partial \mathbf{x} + \mathbf{r}^{-1} \cdot \partial (\mathbf{r} \cdot \mathbf{w}) / \partial \mathbf{r} = 0 \quad (2)$$

where $\mathbf{u}$ and $\mathbf{w}$ are the axial and radial flow velocities, and $\mathbf{x}$ and $\mathbf{r}$ are the axial and radial coordinates, respectively. (The angular flow velocity equals zero because the flow is rotary symmetric.) Equations (1) and (2) with the boundary conditions 1 and 2 bind $\mathbf{w}$ with $\mathbf{u}$, $\mathbf{p}$, and elasticity of the wall material. This allows us to eliminate $\mathbf{w}$ from the final system leading to the well-known Moens (5) that binds $\mathbf{u}$ with $\mathbf{p}$ and elasticity of the wall material [7], [14]. After these eliminations, we obtain the governing system of the four equations: the equation of continuity (the conservation of mass) (3), the axial component of Euler equation (i.e. the conservation of the axial component of momentum without the viscosity term) (4), the Moens equation (5), and the energy conservation equation on a set {fluid + vessel}. The latter equation takes the form of (9), (10), or (11) to describe the state of low, medium, and high level of smooth muscle tone, respectively (Section II-D).

Below we formulate the governing system of equations in the integral form, since only that form permits the SD solutions. (Due to this advantage, the integral form has also been used for dynamical analysis of SD-waves in other physical systems [9].)

The equation of continuity (the conservation of mass)

$$\frac{\partial}{\partial \mathbf{t}} \int \int \int_{\mathbf{D}} \rho d^3 \mathbf{x} = - \iint_{\partial \mathbf{D}} \rho \langle \vec{\mathbf{v}}, \vec{\mathbf{n}} \rangle d\mathbf{S} \quad (3)$$

where ρ is the fluid density, $\vec{\mathbf{v}} = (\mathbf{u}, \mathbf{w}, 0)$ is the flow velocity vector, $d^3 \mathbf{x}$ is the spatial volume element, $\mathbf{t}$ is time, $\langle \rangle$ denotes the spatial scalar product, $\mathbf{D}$ denotes any fixed compact domain in the vessel with a piecewise smooth boundary $\partial \mathbf{D}$ and the outward unit normal $\vec{\mathbf{n}}$, and $d\mathbf{S}$ is an element of the oriented unit area on $\partial \mathbf{D}$.

The axial component of Euler equation (the conservation of the axial component of momentum)

$$\frac{\partial}{\partial \mathbf{t}} \int \int \int_{\mathbf{D}} \rho \mathbf{u} d^3 \mathbf{x} = - \iint_{\partial \mathbf{D}} [\mathbf{p} \mathbf{n}_x + \rho \mathbf{u} \langle \vec{\mathbf{v}}, \vec{\mathbf{n}} \rangle] d\mathbf{S} \quad (4)$$

where $\mathbf{n}_x$ is the axial component of the outward normal on $\partial \mathbf{D}$, $\mathbf{p}$ is the pressure, $\mathbf{u}$ is the axial flow velocity, and the rest of parameters are the same as in (3). Note that (3) and (4) contain the radial component of the velocity vector $\mathbf{w}$, which later will be eliminated from (6) and (7), obtained from (3) and (4), to determine the SD solutions (see Appendix for details).

The Moens equation

$$\frac{\partial}{\partial \mathbf{t}} \iint \mathbf{p} d\mathbf{S} = - \frac{\mathbf{E} \mathbf{h}}{2\mathbf{R}} \cdot \frac{\partial}{\partial \mathbf{x}} \iint \mathbf{u} d\mathbf{S} \quad (5)$$

where $\mathbf{x}$ is the axial coordinate, $\mathbf{E}$ is the effective Young modulus, $\mathbf{R}$ is the radius of a non-deformed vessel, $\mathbf{h}$ is the arterial walls' thickness, and the rest of parameters are the same as in (4). The integrals are taken over a radial cross-section of the vessel.

The Energy Conservation Equation on the Set (fluid + vessel)—The integral form of this equation has not been presented here because its derivation is technically difficult. Instead, this equation has been derived in the algebraic form of a Rankine–Hugoniot-type, as described below [(9)–(11)].

C. The Rankine–Hugoniot-Type Equations That Follow From the Integral Equations (3)–(5)

Rankine–Hugoniot-type equations are algebraic relations that bind together parameters on both sides of the SD front [9]. The following Rankine–Hugoniot-type equations are obtained from

the integral equations (3), (4), and (5), respectively, with the use of the generalized function theory (see Appendix for details)

$$\mathbf{A} \cdot \rho_2 \cdot (1 - \kappa) = \rho_1 \quad (6)$$

$$\mathbf{A} \cdot [\mathbf{p}_2 - \mathbf{c}^2 \cdot \rho_2 \cdot (1 - \kappa) \cdot \kappa] = \mathbf{p}_1 \quad (7)$$

$$\mathbf{A} \cdot [\mathbf{p}_2 - (\mathbf{E}h/2\mathbf{R}) \cdot \kappa] = \mathbf{p}_1 \quad (8)$$

where $\mathbf{A} = (\mathbf{R}_2/\mathbf{R}_1)^2 = [(\mathbf{R} + \delta\mathbf{R}_2)/(\mathbf{R} + \delta\mathbf{R}_1)]^2 = \{[1 + \mathbf{p}_2/(\mathbf{E}h/\mathbf{R})]/[1 + \mathbf{p}_1/(\mathbf{E}h/\mathbf{R})]\}^2$, $\mathbf{S}\mathbf{P} = \mathbf{p}_2$, $\mathbf{D}\mathbf{P} = \mathbf{p}_1$, $\mathbf{c}$ is the velocity of the SD propagation, i.e., the velocity of the pressure wave (in a stationary coordinate system), and κ denotes the ratio of the axial flow velocity to the SD velocity: $\kappa = \mathbf{u}/\mathbf{c}$, where $\mathbf{u} = (\mathbf{u}_2 - \mathbf{u}_1) = \mathbf{u}_2$ and $\mathbf{u}_1 = 0$.

Equations (6) and (7) can also be obtained by equating the matter and the axial momentum of the fluid, respectively, before and after the SD front.

D. The Energy Conservation Equation for Different States of the Smooth Muscle Tone

The complexity and variability of the arterial smooth muscle tone cannot be described in exact mathematical terms. The smooth muscle activity is distributed non-uniformly along the arterial tree, being particularly strong and highly variable in the smaller, peripheral arteries [1], [14]. To overcome this problem, we define vasomotor activity as a piecewise-continuous function that consists of the three states: low, medium, and high level of smooth muscle tone (SMT-1, 2, and 3, respectively). These states are expressed by different versions of the energy conservation equation relating the hydrodynamic parameters of the pulsatile flow and properties of the arterial wall.

In SMT-1 (9), representing the state of low vasomotor activity, the vessels are treated as passive, elastic pipes with blocked (relaxed) smooth muscle tone. Indeed, studies with smooth muscle relaxation of the midsize arteries in humans provide experimental support for the existence of this form of a relation [22]. SMT-1 uses the SD representation of the pressure wave and the thermodynamic state equation of a perfect fluid to describe changes in the energy of the set {blood fluid + vessel}. The perfect fluid is defined as a thermodynamic system that 1) satisfies the Clapeyron–Mendeleev-like state equation ($\mathbf{p}/\rho \propto \mathbf{T}$) [8], and 2) is polytropic, which means that its internal energy depends on Kelvin temperature ($\varepsilon = \mathbf{c}_v \mathbf{T}$, where $\mathbf{c}_v$ is the heat capacity referred to a constant volume) [8]. The internal energy of a perfect fluid contained in a volume $\mathbf{V}$ may be calculated as $\varepsilon = \mathbf{p}\mathbf{V}/(\gamma - 1)$, where γ is the Poisson isentropic exponent ($\gamma = \mathbf{c}_p/\mathbf{c}_v$, the ratio of the heat capacities referred to the constant pressure and volume, respectively) [8]–[10].

For SMT-1, the energy conservation equation is obtained by summing together the instantaneous changes in all energy components of the pulsatile flow and setting this total energy change equal to zero. Changes in the total energy of the arterial walls are estimated from the mechanical work of the blood fluid required for elastic deformation of the walls. Putting the work of the cardiac pump on the left-hand side, and summing together the kinetic energy of the flow, the internal energy of the fluid, before and after crossing the SD front (without small terms of order $\delta\mathbf{R}/\mathbf{R}$ or higher), and the work required for deformation of the elastic walls on the right-hand side, leads to the energy conservation equation in the following form:

$$\begin{aligned} \pi\mathbf{R}^2\mathbf{c} \cdot d\mathbf{t}\mathbf{p}_2\kappa = & \pi\mathbf{R}^2\mathbf{c} \cdot d\mathbf{t}(1 - \kappa)\rho_2(\kappa\mathbf{c})^2/2 + \pi\mathbf{R}^2\mathbf{c} \\ & \cdot d\mathbf{t}[\mathbf{p}_2(1 - \kappa) - \mathbf{p}_1]/(\gamma - 1) + \pi\mathbf{R}^2\mathbf{c} \\ & \cdot d\mathbf{t}\mathbf{p}_2[\mathbf{p}_2(1 - \kappa) - \mathbf{p}_1]/(\mathbf{E}h/2\mathbf{R}). \end{aligned}$$

In this equation, the work of the cardiac pump, which is modeled as a piston moving forward with a constant velocity $\mathbf{u}$ and generating pressure $\mathbf{p}_2$, is expressed as a product of the blood volume displaced by a single advancement of the piston into the vessel during systole and the pressure $\mathbf{p}_2$. The volume of the displaced blood, in turn, is equal to the product of the vessel's cross-sectional area $\pi \mathbf{R}^2$ and the length of the displacement, $\mathbf{u} \cdot d\mathbf{t} = \mathbf{c} \cdot \kappa \cdot d\mathbf{t}$. The first term on the right-hand side follows the definition of the kinetic energy of a flow [9]. The internal energy is expressed through $\varepsilon = \mathbf{pV}/(\gamma - 1)$, and the deformation-related increment, $\delta \mathbf{R}$, in the last term is expressed as $\mathbf{R} \cdot \mathbf{p}/(\mathbf{E}h/\mathbf{R})$ using the elasticity equation (1). Substituting $\mathbf{p}_1$ and ρ_2 from (6) and (7) brings the energy conservation equation to its final form

$$(\gamma - 1) [1 + (\mathbf{A} - 1)/\kappa] \cdot \mathbf{p}_2^2 + \{1 + (\mathbf{A} - 1) [1/\kappa + (\gamma - 1)]\} \cdot \mathbf{p}_2 \cdot \mathbf{E}h/2\mathbf{R} - [\mathbf{A} + (\gamma - 1)\kappa/2] \cdot (\mathbf{E}h/2\mathbf{R})^2 = 0. \quad (9)$$

SMT-2 is the state of a medium vasomotor activity. For the energy conservation equation corresponding to SMT-2, we use an averaged, statistical relationship between the effective Young modulus and arterial pressure [23], [24]

$$\mathbf{E} = \mathbf{E}_0 \cdot \exp(\alpha \cdot \text{MP}) \quad (10)$$

where $\mathbf{E}_0$ is the value of $\mathbf{E}$ referred to zero pressure, α is a small positive constant, and MP is the mean pressure, which can be approximated as $\text{MP} = (\text{SP} + 2 \cdot \text{DP})/3$. Thus, the factors influencing the Young modulus in SMT-2 are represented in an implicit (lumped-parameter) form through a single variable, MP.

SMT-3, the state of a high vasomotor activity, further extends this lumped-parameter approach and approximates the states of heightened smooth muscle tone, both in the experiments described in the Results section and previous investigations with pharmacological modifications of arterial pressure and vasomotor activity [25]. SMT-3 uses a generalized approach of the classical elasticity theory, in which the effective Young modulus is represented by a variable $\mathbf{E}(\mathbf{L})$, and parameter $\mathbf{L}$ links together the main properties of the wall tissues with the pressure and density of the fluid flow [8], [10], [26]. This lumped-parameter representation of the vascular wall properties also includes the role of the smooth muscle tone. (The energy conservation equation for SMT-2 (10) can be considered as a special case of this approach, in which $\mathbf{L} = \text{MP}$). In the first approximation, $\mathbf{L}$ is proportional to the ratio of pressure over density [8], [10], [26]. To derive the energy conservation equation for SMT-3, we have adapted this approximation for the pulsatile flow, in which the pressure wave is represented by an SD. This can be expressed as $\mathbf{L} := \mathbf{p}_2/\rho_2 = \text{SP}/\rho_2$. In the preliminary studies we have found that the formula $\mathbf{E} = \mathbf{E}_0 \cdot \exp(\alpha \cdot \text{SP}/\rho_2)$ gives a good approximation of the experimental data (with a positive constant factor α). Next, ρ_2 is approximately inversely proportional to $1 - \kappa$ which follows from (6) for $\mathbf{A} \approx 1$. The inverse-proportionality factor may be included in the common factor (α), so that the desired equation may be written in its final form as

$$\mathbf{E} = \mathbf{E}_0 \cdot \exp(\alpha \cdot \text{SP} \cdot (1 - \kappa)). \quad (11)$$

Hartung previously used this concept to model experimentally determined characteristics of the stress-strain relation of arterial walls [27]; it is also similar to the lumped-parameter representation of elastic properties in the commonly used Windkessel model [14]. Changes in the arterial radius caused by the propagating pressure wave, vasomotor activity, or shifts in the operating pressure (which determine the position on the stress-strain curve) are lumped together in a single variable $\delta \mathbf{R}$. Because of a parameter $\kappa = \mathbf{u}/\mathbf{c}$, which modifies the relationship between pressure and vascular response, SMT-3 has the strongest coupling between these variables among all the three states of SMT, thus representing an active vasomotor activity.

E. Explicit Expressions for the Systolic and Diastolic Pressure

Since we consider a single cardiac beat without a memory of previous beats (Section II-A), the density before the SD front (ρ_1) is constant. Therefore, pulsatile flow in which the pressure wave is represented by a SD, can be defined by the Rankine–Hugoniot-type system of four equations [(6), (7), (8), and either (9), (10), or (11), depending on the level of the smooth muscle tone] in the six-dimensional space of the following variables: $SP = p_2$, $DP = p_1$, Eh/R , ρ_2 , c , and $\kappa = u/c$. Hence, the pressure waves form a $2(= 6 - 4)$ -dimensional variety of waves. This variety depends on constant parameters [ρ_1 and γ for SMT-1; ρ_1 , α , λ for SMT-2 and SMT-3, see (12), (13), (14)]. This variety can be equivalently defined by expressing the first four (“dependent”) variables (SP , DP , Eh/R , ρ_2) through the last two (“independent”) ones (c , κ). For SMT-1, assuming $A = 1$ (or, equivalently, considering $A \cdot SP$, $A \cdot \rho_2$, $A \cdot E$ in place of SP , ρ_2 , E , respectively), a simple computation with (6), (7), (8), (9) yields the following expressions:

$$SP = \rho_1 c^2 \Phi(\kappa, \gamma), DP = SP - \rho_1 c^2 \kappa \quad (12)$$

$$\text{where } \Phi = \left\{ \left[1 + 4(\gamma - 1) + 2\kappa \cdot (\gamma - 1)^2 \right]^{1/2} - 1 \right\} / 2(\gamma - 1).$$

These expressions can be sharpened using the exact value of $A = \{ [1 + SP/(Eh/R)] / [1 + DP/(Eh/R)] \}^2$ in the system of (6), (7), (8), (9) and solving it iteratively. However, the improvement in accuracy would be small, because $A = 1 + O(\kappa)$ [from (8)].

Using the Moens–Korteweg equation [14] with the average physiological values of $\rho = 1.06 \text{ g/cm}^3$ [14] and $c = 800 \text{ cm/s}$ [1], [2], we compute $E \cdot h/R = 2c^2 \rho = 1.3568 \cdot 10^6 \text{ dyn/cm}^2$. Then substituting this value and the average physiological values of $SP = 110 \text{ mm Hg}$ and $DP = 70 \text{ mm Hg}$ [28] (multiplied by a 1333 (dyn/cm²)/mm Hg, a unit-conversion factor) into the above equation, yields $A = 1.075$ or less than 8% error compared to $A = 1$. Substituting $A = 1.075$ into the (6) would produce only a 6% difference between ρ_1 and ρ_2 , which is still within range of the theoretical accuracy of Moens–Korteweg and other equations used in our model and significantly smaller than the average measurement error [14], [30]. On the other hand, substitution of $A = 1$ and the average physiological values of $\rho_1 = 1.06 \text{ g/cm}^3$ and $\kappa = 0.01$ [14] into the (6), shows that in this case, the difference between ρ_1 and ρ_2 is very small (0.94%). Thus, an approximate value of $A = 1$ used in our model effectively leads to a simplified treatment of blood density as an average constant $\rho = 1.06 \text{ g/cm}^3$.

The explicit expressions (12) were derived for SMT-1. For SMT-2 or SMT-3, one should replace (9) by (10) or (11), respectively, which yields the following formulations instead of formulas (12). For SMT-2

$$SP = \log(c^2)/\alpha + 2\rho_1 c^2 \kappa/3 + \lambda, DP = SP - \rho_1 c^2 \kappa \quad (13)$$

where λ is a constant parameter defined as $\lambda = \log(2\rho_1 R/E_0 h)/\alpha$, where h is the thickness of the vessel wall and R is the radius of the nondeformed vessel. For SMT-3

$$SP = \left[\log(c^2)/\alpha + \lambda \right] / (1 - \kappa), DP = SP - \rho_1 c^2 \kappa. \quad (14)$$

Because the present model is mathematically closed, other variables, including cardiac output, vascular resistance and compliance, can be also explicitly derived; these derivations are not shown here for brevity.

F. Experimental Protocol

In this section, we describe a procedure for estimating the model variables through a small number (two) of noninvasively measurable parameters and then apply this procedure to the analysis of arterial pressure dynamics in human subjects undergoing the bicycle test and Valsalva maneuver. Our measurement procedure is similar to that described earlier by P. Elter [15]. The model-predicted values of arterial pressure are validated against the reference measurements obtained by medical pressure-measurement devices. Note that the two measured parameters used in this study (the pulse transit time and the peak amplitude of the photoplethysmographic signal) are not unique; they are determined by the experimental setup, and their relation to the core parameters of the model is approximate. The software implementing the model has been programmed using Matlab 6.0 (MathWorks, Natick, MA) in a Windows XP environment and tested with the digitally recorded experimental data offline.

Experimental Protocol—Two protocols were used in this study to test the validity of our modeling approach, the bicycle test (Protocol 1) and the Valsalva maneuver (Protocol 2). Protocol 1 was used to exert post-exercise relaxation of the smooth muscle tone, so that the dynamics of pulse wave velocity, predominantly determined by vascular stiffness, could be examined over a wide range of systemic pressure changes. The protocol was performed on a mechanically braked bicycle ergometer (Monark 818E; Vansbro, Sweden), using a target heart rate of 110 bpm [31]. This heart rate was chosen because the study participants did not exercise regularly at high exertion levels and because this modest target would allow the subjects to maintain the load comfortably for 10 min [31]. Baseline heart rate and blood pressure were recorded immediately prior to the start of exercise, while the subjects were sitting on the bicycle. The subjects then were asked to start pedaling, keeping the pedal speed between 50 and 60 rpm, with a starting workload of 25 W, and adjusting resistance every 2 min until the heart rate reached 110 beats/min. Blood pressure measured at 3-min intervals by a cuff manometer (Dyapulse, ALP-236, AccuLab Product, Modesto, CA) above the elbow of the left arm was used as reference data for comparison with model predictions in Protocol 1. After 10 min, the pedaling was stopped, and a custom data acquisition device was applied for simultaneous acquisition of photoplethysmographic and electrocardiographic signals. The photoplethysmographic (PPG) sensor was attached to the palmar surface of the distal phalanx of the second finger on the right hand. A bipolar electrocardiographic (ECG) signal was recorded from the two electrodes positioned on the left and right mid-scapular lines in the 2nd intercostal space with the reference electrode positioned in the 5th intercostal space on the right mid-scapular line. The PPG-sensor and the cuff were positioned on different arms to avoid artifacts of the cuff inflation on the PPG-measurements. The signals were digitized at 256 Hz and 12-bit resolution and stored digitally.

Protocol 2 was used to enhance vasomotor activity in the setting of relatively small changes in systemic pressure and cardiac output. The protocol was performed in a supine position. The simultaneous ECG and PPG measurements were performed using custom data acquisition hardware described above. Blood pressure measurements obtained every second with an oscillometric device (Finapres, Datex-Ohmeda Inc., Madison, WI) were used as reference data for comparison with model predictions in Protocol 2; the oscillometric sensor was attached to the second finger of the right hand. Subjects arrived at the laboratory after having abstained from caffeine and exercise for at least 12 h. After a 10-min baseline period of comfortable rest in a supine position, the subject was asked to interrupt breathing and keep blowing against a pneumatic resistance, while maintaining a predetermined pressure during 15 s. This led to an abrupt, transient elevation of intrathoracic and intraabdominal pressures. Fig. 2(a) shows a typical example of changes in pressure during the Valsalva maneuver. The shaded area indicates phases II–IV, which reflect autonomic adjustments with predominant

vasoconstriction, whereas phases I – II_c (without shading) are not related to vasomotor effects. The hallmark of the start of phase II₁ is the rise of blood pressure due to vasoconstriction after the fall of the pressure during the preceding phase. Because vasoconstriction occurs during Phases II₁ – IV of the test, we investigated the pressure-pulse wave velocity relation during these phases separately (shaded area) from that during the entire test.

Baseline Correction and Signal Processing—Baseline wander was removed from the ECG and PPG signals by high-pass filtering with a second-order Butterworth filter applied bi-directionally (cutoff frequency 0.05 Hz), which effectively resulted in a fourth-order filter with a zero phase shift. The peak amplitude of the pressure wave (PA) and the time interval between the greatest (positive or negative) peak of the electrocardiogram and the time of occurrence of PA, referred to as the pulse transit time (PTT), were determined using custom software [Fig. 2(b)].

System Calibration—The calibration is performed at the beginning of each test to find individual values of the constant parameters ρ_1 , α , γ , λ (defined above) and the constant C (defined below in this section) by adjusting the model-predicted values of systolic and diastolic pressure to the corresponding reference values. (The reference measurements were obtained by a cuff sphygmomanometer in Protocol 1 or an oscillometric device in Protocol 2, as described above.) The model-predicted values of systolic and diastolic pressure were derived using the equations presented in Section II, in which the required parameters c and

κ were determined from the beat-to-beat measurements of PTT and PA using (15) and (16) below. The individual values of adjusted parameters were determined by the substitution of simultaneously measured systolic and diastolic pressure, PTT, and PA directly into the equations from Section II (for SP and DP, respectively), and (15), (16), and solving them for ρ_1 , α , γ , λ , and C .

Determining the Pressure and Flow Velocity—The goal of the measurement procedure is to estimate the pressure wave velocity, c , and the flow velocity, u (or, equivalently, the ratio of flow velocity to the pressure wave velocity, $\kappa = u/c$). The pulse wave velocity, c , can be evaluated as

$$c = L/PTT \quad (15)$$

where L is the length of the path that the pressure wave travels from the heart to the digital artery. Since $L \approx 1$ m in most human subjects, $c \approx 1/PTT$ [14]. The peak amplitude (PA) reflects changes in the local blood volume caused by the passage of the pressure wave in the artery under the sensor. Thus

$$\begin{aligned} PA &\propto \Delta(\text{volume}) \propto (R + \delta R_2)^2 - (R + \delta R_1)^2 \\ &= 2R^2 \cdot [(\delta R_2 - \delta R_1)/R] + o(\delta R/R). \end{aligned}$$

Using the elasticity equation (1) and the Rankine–Hugoniot-type equation (8), and omitting the terms of higher order $o(\delta R/R)$, this equation can be transformed to $PA \propto \kappa/(1 + 2 \cdot \delta R_2/R - \kappa)$, where $\delta R_2/R$ is small compared to 1, so that we can simplify this expression as $PA = C \cdot \kappa/(1 - \kappa)$, where the coefficient C is determined using the calibration measurements as described above. Then, κ and u can be determined from PA and c by the formulas

$$\kappa = 1/(C/PA + 1), u = \kappa \cdot c = c/(C/PA + 1). \quad (16)$$

The above-described procedure allowed beat-to-beat estimation of the pulse wave velocity (c), and flow velocity (u), or equivalently, $\kappa = u/c$, from which beat-to-beat changes in the systolic and diastolic pressure, as well as vascular characteristics could be determined as described in Section II.

Statistical Analysis—The errors were estimated by comparing the model-predicted and reference values registered simultaneously. The number of compared pairs of predicted and measured values was limited by the frequency of reference measurements (3 min in Protocol 1 and 1 s in Protocol 2). Thus, in each subject, there were four pairs of compared values in Protocol 1 and approximately 700 pairs in Protocol 2. To determine the magnitude of the mean differences between the model-predicted and measured pressure values, we computed the absolute errors for systolic (AE_{SP}) and diastolic pressure (AE_{DP}) [30]

$$AE_{SP} = \frac{1}{N} \sum_{i=1}^N |SP_M - SP_R|$$

and

$$AE_{DP} = \frac{1}{N} \sum_{i=1}^N |DP_M - DP_R|$$

where N is the number of compared pairs of model-predicted and measured pressure values, SP_M and DP_M are the model-predicted systolic and diastolic pressure, respectively, and SP_R and DP_R are the reference pressure values measured directly using a reference measurement system. Since the magnitude of the absolute error depends on the magnitude of pressure variations, we also calculated the relative errors (RE_{SP} and RE_{DP}) as

$$RE_{SP} = \frac{\frac{1}{N} \sum_{i=1}^N |SP_M - SP_R|}{SP_{\text{Median}}}$$

and

$$RE_{DP} = \frac{\frac{1}{N} \sum_{i=1}^N |DP_M - DP_R|}{DP_{\text{Median}}}$$

where SP_{Median} and DP_{Median} stand for the median values of the systolic and diastolic pressure, respectively. The median values were used because the distributions were highly skewed.

III. Results

A. Theoretical Analysis of the Accuracy of the Model

We start theoretical analysis of the simplified strong-discontinuity representation of the blood pressure waves by formulating an immediate result of (6), (7), (8). Subtracting (8) from (7) and substituting ρ_1 for $\mathbf{A} \cdot \rho_2(1 - \kappa)$ in (6) gives

$$\mathbf{c}^2 = \mathbf{A} \cdot \mathbf{Eh} / (2\rho_1 \cdot \mathbf{R}). \quad (17)$$

If $\mathbf{A} = 1$, then (17) gives the same velocity for the SD in immovable fluids ($\mathbf{u}_1 = 0$) as the classical Moens–Korteweg equation [14], [32]. Next, we recall that in a real pressure wave, an upstroke and a downstroke have apparently identical propagation velocities. In our model, however, the upstroke (strong-discontinuity wavefront) and the downstroke (rarefaction segment) are considered as separate entities, which might have different propagation velocities. Unequal velocities of the two segments would result in their interaction and a decay of the propagating pressure wave that does not occur in real physiological systems. Therefore, we have to show that the two segments of the pressure wave have identical propagation velocities in our model.

To achieve this goal, we approximated the instantaneous rarefaction segment by a linear function, whose maximum is equal to the systolic pressure on the rarefaction wavefront, and a minimum lies at the level of diastolic pressure in the vessel after the passage of the pressure wave [Fig. 2(c)]. This linear approximation is equivalent to a weak-discontinuity (WD) description of the rarefaction wavefront [9]. It is interesting to note that the equality of the propagation velocities of the SD-upstroke and the WD-downstroke of the pressure wave is unique for fluids flowing in elastic reservoirs. No waves (SD or WD) can be generated in incompressible Euler fluids flowing in unbounded reservoirs or vessels with rigid walls. In this setting, the fluid behaves like a rigid body; the velocity of waves would be infinite, instantaneously translating the wave over the length of the entire vessel. An important physiological analogy is related to aging; a gradual increase in vascular stiffness leads to the enhanced pulsation of peripheral arteries [33]. By contrast, in gases, waves can exist within any reservoirs, but WD propagates faster than SD behind the SD-front and slower than SD before the SD-front (Jouget–Zempen–Landau theorem [9]).

The velocity of WD rarefaction segment is obtained by direct calculation of characteristics of the governing system shown in Section II; the resulting formula generalizes the Moens–Korteweg equation for the velocity. Specifically, we have found that in a rotary symmetric flow that has the axial velocity $\mathbf{u}$, weak discontinuities propagate with the velocity

$$\begin{aligned} \mathbf{c}'_0 &= -\mathbf{u}/2 \pm \left[\mathbf{c}_0^2 + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{c}_0 \cdot \left[\pm 1 - \mathbf{u}/2\mathbf{c}_0 + O((\mathbf{u}/\mathbf{c}_0)^2) \right] \end{aligned}$$

where $\mathbf{c}_0$ is computed by the Moens–Korteweg formula, $\mathbf{c}_0 = [\mathbf{E}h/(2\rho \cdot \mathbf{R})]^{1/2}$. (Thus, $\mathbf{c}'_0 = \mathbf{c}_0$ when $\mathbf{u} = 0$, that is, our formula is equivalent to the Moens–Korteweg one for the case of immovability.) Obviously, for a stationary observer, the velocity of WD would be greater by $\mathbf{u}$. For instance, if WD has the same direction as the flow, a stationary video camera will register

$$\begin{aligned} \mathbf{c}'_{\mathbf{u}} &= \mathbf{c}'_0 + \mathbf{u} = \mathbf{u}/2 + \left[\mathbf{c}_0^2 + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{c}_0 \cdot \left[1 + \mathbf{u}/2\mathbf{c}_0 + O((\mathbf{u}/\mathbf{c}_0)^2) \right]. \end{aligned}$$

For the WD rarefaction segment, $\mathbf{c}_0 = \mathbf{c}_{02} = \mathbf{E}h/(2\rho_2 \cdot \mathbf{R})$. Taking into account the first Hugoniot-type relation (6)

$$\begin{aligned} \mathbf{c}'_{\mathbf{u}} &= \mathbf{u}/2 + \left[\mathbf{E}h/(2\rho_2 \cdot \mathbf{R}) + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{u}/2 + \left[\mathbf{A} \cdot \mathbf{E}h(1 - \kappa) / (2\rho_1 \cdot \mathbf{R}) + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{u}/2 + \left[(1 - \kappa) \cdot \mathbf{c}^2 + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{u}/2 + \left[(\mathbf{c} - \mathbf{u}) \cdot \mathbf{c} + (\mathbf{u}/2)^2 \right]^{1/2} \\ &= \mathbf{u}/2 + \left[(\mathbf{c} - \mathbf{u}/2)^2 \right]^{1/2} = \mathbf{c} \end{aligned}$$

[where $\mathbf{c} = [\mathbf{A} \cdot \mathbf{E}h/(2\rho_1 \cdot \mathbf{R})]^{1/2}$, in agreement with (17)], QED.

In summary, this analysis confirms the equality of the propagation velocity of the leading and trailing fronts of the pressure wave in our model, which were represented by SD and WD, respectively. The analysis also shows that this velocity for a stationary observer is consistent with the classical Moens–Korteweg velocity of the pressure waves.

B. Comparison of Model Predictions With Published Data

In Fig. 3, Panels A and B show the relationship between the pressure wave velocity, $\mathbf{c}$, the ratio of pressure wave velocity to flow velocity, κ , and the systolic/ diastolic pressure. The pressure wave velocity was varied in a physiological range, between 3 and 24 m/s [28], [29]. The ratio κ also was varied in a physiological range between 0.008 and 0.08 [14]. Note that an increase

in κ leads to a nonlinear rise in blood pressure at high pressure wave velocities c . This nonlinear effect is manifested by a peak in the graph of systolic pressure at the highest values of c and κ (Panel A), and to a lesser extent, in the graph of diastolic pressure (Panel B). However, for pressure wave velocities between 6 and 12 m/s, which are observed in most people at rest and during mild physical exercises, and at the average values of κ (0.008–0.02), the relationship is approximately linear. This is not in disagreement with experimental observations of an approximately linear relationship between the arterial pressure and pressure wave velocity for this range of parameters [29], [34], [35].

The experimental and model-predicted relationships between arterial pressure and pressure wave velocity for all three states of vasomotor tone (SMT-1, 2, and 3) are shown in Fig. 3(c) for $\kappa = 0.01$, an average value of κ in the cardiovascular system [14]. The experimental data (from 49 subjects) were reconstructed from Loukogeorgakis, *et al.* [28], Gribbin *et al.* [29], and Stewart *et al.* [25]. Because these data were collected in resting conditions with intact vasomotor activity, the correspondence between the model-predicted curve for SMT-1 (blocked smooth muscle tone) and the experimental data is mediocre (RMS error = 45.5 mm Hg), although the correlation coefficient is relatively high (0.83, $p < 0.001$). For SMT-2 and SMT-3, the RMS error is more than 30% smaller than for SMT-1 (27.1 and 31.6 mm Hg, respectively).

The SMT-1 and SMT-3 curves are approximately mirror images of each other with respect to a line $y = ax + b$ (not shown on the figure) with $a = 16.55$ and $b = -56.71$. Indeed, in the next section, we will show that a combination of SMT-1 and SMT-3 may lead to a linear relation when the two effects are averaged. The slope of the curve for SMT-1 is the steepest among the three curves, which makes it very sensitive to pressure wave velocity variations. Indeed, the smooth muscle relaxation with nitroglycerin increased the slope of the pressure—pulse wave velocity curve in the human brachial artery, making it similar to that for SMT-1 [22]. By contrast, inhibition of endothelium-derived vasodilator NO, analogous to vasoconstriction, reduced the curve's steepness shifting it towards SMT-3 [22]. In resting subjects with intact smooth muscle tone, infusion of adrenergic stimulators also produced a curve of the relation between pressure and pulse wave velocity analogous to SMT-3 [25].

Variations in the radius of the artery, R , or the wall thickness, h , did not affect the form of the curves [corresponding to (12)] in Fig. 5, because of proportionality between the squared pressure wave velocity, c^2 , and the ratio h/R , as can be seen from (17). Dividing the product of $E * h/R = 1.3568 * 10^6$ dyn/cm² (obtained in Section II-E for the average physiological values of ρ and c) by $h/R = 0.25$, the average physiological value in medium-size arteries, gives $E = 5.4272 * 10^6$ dyn/cm², which is similar to the Young modulus registered in the canine carotid and feline mesenteric arteries after blockage of the smooth muscle tone [36] and other experimental models [37].

C. Model Validation in Humans Undergoing Exercise and Valsalva Tests

Twenty three subjects (age: 32 ± 12 years old, four females) without a history of cardiovascular diseases participated in the studies. As expected, changes in the systolic pressure were greater in Protocol 1 compared to Protocol 2 (39 and 22 mm Hg, respectively), whereas changes in diastolic and mean pressure were greater in Protocol 2 (DP: 4 and 22 mm Hg, MP: 13 and 22 mm Hg).

Examples of systolic and diastolic pressures predicted by the model and measured by the reference devices in four subjects undergoing Protocol 1 and four subjects undergoing Protocol 2 are shown in Fig. 4. The model accurately predicted the direction and the magnitude of changes that occurred during the tests. Fig. 5 shows changes in the relation between the mean pressure and pulse wave velocity during the tests. Panel A shows typical changes in pulse wave

velocity-pressure relation in a subject, whose mean pressure reached 100 mm Hg during the test. Combined data from subjects whose mean pressure was ≥ 100 mm Hg during the test ($n = 4$) are presented in Panel B, whereas data from those subjects whose mean pressure was < 100 mm Hg during the test are shown in Panel C. The red lines show the second-order polynomials fitted to the data by the least squares approach. The curves in Panel A and B are closely approximated by a polynomial, whose shape was similar to that predicted by SMT-1 in Fig. 3(c) ($y = 141x^2 - 666x + 874$). However, in Panel C the nonlinearity almost disappeared, so that the leading-term coefficient of the fitted polynomial became small ($y = 2.4x^2 + 5.5x + 54$), because the nonlinearity could be observed only at relatively high pressures.

By contrast, during the Valsalva test and particularly its vasoconstrictive Phases II₁ – IV shown in Panels D and E the data could be approximated by a polynomial, whose shape was similar to that predicted by SMT-3 in Fig. 3(c) ($y = 187x^2 + 911x - 1006$). Fig. 5(f) reproduces two fitted polynomials from Panels 5B and 5E, in a common coordinate system. The curve on the left was obtained during the Valsalva-induced vasoconstriction (“the Protocol-2 curve”), whereas the curve on the right was obtained during the post-exercise smooth muscle relaxation (“the Protocol-1 curve”). Again, note the similarity between the theoretically predicted SMT-1 and SMT-3 curves in Fig. 3(c), and those obtained experimentally in Fig. 5(f). Although these two curves have different operating pressures, in the middle of the physiological pressure range marked by horizontal lines, both SMT-1 and SMT-3 couplings are active, and their combination, if averaged, produces a linear relation ($y = 46.6x - 17.1$). The slope and the y-intercept of the line obtained by averaging of the two curves in Fig. 5(f) are different from those in the model-predicted relations shown in Fig. 3(c). The difference is due to the methodological differences in calculation of the pulse transit time [7], [14], [22]. In our study, PTT was calculated as the time difference between the greatest peak of the electrocardiogram, representing electrical activation of the ventricles, and the PA in the photoplethysmographic signal [Fig. 2(b)]. Therefore, PTT in our study was longer than the “true” PTT between the time of pulse wave initiation in the aorta (immediately after mechanical contraction of the ventricles) and the PA. Nevertheless, since the time interval between electrical activation and mechanical contraction of the ventricles is relatively constant in healthy subjects, these methodological differences could not affect qualitatively the form of the relation between the mean pressure and pulse wave velocity shown in Figs. 5 and 3(c).

Table II demonstrates the prediction error compared to the reference measurements. SMT-1 predicted the dynamics of pressure during post-exercise (cycling) vasomotor relaxation better than SMT-3, whereas during enhanced vasomotor activity induced by the Valsalva maneuver, SMT-3 was more accurate than SMT-1. Predictions given by the statistically-averaged SMT-2, as expected, were in-between those produced by SMT-1 and SMT-3.

IV. Conclusion

A large-scale, energetic model of the balance of forces determining cardiovascular homeostasis has been developed and applied to track the dynamics of arterial pressure through a relatively small number of input parameters. This approach is based on a simplified, strong-discontinuity (shock-wave) representation of the pressure wave dynamics. Although this representation of the blood pressure wave has been proposed previously, theoretical and experimental analysis of the shock-wave dynamics in the vascular system has lagged due to the deficit of knowledge about the behavior of shock-waves in the elastic tubes [13]. Because the classical theory of shock waves applies only to compressible fluids, here we extend this theory to make it applicable to incompressible fluids flowing in elastic vessels.

Previous studies commonly employed analog models, in particular, various extensions of Windkessel model [5]. Although these models provided valuable knowledge about

hydrodynamic properties of the flow in the vascular system, they could not be used for studying the large-scale, energetic balance of forces determining cardiovascular homeostasis. To describe propagation of the pressure wave, the Windkessel model could be extended by combining elementary blocks, representing different segments of the arterial tree, into a transmission-line ensemble [13]. However, this extension leads to a large number of parameters and relations, whose combinations might be unpredictable [13]. Our approach provides a unique, explicit solution that is rigorously derived using the fundamental principles of hydrodynamics and elasticity at the expense of a simplified, step-function representation of the pressure wave. We used this formalism because an accurate reproduction of the pressure waveform was not the primary goal of this study. Indeed, the shape of the waveform would not affect the formulations for the conservation laws that lay the background for the model. The accuracy of the model was confirmed by theoretical analysis and comparison with previously published experimental data [Fig. 3(c)]. Furthermore, the model accurately predicted the dynamics of arterial pressure in humans undergoing physiological tests and provided insights into the relationships between arterial pressure and pressure wave velocity. The results show feasibility of the modeling approach presented here for tracking beat-to-beat changes in the large-scale balance of forces in the cardiovascular system. Our study suggests that tracking of the energetic balance and its optimization might be important for the long-term management of cardiovascular diseases.

Acknowledgment

The authors wish to thank Drs. A. Chernin, A. Kaganovich, W. J. Layton, E. Liverts, and W. C. Troy for fruitful discussions and advice about technical aspects of this work.

This work was supported in part by the National Heart, Lung, And Blood Institute under Grant R44HL077116.

Appendix

Derivation of the Algebraic Equations (6), (7), (8) From the Governing System in the Integral Form

A derivative of a function $F(X)$, where $X = (X_1, X_2, \dots)$, with a strong discontinuity along a hypersurface (the SD front) $\mathbf{S}$ can be represented with the use of the generalized function theory (also referred to as the distribution theory) as a sum of the usual ("classical") derivative calculated on the complement of $\mathbf{S}$ and a term proportional to the Dirac δ -function concentrated on $\mathbf{S}$. For $\mathbf{S} = \{\phi(X) = 0\}$ [38]

$$\frac{\partial F}{\partial X_1} = \left\{ \frac{\partial F}{\partial X_1} \right\}_{\text{classical}} + \cos \angle(\partial/\partial X_1, \nabla \phi) \cdot [F(X)] \cdot \delta(\phi(X)) \quad (\text{A1})$$

where $[F]$ denotes the value of a jump on $\mathbf{S}$: $[F] = F_1 - F_2$ (i.e., the difference of the values before and after the front). The generalized solution of the governing system with SD (Sections II-A and II-B) is a vector-valued function of time $\mathbf{t}$ and the spatial coordinates $\mathbf{x}, \mathbf{y}, \mathbf{z}$, with components $\rho, \mathbf{p}, \dots$ that are smooth before and after the SD front but jump on the front. These functions satisfy the system in the generalized sense when (A1) is used for the derivatives ($X = (\mathbf{t}, \mathbf{x}, \mathbf{y}, \mathbf{z})$, $\phi = \mathbf{x} - \mathbf{x}_0 - \mathbf{c}\mathbf{t}$). Consider an intra-arterial region $\mathbf{D}$ encompassed by the arterial walls and two radial cross-sections. The instantaneous (at the moment $\mathbf{t}$) SD front, $\mathbf{S} = \{\mathbf{x} = \mathbf{x}_0 + \mathbf{c}\mathbf{t}\}$, divides $\mathbf{D}$ in two regions $\mathbf{D}_1$ and $\mathbf{D}_2$, before and after the SD front (Fig. 1). The above solution is smooth in $\mathbf{D}_1$ and $\mathbf{D}_2$. However, for $\mathbf{D} = \mathbf{D}_1 \cup \mathbf{D}_2 \cup \mathbf{S}$ the derivatives include δ -terms. If we sum (3) for $\mathbf{D}_1$ and $\mathbf{D}_2$ that are integrated over an infinitesimal interval of time $d\mathbf{t}$ and subtract the similarly integrated equation for $\mathbf{D}$, then, all the terms containing the volume integrals or the surface integrals, except for the integrals over $\mathbf{S}$, will be cancelled. Taking into

account that the area element for the front in the space-time equals to $\left[\cos \angle \left(\frac{\partial}{\partial \mathbf{t}}, \nabla_{\phi} \right) \right]^{-1} \cdot d\mathbf{x}d\mathbf{y}d\mathbf{z} = \mathbf{c} \cdot \left[\cos \angle \left(\frac{\partial}{\partial \mathbf{t}}, \nabla_{\phi} \right) \right]^{-1} \cdot d\mathbf{t}d\mathbf{y}d\mathbf{z}$, and using (A1) we obtain

$$\begin{aligned} dt \iint_{s_2} \rho_2 \mathbf{c} d\mathbf{y}d\mathbf{z} - dt \iint_{s_1} \rho_1 \mathbf{c} d\mathbf{y}d\mathbf{z} \\ = dt \iint_{s_2} \rho_2 \mathbf{u}_2 d\mathbf{y}d\mathbf{z} - dt \iint_{s_1} \rho_1 \mathbf{u}_1 d\mathbf{y}d\mathbf{z}. \end{aligned}$$

Since the functions under the integrals are constant within a cardiac cycle (Section II-A), this can be transformed into the algebraic Rankine–Hugoniot-type equation

$$\mathbf{A} \cdot \rho_2 \cdot (\mathbf{c} - \mathbf{u}_2) = \rho_1 \cdot (\mathbf{c} - \mathbf{u}_1).$$

With $\mathbf{u}_2 = \mathbf{u}$ and $\mathbf{u}_1 = 0$, we obtain (6). Equations (7) and (8) are derived similarly.

Biography

Alexander Roytvarf was born in Odessa, Ukraine, in 1952. He received the M.S. degree in mathematics from Tomsk University, Tomsk, Russia, in 1976 and the Ph.D. degree in mathematics and mathematical physics from Moscow State University, Moscow, Russia, in 1989 for his thesis in the field of Differential Equations and Theory of Singularities (Advisor: V. I. Arnold).

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Fig. 1.

Model design. **Panel A.** Propagating pressure wave as a strong discontinuity (SD). **Panel B.** Changes in the arterial pressure (p) and axial flow velocity (u). **Panel C.** Changes in the radius of the artery caused by propagating pressure wave. R^{const} = Radius of the nondeformed vessel ($R = 3$ mm in the intermediate-size systemic artery [13], [14]); R_1 = Radius of the deformed vessel before the strong-discontinuity wavefront; R_2 = Radius of the deformed vessel after the strong-discontinuity wavefront; δR_1 and δR_2 are the deformational increments in the vessel radius before and after the SD wavefront, respectively, SP, DP = systolic and diastolic pressure, respectively.

Fig. 2.

Panel A. A typical example of changes in arterial pressure during the Valsalva maneuver. Shaded area indicates phases II_l – IV, which reflect autonomic adjustments with predominant vasoconstriction. **Panel B.** Simultaneous measurement of beat-to-beat changes in pulse transit time (PTT) and peak amplitude of the pressure wave (PA). **Panel C.** Pulse signal recorded from a volar surface of the distal phalanx of the second finger of the right hand by a piezoelectric sensor [39]. Dashed lines superimposed on the 2nd and the 3rd waves show approximation of the upstrokes by a step-function (strong discontinuity, SD) and the downstrokes by a linear function (weak discontinuity, WD).

A. Systolic Pressure

B. Diastolic Pressure

C. Mean Pressure and Experimental Data

Fig. 3.

Systolic (**Panel A**) and diastolic (**Panel B**) pressure versus pressure wave velocity, c , and the ratio of pressure wave velocity to the flow velocity, κ . The density of blood, $\rho = 1.06 \text{ g/cm}^3$ [14], c is varied in the physiological range between 3 and 24 m/s [14], [29], κ is also varied in the physiological range between 0.008 and 0.08 [5], [14]. **Panel C.** Relationships between the mean arterial pressure and pressure wave velocity. The curves are model-predicted relationships for SMT-1, 2, and 3. Dots indicate experimental data from Loukogeorgakis, [28], Gribbin [29], and Stewart [25]. We used $R = 3 \text{ mm}$ and $h/R = 0.25$ for intermediate-size systemic arteries [13], [14], however, modifying R and h/R would not change the shape of the relationship between systemic pressure and pressure wave velocity, because of proportionality

between c^2 and the ratio $\mathbf{h}/\mathbf{R}$, as can be seen from (17). (a). Systolic pressure; (b) diastolic pressure; (c) mean pressure and experimental data.

Fig. 4.

Examples of changes in systolic and diastolic pressure during bicycle test (left column) and Valsalva maneuver (right column) in eight subjects. The predictions of the model are shown by solid lines. The predictions were obtained using SMT-1 during the bicycle test or SMT-3 during the Valsalva maneuver. **Left column**, bicycle test; circles denote measurements that were used for initial calibration of the model; crosses indicate the measurements used for testing and error analysis presented in Table II. **Right column**, Valsalva maneuver; dots mark oscillometric measurements obtained at 1-s intervals. The first 50 measurements (dots) were used for model calibrations; the rest was used for testing of the accuracy of model predictions (Table II).

Fig. 5.

Relationship between the mean arterial pressure and pulse wave velocity during bicycle test (left column) and Valsalva maneuver (right column). Dots indicate experimental data; solid lines show second-order polynomial functions fitted to the data using least squares. **Panel A**, Data from a subject, whose mean pressure reached 100 mm Hg; the shape of the fitted curve is similar to that in SMT-1 (Fig. 3(c)). **Panel B**, combined data from all subjects whose mean pressure reached 100 mm Hg (n = 4); compare the fitted curve to that for SMT-1. **Panel C**, combined data from the rest of the subjects, whose mean pressure was < 100 mm Hg (n = 6). The shape of the fitted function is almost linear; nonlinearity was present only when the pressure reached 100 mm Hg. **Panel D**, Data from a subject undergoing Valsalva maneuver (Phase I–IV). **Panel E**, Data obtained in Phases II₁ – IV of the test shown in the previous panel; compare the fitted function with the SMT-3 curve in Fig. 3(c). **Panel F**, Fitted curves from Panels B and E are reproduced in a common coordinate system; compare with the model-predicted curves in Fig. 3(c).

TABLE I

Definitions of Variables and Parameters Used in the Model

Variable/Parameter	Description
SD	A strong discontinuity.
SMT-1,2,3	The 3 states of low, medium and high level of the smooth muscle tone, respectively.
c	Velocity of the SD wave propagation in a stationary coordinate system (range: 3–24 m/s [29]).
E	Effective (variable, incremental elastic) Young modulus.
E_0	Young modulus referred to zero pressure
h^{const}	Thickness of the vessel wall ($h = 0.75$ mm and $h/R=0.25$ in the intermediate-size systemic arteries [13,14]).
$\kappa = u / c$	Ratio of the axial flow velocity to the SD propagation velocity; ($\kappa=0.01$ is the average value in the cardiovascular system, range: 0.008 – 0.08 [14]).
R^{const}	Radius of the nondeformed vessel ($R = 3$ mm in intermediate-size systemic artery [13,14]).
$R_1 (R_2)$	Radius of the deformed vessel before (after) the SD wavefront.
$A = (R_2/R_1)^2$	Here we assumed that $A \approx 1$.
$\delta R_1 (\delta R_2)$	Deformational increment in the vessel radius before (after) the SD wavefront.
p	Arterial pressure.
SP = p2	Systolic pressure (arterial pressure after the SD wavefront).
DP = p1	Diastolic pressure (arterial pressure before the SD wavefront).
u	Axial component of the flow velocity vector field.
$u_1 (u_2)$	Axial component of the flow velocity vector field before (after) the SD wavefront.
ρ	Blood density (in humans, $\rho=1.06$ g/cm ³ [14]).
$\rho_1 (\rho_2)$	Blood density before (after) the SD wavefront.
$\gamma^{\text{const, cal}}$	Poisson isentropic exponent.
$\alpha^{\text{const, cal}}$	A model parameter having the dimensionality of pressure ⁻¹ .
$\lambda^{\text{const, cal}}$	A model parameter having the dimensionality of pressure.
const	indicates a constant parameter, ^{cal} shows that the constant is determined by calibration.

TABLE II

Mean Absolute/Relative Error of the Model Prediction for SMT-1, 2, and 3 Compared to the Reference Measurements

Pressure	Bicycle test, N=10	Valsalva test, N=13	Total, N=23
Systolic Diastolic	7.9±3.4 / 6.2±2.6 8.9±4.5 / 7.0±3.4	SMT-1 7.4±3.6 / 5.8±2.4 4.1±1.7 / 5.6±1.6	7.6±3.4 / 6.0±2.4 6.2±4.0 / 6.2±2.6
Systolic Diastolic	8.4±2.0 / 6.7±1.2 6.1±2.9 / 4.4±2.1	SMT-2 5.6±2.0 / 4.4±1.5 3.1±1.0 / 4.2±1.1	6.8±2.4 / 5.4±1.7 4.4±2.5 / 4.3±1.6
Systolic Diastolic	15.8±14.8 / 11.9±9.6 10.6±13.2 / 9.2±8.2	SMT-3 4.1±1.5 / 3.3±1.3 4.5±1.8 / 6.2±2.9	9.2±11.2 / 7.1±7.6 7.1±9.1 / 7.4±5.8