Simulation of Hemodynamic Responses to the Valsalva Maneuver: An Integrative Computational Model of the Cardiovascular System and the Autonomic Nervous System

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Abstract: The Valsalva maneuver is a frequently used physiological test in evaluating the cardiovascular autonomic functions in human. Although a large pool of experimental data has provided substantial insights into different aspects of the mechanisms underlying the cardiovascular regulations during the Valsalva maneuver, so far a complete comprehension of these mechanisms and the interactions among them is unavailable. In the present study, a computational model of the cardiovascular system (CVS) and its interaction with the autonomic nervous system (ANS) was developed for the purpose of quantifying the individual roles of the CVS and the ANS in the hemodynamic regulations during the Valsalva maneuver. A detailed computational compartmental parameter model of the global CVS, a system of mathematical equations representing the autonomic nervous reflex regulatory functions, and an empirical cerebral autoregulation (CA) model formed the main body of the present model. Based on simulations of the Valsalva maneuvers at several typical postures, it was demonstrated that hemodynamic responses to the maneuver were not only determined by the ANS-mediated cardiovascular regulations, but also significantly affected by the postural-change-induced hemodynamic alterations preceding the maneuver. Moreover, the large-magnitude overshoot in cerebral perfusion immediately after the Valsalva maneuver was found to result from a combined effect of the circulatory autonomic functions, the CA, and the cerebral venous blood pressure.

Key words: computational model, cardiovascular system, autonomic nervous system, Valsalva maneuver.

The Valsalva maneuver, first described by the Italian anatomist Antonio Maria Valsalva in 1704 [1], entails straining against a closed glottis by forcefully constricting the chest muscles, which as a consequence will lead to a marked elevation of intrathoracic pressure. Such an increase in this pressure will largely impede venous return, subsequently reduce cardiac output, and ultimately result in a rapid fall in arterial blood pressure that will seriously challenge the cardiovascular nervous reflex regulatory functions. In literature, many experimental results have been presented concerning the mechanisms by which the cardiovascular and autonomic nervous systems respond to the Valsalva maneuver. Nevertheless, most of these experiments have until now been conducted with emphases on some limited aspects of the hemodynamic regulations. A comprehensive understanding of the mechanisms underlying the Valsalva maneuver remains unobtainable simply by experimental studies. At this point, an integrative mathematical model representing the hemodynamics of the whole CVS along with the regulatory functions of the ANS can serve as a useful adjunct for in vivo experiments. This model may provide a rational framework that quantitatively defines interactions among many cardiovascular and nervous reflex regulatory parameters and supports the critical interpretation of experimental results and the testing of hypotheses.

From the point of view of model development, a mathematical model of the CVS fit for the simulation of the Valsalva maneuver should have the ability to represent the global closed-loop hemodynamic behavior, inasmuch as hemodynamics in any separate cardiovascular segment is not isolated in nature, but closely correlates with hemodynamics in the remainder of the entire CVS. Furthermore, mathematical functions describing the ANS must ensure a comprehensive inclusion of the main reflex branches that may participate in nervous reflex regulation during the maneuver. There have been various models of the CVS and its interaction with the ANS varying in complexity and form depending on the purpose of study, ranging from very simple open-loop models to complex multicompartamental closed-loop ones. A typical early one is the Guyton model [2] of overall circulation, which includes a three-compartmental representation of the CVS function. Sun et al. [3] presented an elaborate computational model for the right-left heart interaction. Thomas et al. [4] developed an integrated model of the CVS and the nervous re-
flex system capable of simulating the short-term transient and steady-state hemodynamic responses to head-up tilt and lower body negative pressure. Elisa et al. [5] investigated the effect of a total cavopulmonary connection on the main hemodynamic quantities by combining a mathematical model of the CVS with a series of equations for the nervous reflex control. Olufsen et al. [6] recently presented a mathematical model to predict a person’s dynamic changes in arterial blood pressure and middle cerebral artery blood flow when standing up from a sitting position. Although these models have achieved various degrees of success in predicting hemodynamic parameters of interest, they are not readily applicable to a simulation of the Valsalva maneuver because they were often developed with specific narrow objectives in mind, which limited their abilities to predict general physiological phenomena pertaining to cardiovascular regulations. A recent report on a mathematical model designed to simulate the Valsalva maneuver was in a paper by Lu et al. [7] The model represented the closed-loop cardiopulmonary system by means of a comprehensive inclusion of the descriptions of the multiplicity of mechanics and systems, yielding various predictions comparable to experimental results. In their study, however, only the carotid sinus baroreflex was accounted for in the ANS model, and the model of the CVS lacked a detailed description of the peripheral circulations, which largely limited its capability to quantitatively investigate the relative contributions of different regional circulations to the hemodynamic regulations during the Valsalva maneuver. In fact, many in vivo experiments have demonstrated that besides the well-known carotid sinus arterial baroreceptors, the aortic arterial and cardiopulmonary receptors might also simultaneously play important roles in hemodynamic regulations. Moreover, Frank et al. [8] proved that changes in arterial blood pressure, heart rate, and cerebral perfusion induced by the Valsalva maneuver were remarkably influenced by postural change. Gauer et al. [9] pointed out that the time-

Fig. 1. (a) An electric analog circuit of the cardiovascular system. The compartments representing the main cardiovascular components are indicated by a series of numbers. (Each compartment consists of a compliance variable E or C, a resistance R, a viscoelasticity S, and an inertance L.) 1. Ascending Aorta (AA); 2. Descending Aorta (DA); Upper Limb Circulation (ULB) [3. arteries, 4. arteriolar bed, 5. capillary and venule beds, 6. veins]; Cerebral Circulation (CER) [7. arteries, 8. arteriolar bed, 9. capillary and venule beds, 10. veins]; Thoracic Aorta (TA); Splanchnic Circulation (SPL) [12. arteries, 13. arteriolar bed, 14. capillary and venule beds, 15. veins]; 16. Upstream of Abdominal Aorta (ABDU); Renal Circulation (KID) [17. arteries, 18. arteriolar bed, 19. capillary and venule beds, 20. veins]; 21. Downstream of Abdominal Aorta (ABDD); Right Lower Limb Circulation (RLB) [22. arteries, 23. arteriolar bed, 24. capillary and venule beds, 25. veins]; Left Lower Limb Circulation (LLB) [26. arteries, 27. arteriolar bed, 28. capillary and venule beds, 29. veins]; 30. Abdominal Vena Cava (AVC); 31. Inferior Vena Cava (IVC); 32. Intrathoracic Inferior Vena Cava (VC1); 33. Intrathoracic Vena Cava (VC2). Note that blood flow waveforms through each circulation can be identified in sequence: for instance, in the left lower limb circulation, flow toward 26 is arterial flow; from 26 to 27, arteriolar flow; from 27 to 28, capillary flow; from 28 to 29, venule flow; and from 29 to 30, venous flow. (b) A 3D computer model of the arterial tree in a human body.
dependent arterial blood pressure and heart rate responses to the maneuver varied obviously with postures. Therefore an investigation of the latent hemodynamic alterations resulting from postural change is essential to a better understanding of the regulatory mechanisms behind the cardiovascular responses to the Valsalva maneuver.

The objective of the present work is to develop a comprehensive computational model of the closed-loop CVS and its interactions with the ANS, aiming at quantitatively investigating the relative roles of different mechanisms underlying the hemodynamic regulations during the Valsalva maneuver. The present model was designed to allow experiment-specific predictions by adjusting its parameters to a specific experimental condition. This model has the capability to quantify the influence of posture on the hemodynamic responses to the Valsalva maneuver and to evaluate the individual roles played by the cardiovascular nervous reflex regulation and cerebral autoregulation in maintaining cerebral perfusion during the maneuver. To this end, we performed a detailed representation of the circulatory system by including a four-chamber heart, the vascular networks in the lung, the brain, the upper limbs, the splanchnic organs, the kidneys, and the lower limbs as well as the aorta and the vena cava. In modeling the ANS, the aortic, the carotid sinuses, and the cardiopulmonary receptors that are considered responsible for the elicitation of the main nervous reflex signals were included. Also, an empirical CA model was constructed for the end of quantifying the role of local cerebrovascular resistance regulation in compensating for the impaired cerebral perfusion during the Valsalva maneuver.

MODEL DEVELOPMENT

Construction of a closed-loop compartmental model of the CVS

(1) Model description. For the purpose of a physiologically realistic representation of hemodynamic transfer in the CVS and quantification of contributions of local circulations to the hemodynamic regulations during the Valsalva maneuver, the present CVS model was designed to allow a comprehensive inclusion of the vascular networks that distribute in the main organs and tissues. To this end, an anatomically reasonable compartmentalization of the entire CVS is foremost entailed. With this in mind we first constructed a three-dimensional computer model of the arterial tree, based on the anatomical data, as shown in Fig. 1b, which includes 266 arteries with the diameters ranging from 2.4 cm to less than 1.5 mm. Based on the arterial tree model, the whole circulatory system was divided into nine main compartments, which included a four-chamber heart, the vascular networks in the lung, the brain, the upper limbs, the splanchnic organs, the kidneys, the lower limbs, the aorta, and the vena cava. Furthermore, to represent the time-variant dynamic transfer of hemodynamic variables through each compartment, we further made distinctions among arteries, vascular beds of arteriole, capillary, and venule, as well as veins. The construction of the lumped parameter model for the CVS was accomplished through a phenomenological characterization of hemodynamics with an electric analog method. The closed-loop electric analog circuit for the CVS is illustrated in Fig. 1a, which consists of 42 compartments that respectively represent the main cardiovascular components in a human body.

To represent the time-variant nonlinear hemodynamic behavior of the CVS, numerous submodels were introduced, including a representation of the heart, the intrathoracic pressure model, the models that describe the nonlinear vascular compliances of arteries and veins, and the equations that characterize the nonlinear variation of venous resistance with venous blood volume. Details of the mathematical descriptions of these models are summarized in the appendix.

(2) Governing equations and numerical method. The governing equations of the CVS model comprise the different equations representing the electrical analog circuit and the mathematical formulas of the submodels.

(I) Derivation of governing equations of the electrical analog circuit: The mathematical governing equations of the electrical analog circuit were formulated by enforcing mass balance or force equilibrium at the nodes of elastance (E), capacitor (C), and inertance (L), respectively. According to Fig. 2, a and b, the equations can be written in two general forms.

At nodes E and C:

\[
\frac{dE}{dt} = q_{in} - q_{out}
\]

(1)

And at node L:

\[
\frac{dq}{dt} = \left( -S_{up} \cdot \frac{dE}{dt} - q \cdot R - S_{down} \cdot \frac{dq}{dt} \right) / L
\]

(2)

where \( q_{in} \) and \( q_{out} \) [ml/s] are the inflow and outflow of a compartment, respectively.

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\]

(2)

where \( S_{up} \) and \( S_{down} \) [mmHg s/ml] refer to the viscoelasticity of vessel, and \( p_{up} \) and \( p_{down} \) [mmHg] denote the

\[ q_{in} \quad q_{out} \]

\[ S \]

\[ E \ (C) \]

\[ S_{up} \]

\[ E_{up} \ (C_{up}) \]

\[ S_{down} \]

\[ E_{down} \ (C_{down}) \]

\[ L \]

\[ R \]

Fig. 2. Typical elements in the electric analog model.
blood pressures upstream and downstream of $L$, respectively. Note that for different vascular compartments, the calculations of $p$ are in different ways.

For the arterial compartment:

$$p = E \cdot Z,$$

and for other vascular compartments:

$$p = V/C.$$

(II) Numerical method: In total, 82 differential equations were derived for the CVS model at the 82 nodes. The coupling solution of these equations was performed by the use of a fourth-order Runge-Kutta method with adjustable time steps ranging from 0.5 ms to 2 ms. Equations for other nonlinear elements such as the elasticities of the heart and the cardiac and venous valves were solved in intervals of 5 time steps. Such a numerical scheme was proved numerically stable. The simulation software was completely written in a C++ language and run on a DELL workstation.

Mathematical model of the ANS

The ANS is a complicated system, and the mechanisms by which it works still remain incompletely understood. For modeling purposes, we divided it into four functional compartments, as depicted in Fig. 2, which includes the receptors at the afferent end, the CNS, the effectors responsive to control signals, and the sympathetic and parasympathetic nerves. Numerous mathematical models describing the functions of these compartments are available in literature. Ursino [10] recently developed a mathematical model system that fulfilled a detailed mathematical representation of the ANS function and was demonstrated as being able to reasonably reproduce the behavior of the ANS over a wide range of input pressure. This system was employed in the present study to provide a framework for devising a new ANS model that includes three baroreflex branches thought to participate in nervous reflex regulation during the Valsalva maneuver. Details of the mathematical description of the ANS model can be found in the APPENDIX.
(1) Baroreceptors and afferent pathways. Among baroreceptors in a human body, the carotid sinus, aortic baroreceptors, and the cardiopulmonary receptors, which distribute at different locations of the CVS, are considered the most dominant sensors in the elicitation of short-term reflex responses to stress stimulations. The carotid sinus and aortic baroreceptors are well known as being responsible for the regulation of arterial blood pressure via modulating cardiac functions, such as heart rate and cardiac contractility, vascular tone such as vascular resistance, and venous unstressed volume. Besides the regulatory function of the arterial baroreceptors, the low-pressure cardiopulmonary receptors in atria and pulmonary veins have been demonstrated to be able to respond to changes in preload, afterload, and contractility of the heart [11–14], and to be capable of modulating the arterial baroreflex control of heart rate and vascular resistance [15, 16]. During the Valsalva maneuver, since significant hemodynamic variation may occur over the whole CVS, the inclusion of the three types of receptor in the ANS model may facilitate a more comprehensive representation of the ANS function. In this paper, the afferent pathways of the arterial baroreceptors were mathematically described by a linear derivative first-order dynamic block and a sigmoidal static characteristic suggested in Ursino [10]; the afferent discharges of the cardiopulmonary receptors were represented by the equations derived from Magosso et al. [5].

(2) CNS and efferent pathways. The CNS is an integrating element of the overall nervous reflex system, which gathers input information coming from receptors via afferent nerves and sends out modulatory signals to effectors via efferent sympathetic and parasympathetic nerves. To
avoid the treatment of the complex structure of the CNS in model development, we employed a system of mathematical functions to relate the input signals to the output signals of the CNS, namely, afferent-efferent discharge relationship. With respect to the interaction among different receptors, in fact, in a normal intact autonomic nervous system, all receptors work in concert through nonlinear combination in the CNS to guarantee the achievement of a uniform control target. In this regard, in the present model a weighted summation of the input signals from the aortic and the carotid sinus baroreceptors at the afferent level of the CNS was employed. Note that although the cardiopulmonary receptors might interact with the arterial baroreceptors, there is still a lack of sufficient experimental evidence concerning at which level of the CNS and in what way the interaction is done to support the development of a reasonable interaction model; therefore in the present study, the contribution of the cardiopulmonary receptors to the outputs of the CNS was superimposed on the efferent pathways without direct combination with the arterial baroreceptors at the afferent pathway level.

(3) Effectors. The effectors responding to nervous stimulation include heart rate, peak value of systolic cardiac elastance, peripheral resistance, and unstressed volume of vein. Among them, cardiac elastance, resistance, and venous unstressed volume are modulated by sympathetic stimulation, and cardiac cycle is regulated via an interaction between sympathetic and parasympathetic stimulations. Cardiac elastance, resistance, and unstressed volume respond to sympathetic stimulation according to a series of functions that comprise a pure latency, a monotonic logarithmic static function, and a low-pass first-order dynamics [10]. The function of sympathetic regulation of cardiac cycle has a similar form to that of resistance, whereas parasympathetic regulation of it follows a linear relationship between the change in cardiac cycle and the intensity of parasympathetic stimulation.

CA model
The brain is an organ with higher oxygen need. During the Valsalva maneuver, the pronounced fall in arterial blood pressure and the increase in intrathoracic pressure will significantly reduce blood supply to the brain. A variety of feedback loops and mechanisms are involved in the maintenance of cerebral perfusion; among them, CA plays an important role. Detailed mathematical models of CA can be found in [17–19]. For the sake of simplification, in the present study an empirical CA model was constructed by characterizing the change in cerebral arteriolar resistance as a function of cerebral arteriolar blood flow (CABF) [cm³·s⁻¹] and cerebral arteriolar pressure (CAP) [mmHg].

For details on models of the CVS, the ANS, and the CA, please refer to the APPENDIX.

RESULTS

Simulations of baseline hemodynamic parameters under normal rest conditions
A reasonable reproduction of hemodynamics throughout the CVS is a basis for the further application of the computational model to simulate cardiovascular responses to the Valsalva maneuver. To verify this ability of the present model, in this section we discuss some typical baseline hemodynamic parameters predicted by the CVS model under normal rest conditions, which include cardiac hemodynamics, transfer of blood flows, and propagation of blood pressures through arteries, arteriolar, capillary and venule beds, and veins.

(1) Hemodynamics of the heart. Figure 4 illustrates the model-based simulations of the atrioventricular pressure waveforms in the left and right hearts over a cardiac cycle. According to Fig. 4, the present model yields reasonable predictions of the atrioventricular pressure waveforms in terms of both shapes and magnitudes. Typically, the a
wave, x descent, v wave, and y descent on the atrium pressure curves are observed to have been accurately reproduced. The model-based simulations of the volume variation curves of the left and right hearts over a cardiac cycle are shown in Fig. 5, a and b. For ventricles, the typical volume variation curve characterized by a quick systolic reduction in systole and a two-stage diastolic increase has been reasonably reproduced. Figure 5, c and d, show the simulated transatrial and transmitral flows and venous flows to the left and right atria, respectively. The typical E, A waves of ventricular perfusion flows and the S, D waves of atrial perfusion flows have been reasonably predicted.

To investigate the changes in blood flow waveforms through arteries and the vascular beds of arterioles, capillaries, and venules, model-generated blood flow waveforms through the vascular system of the left lower limb are shown in Fig. 7a, where the pulsatile feature of blood flow can be observed to attenuate gradually while moving through the vascular systems. At the levels of capillary and venule beds, blood flows show near-steady flow waveforms with the pulsatile amplitudes being less than 1.5 ml·s⁻¹, which can mainly be ascribed to the existence of large resistances in these vascular systems.

Leading from venule beds to the right atrium are the systemic veins and the vena cava. Simulated blood flow waveforms through these vessels are plotted in Fig. 7b, which indicates that the symmetrical blood flow pattern resulting from the marked buffer function in arteriolar and capillary beds is maintained at the systemic venous level; however, in the large veins and the vena cava, blood flows again become more and more pulsatile because of the sucking of the pulsating right heart downstream.

(2) Transfer of blood flows through peripheral circulations. Shown in Fig. 6, a and b, are the predicted blood flow waveforms through the aorta and the big arteries leading to the upper limbs and brain, the splanchic organs, the kidneys, and the lower limbs. The predicted results are in qualitative accordance with the in vivo measurements [20] in terms of the shape, the flow phase difference, and the diastolic reverse flow.

(3) Propagation of blood pressure along vascular system. Model-generated blood pressure waveforms in the ascending aorta and in the arteriolar, capillary, and venule beds of the left lower limb circulation over two cardiac cycles are shown in Fig. 8a. As pressure waveform propagates from the aorta to the venule bed of the left lower limb, the mean value of it is attenuated gradually from 100 mmHg at the arterial level, to 48 mmHg at the arteriolar level, to 16 mmHg at the capillary level, and to about 9 mmHg at the venule level.

Simultaneously the amplitude of pulsatile blood pressure decreases from approximately 40 mmHg at the arterial level to less than 0.3 mmHg at the venule level. These predictions reflect a physiological truth that at the capillary and venule levels a quasi steady-state blood pressure circumstance is desired to allow a normal exchange of oxygen, nutrition, and metabolic wastes between intravascular blood and surrounding cells and tissue fluid.

Figure 8b illustrates the model-generated 10 s continu-al blood pressure waveforms in different segments of the vena cava. Two marked characteristics of venous blood pressure can be observed. The first is that the pulsatile feature of waveform enhances significantly along the vena cava toward the right heart. The second is that the small magnitude of venous blood pressure waveform makes it greatly sensitive to intrathoracic pressure. As shown in Fig. 8b, the periodic variations in inspiration-expiration–induced intrathoracic pressure lead to corresponding periodic changes in the amplitudes of the venous pressures.

Simulation of the Valsalva maneuver

In vivo measurements of the hemodynamic responses to the Valsalva maneuver demonstrated that even in normal objects free from known cardiovascular diseases,
The measured results might differ from one to another; e.g., both square-wave and sigmoidal arterial pressure responses have been observed in different subjects in a 40 mmHg Valsalva maneuver test [21]. Furthermore, for a single object the characteristics of the hemodynamic responses to the Valsalva maneuver may be markedly altered by postural change [22]. In this section, the feasibility of the present model in reproducing the typical hemodynamic responses to the Valsalva maneuver was first validated against experimental results. Then the effect of posture was investigated by comparing simulations of the Valsalva maneuvers performed in supine, sitting, and standing positions with previous experimental data. Furthermore, for the purposes of evaluating the relative contributions of the cardiovascular nervous reflex functions and the CA to the maintenance of cerebral perfusion during the Valsalva maneuver, predicted arteriolar and capillary blood flows through the cerebral circulation were also presented.

(1) Typical hemodynamic responses to the Valsalva maneuver. The simulated arterial blood pressure and heart rate responses to a 15 s Valsalva maneuver conducted by elevating $P_{it}$ to 40 mmHg in a supine position are illustrated.
in Fig. 9b, and the corresponding experimental results by Bannister et al. [23] are shown in Fig. 9a. Model-based simulations agree reasonably well with the experimental results. The typical time course of change in arterial pressure during the Valsalva maneuver can be divided into four typical phases. During phase I there is a brief increase in arterial blood pressure. Subsequently, during phase IIa arterial blood pressure undergoes a rapid reduction followed by a gradual recovery toward normal value during phase IIb. During phase III, the release of strain results in a sudden decrease in arterial blood pressure. Thereafter, in phase IV, arterial pressure recovers rapidly, and at the late stage of phase IV, an overshoot in arterial blood pressure occurs.

It is well known that the ANS plays an important role in maintaining arterial blood pressure during the Valsalva maneuver. In this paper, the monitored discharges of the baroreceptors, as illustrated in Fig. 10, and the corresponding ANS-mediated changes in heart rate, cardiac contractility, and peripheral resistance provide some quantitative evidences for identifying the individual contributions of different receptors and effectors to hemodynamic regulations during the Valsalva maneuver. During phase I, the increase in arterial pressure that lasts 2 to 3 heartbeats is caused by the sudden elevation of intrathoracic pressure that expels blood contained in the heart and the pulmonary circulation into the peripheral circulation. In this phase, only heart rate is found to respond by a rapid increase, which is mediated by the quick withdrawal of vagal stimulus resulting from the unloading of the aortic and the cardiopulmonary receptors. Thereafter during phase IIa, the reduction in venous return and the subsequently resultant decrease in cardiac output lead to a continual 6- to 8-heartbeat fall in arterial blood pressure. During this phase, heart rate keeps increasing to help maintain arterial blood pressure. At the same time, sympathetic vasoconstriction and enhancement of cardiac contractility also begin to work against hypotension. However, because of the latency of sympathetic response, sympathetic activation is at a low level in this phase. During phase IIb, which lasts 7 to 9 heartbeats, continual tachycardia, augmented sympathetic vasoconstriction, and enhanced cardiac contractility, function together to promote the active recovery of arterial blood pressure. During phase III, the release of the strain results in a short-term sudden fall in arterial blood pressure, in response to which parasympathetic and sympathetic activations are further strengthened. Thereafter, during phase IV the enhancement of vagal stimulus results in a negative overshoot in heart rate at the early stage, and the recovery of venous return along with the ANS-mediated regulation lead to a rapid increase in arterial blood pressure. At the late stage of phase IV, an overshoot in arterial blood pressure occurs because of the enhanced cardiac contractility and vasoconstriction caused by the delayed sympathetic activations.

In the present model, we have included the aortic, the carotid sinus baroreceptors, and the cardiopulmonary receptors to distinguish their different roles in nervous reflex regulation during the Valsalva maneuver. Figure 10, a–c, show the simulated discharges of the afferent pathways of the aortic, the carotid sinus baroreceptors, and the cardiopulmonary receptors during the Valsalva maneuver, respectively. Simulated results indicate that during the Valsalva maneuver, the intrathoracic aortic arterial baroreceptors, which are unloaded by the elevated intrathoracic pressure (Pit), exhibit discharges markedly lower than the carotid sinus baroreceptors that are free from the direct influence of Pit. For this reason, the aortic arterial baroreceptors may be predominant in terms of the baroreflex hemodynamic regulation against the Valsalva maneuver. Further, the intrathoracic cardiopulmonary receptors, the afferent discharges of which are largely attenuated because of the reduced venous return and the increased Pit, may also play a significant role in the ANS-mediated hemodynamic regulation, especially in the regulation of the extrasplanchnic vascular resistances and heart rate. Even though afferent signals from different receptors combine
in the CNS in an excessively complicated nonlinear way, the nonlinear summation law proposed in the present paper has been proved reasonable in representing the integrated regulatory function of different receptors.

(2) Arterial blood pressure response to the Valsalva maneuver with baroreflex control blocked. To further highlight the role of nervous reflex in the hemodynamic regulations against the Valsalva maneuver, arterial blood pressure response to the Valsalva maneuver with nervous baroreflex control blocked was simulated. The predicted result is compared with the experimental result [24] in Fig. 11, and good agreements between them are obtained. Without the regulation of the autonomic nervous system, arterial blood pressure suffers from a continual fall during the Valsalva maneuver, and during the recovery stage after the release of Valsalva strain, it increases gradually following the recovery of venous return without occurrence of overshooting.

Fig. 12. (a) Gravitational stresses at the levels of heart, carotid sinus, brain, splanchnic, and renal circulations, as well as lower limb circulations in supine, sitting, and standing positions. (b) Measured responses of arterial blood pressure and heart rate to the Valsalva maneuver in supine, sitting, and standing positions (by Harkel et al.). (c) Model-based simulations of the responses of arterial blood pressure and heart rate to the Valsalva maneuver in supine, sitting, and standing positions.
(3) Hemodynamic responses to the Valsalva maneuver in supine, sitting, and standing positions. Besides the ANS-mediated hemodynamic regulation, hemodynamic interaction in the closed-loop CVS is another important determinant of the hemodynamic responses to the Valsalva maneuver. In particular, blood volume redistribution among the regional circulations during the maneuver is thought to be the most influential hemodynamic preadaptation possibly affecting the filling of the heart, and dominating the degree of fall in arterial blood pressure during phase IIa [21, 25]. A change in posture from supine to sitting or standing will elicit pronounced venous blood pooling in peripheral circulations because of gravitational force. It was estimated that standing from supine would result in approximately 500 ml blood pooling in the splanchnic organs and the lower extremities [18]. Such a large volumetric blood pooling in a short term may significantly hinder venous return to the heart, subsequently reduce cardiac output, and ultimately decrease arterial blood pressure. In response to these hemodynamic changes, the ANS will be forced to reset the nervous tones to recover arterial blood pressure to a normal level. All these preadaptive alterations in baseline hemodynamic parameters and nervous tones in sitting or standing position might promise different hemodynamic responses to the Valsalva maneuver from those in supine position. To address this issue in quantitative terms, the present study simulated the hemodynamic responses to the Valsalva maneuver for three typical positions, namely, supine, sitting, and standing.

Gravitational stresses at the levels of the heart, the carotid sinus, the brain, the splanchnic, and the renal circulations, as well as the lower-limb circulations, are schematically depicted in Fig. 12a for the three positions. The values of the gravitational stresses were derived from [26]. Shown in Fig. 12b are the in vivo experimental results [22] of arterial blood pressure and heart rate responses to the 40 mmHg Valsalva maneuvers performed in the three positions. The corresponding model-based simulations are illustrated in Fig. 12c. Model-based simulations show satisfactory qualitative agreements with the experimental results in both the time course of arterial blood pressure and the time-dependent change in heart rate. Comparisons of the time-dependent hemodynamic responses among the three positions reveal that the magnitudes of changes in arterial blood pressure and heart rate during the Valsalva maneuvers and the overshoot in arterial blood pressure after the release of strain are significantly affected by position. From supine to sitting and to standing, the fall in arterial blood pressure during phase IIa is enlarged, and simultaneously the overshoot in arterial blood pressure during phase IV is enhanced. With respect to heart rate response, the peak value during the Valsalva maneuver is observed to be markedly increased, from 95 to 108 to 118 beats per minute.

Among peripheral circulations, the splanchnic, the renal, and the lower limb venous systems are most sensitive to gravitational stress because they have large vascular compliances and contain up to 60% of the total blood volume in a human body. Figure 13 illustrates the changes in the sum of the stressed blood volumes contained in the splanchnic, the renal, and the lower limb venous systems during the Valsalva maneuver in supine, sitting, and standing positions, respectively. Wiggles, the amplitudes of which decrease accompanying postural change from supine to sitting and standing, can be observed on the three volume curves before the onset of the Valsalva maneuver, whereas during the Valsalva maneuver, such wiggles almost disappear. This phenomenon is considered to result from the sensitivity of venous volume to pressure variation. In normal supine position when venous compliance is large, small variations in perfusion pressure may lead to marked changes in venous volume; however, after a postural change or the onset of the Valsalva maneuver, the veins will undergo severe hyperemia, which makes them stiffer and consequently insensitive to small-amplitude pressure variation. Preceding the onset of the Valsalva maneuver, baseline venous volumes exhibit obvious increases accompanying the postural change, and this phenomenon persists during the Valsalva maneuver. The marked increases in the blood volume contained in these peripheral circulations during the maneuvers imply serious transmissions of blood from the thoracic chamber to the peripheral circulations, which may be a major explanation of the impairment in venous return and the resultant fall in arterial blood pressure during the Valsalva maneuvers. The different degrees of blood pooling in these circulations preceding the onset of the Valsalva maneuver should be a major factor determining the magnitude of the fall in arterial blood pressure when a position is changed from supine to sitting or standing. Moreover, after a postural change the carotid sinus arterial baroreceptors will be unloaded by the orthostatic stress difference between
the heart and the carotid sinus, and simultaneously the cardiopulmonary receptors will be unloaded by the impaired venous return. All these factors together alter the baseline tonic of the carotid sinus and cardiopulmonary baroreflexes, consequently resulting in an enhancement in nervous reflex response during the Valsalva maneuver.

(4) Regulation of cerebral perfusion. One of the most challenging hemodynamic events during the Valsalva maneuver is the maintenance of cerebral perfusion. Besides the circulatory autonomic function that is mainly responsible for the global hemodynamic regulation, local CA plays a crucial role in compensating for the reduced blood supply to the brain. It is well known that blood flow through cerebral circulation depends crucially on cerebral arterial blood pressure and cerebrovascular resistance, in addition to which intrathoracic cerebral venous pressure, which functions as the afterload of cerebral circulation, may be another important determinant of cerebral perfusion. During the Valsalva maneuver, because of the elevation of intrathoracic pressure, the correspondingly increased cerebral venous pressure will hinder cerebral venous return, thereby considerably affecting blood flow through cerebral circulation; in contrast, after the release of strain, a rapid decrease in cerebral venous blood pressure will benefit cerebral blood flow. Suzanne et al. [27] introduced a critical closing pressure conception to explain cerebral blood flow regulation during the Valsalva maneuver. They found that calculating beat-to-beat values of critical closing pressure could provide a coherent explanation for the larger magnitude overshoot in cerebral blood flow than in arterial blood pressure during phase IV. On the basis of their findings, the present study was further focused on quantitatively identifying the relative roles of the circulatory autonomic function, the CA, and the cerebral blood...
flow afterload in regulating cerebral perfusion during the Valsalva maneuver. To this end, we traced the time course of cerebral arteriolar and capillary blood flows during a 40 mmHg Valsalva maneuver with the intact ANS function and the CA, with the preclusion of the CA and without both the ANS function and the CA, respectively. The simulated results with the intact ANS function and the CA are shown in Fig. 14b. For purpose of qualitative comparison, the population mean measurements of arterial blood pressure and cerebral blood flow by Suzanne et al. [27] are illustrated in Fig. 14a. Reasonable agreements between the experiment and simulations are obtained for both arterial blood pressure and cerebral blood flow. In the case of the intact ANS function and the CA, predicted results show that the most noteworthy distinction between arterial blood pressure and cerebral blood flow responses to the Valsalva maneuver is that the magnitude of the overshoot in cerebral flow is significantly larger than that of arterial blood pressure during phase IV. Another difference is that cerebral blood flow does not undergo a sudden decrease as arterial blood pressure does immediately after the release of the Valsalva maneuver strain. This may be explained by the rapid decrease in cerebral venous blood pressure during phase III and phase IV, which latently compensates for the fall in cerebral arterial blood pressure. To investigate the causation of the large overshoot in cerebral blood flow during phase IV, model-based simulations of cerebral blood flows with the preclusion of the CA, and without both the ANS function and the CA, are illustrated in Fig. 15. It can be observed that without the CA, the Valsalva-maneuver-induced fall in cerebral perfusion is deteriorated during phase II, and the magnitude of the overshoot in cerebral flow during phase IV is markedly attenuated compared with the predicted results with the intact CA. This indicates that the CA actually plays an important role in compensating for the impairment in cerebral perfusion and is responsible for producing the large magnitude overshoot in cerebral blood flow. Furthermore, if both the ANS function and the CA are blocked, cerebral perfusion will undergo a continual decrease during the Valsalva maneuver, which underlines the importance of the ANS function and the CA in maintaining cerebral perfusion during the Valsalva maneuver.

**DISCUSSION**

The effect of posture on the hemodynamic responses to the Valsalva maneuver is an important issue of the present study. Predictions reveal that blood volume distribution among different circulations is a key factor dominating the characteristics of the time-dependent arterial blood pressure and heart rate responses to the Valsalva maneuver. During the maneuver conducted in sitting or standing positions, large volumetric blood pooling in the peripheral circulations resulting from gravitational stress significantly impairs the venous return, subsequently reduces the cardiac output, and ultimately elicits larger amplitude responses of arterial blood pressure and heart rate than those seen in a supine position. In comparison with previous similar models, the present model has been constructed in more complexity and detail by involving all the main circulations. It was constructed complexly, even at the expense of increasing difficulties in value assignment and numerical solution, with the intention of providing a comprehensive analysis of the hemodynamic responses to the Valsalva maneuver in terms of the contributions of different local circulations to the global hemodynamic regulation. Through qualitative comparisons of model-based simulations with the experimental data, the present model is demonstrated to be able to predict hemodynamic variables over a wide range from cardiac hemodynamics to time-variant blood flow and pressure transfer in various vascular systems. A model of this kind may provide a reasonable mathematical platform for further “mathematical experiments” on the Valsalva maneuver.

With respect to the individual roles of the carotid sinus, the aortic, and the cardiopulmonary baroreflexes, during the Valsalva maneuver the aortic arterial baroreceptors are unloaded by the elevated intrathoracic pressure and thus exhibit a more pronounced role in regulating arterial blood pressure and heart rate than the carotid sinus baroreceptors do. Furthermore, the cardiopulmonary receptors that are unloaded by the impaired venous return also contribute considerably to the hemodynamic regulations via modulating heart rate and extraplanchnic vascular resistances. When posture is changed from a supine position to a sitting or standing position, gravitational stress difference between the carotid sinus and the heart will latently unload the carotid sinus baroreceptors and lead to an enhancement in the sympathetic tone even in a normal rest condition. This preadjustment may contribute partially to the different hemodynamic responses to the Valsalva maneuver in different positions. Therefore an integrative consideration of the three types of receptors is fundamental to a comprehensive understanding of the role of the ANS in the hemodynamic regulations during the maneuver. The exclusion of any receptor may result in either overestimation or failure in evaluating other baroreflex functions. Although it is true that the summation model for the three receptors was constructed empirically, the reasonable agreements we obtained between the predictions with the in vivo experimental results may partially validate the feasibility of the present baroreflex summation methodology.

The present study also provides quantitative evidence for identifying the relative contributions of the circulatory autonomic functions, the CA, and the cerebral venous blood pressure to the regulation of cerebral perfusion during the Valsalva maneuver. According to the simulated results, the circulatory autonomic functions are responsible...
for the maintenance of the basic cerebral blood flow via regulating arterial blood pressure, and the local CA mainly functions to compensate for the impaired cerebral perfusion through the regulation of cerebrovascular resistance. The two mechanisms together dominate the main part of cerebral perfusion regulation. Furthermore, cerebral venous blood pressure should be another important hemodynamic parameter affecting blood flow through cerebral circulation. During the Valsalva maneuver, the marked increase in cerebral venous blood pressure resulting from the elevation of intrathoracic pressure impedes cerebral blood flow. After the release of strain, however, a rapid decrease in cerebral venous blood pressure will compensate for the fall in arterial blood pressure, thereby benefiting blood flow through cerebral circulation. The marked overshoot in cerebral blood flow during phase IV cannot be simply attributed to any single regulatory function; it is an integrated outcome of the circulatory autonomic functions, the CA, and the cerebral venous blood pressure.

In summary, most of the hemodynamic parameters predicted by the present model are either consonant with the available in vivo measurements or within reasonable physiological ranges. This model is applicable but not limited to the simulation of the short-term transient hemodynamic responses to the Valsalva maneuver. If further refinements are made, this model may be expected to yield a useful mathematical tool for interpreting experimental results, guiding experimental design as well as assisting in clinical practice.

LIMITATIONS

Limitations of the present study mainly arise from the difficulty in accurately assigning values for several parameters involved in the CVS model and from the empirical nature of the mathematical functions representing the ANS and the CA model. Many parameters unavailable in our known literature have been estimated based either on the anatomical data or on the general physiological knowledge, such as blood volume and flow distribution among different circulations [4] and blood pressure fall at different vascular levels [20]. Sensitivity analysis showed that the parameters to which model-based simulations are mostly sensitive were the baseline compliances of the veins, the nonlinear venous P–V relationships, and the coefficients in the heart model. In the present model, the baseline compliances of the veins of the peripheral circulations were adopted from [4], and the mathematical equations characterizing the nonlinear property of venous compliance were derived from [28] and [29]. Although the venous compliance model has been proved in the present paper able to provide reasonable reproduction of venous volume at a large range of pressure, it is far from a universal one. In fact, to our knowledge there is still no model that can be recognized as fit for a rigorous universal representation of the nonlinear vascular compliance for a large number of veins distributing in different regions of a human body. The heart model was constructed on the basis of Sun’s work [3] with several modifications made to permit involvement of the nervous control. Although we incorporated many new concepts in the present ANS model, its form still follows that of the model proposed in [10] with most of the parameters kept unchanged. However, other than the single-carotid-baroreceptor model, the present ANS model simultaneously includes the aortic, the carotid sinus, and the cardiopulmonary receptors, which raises a problem of how to model the combination of the receptors. Concerning this issue, we developed a weighted summation model where fractional factors were introduced to reflect the relative contributions of different baroreflexes to the control of different effectors. Nevertheless, because of the lack of direct experimental evidence, the present summation model is empirical in nature. Among all the parameters involved in the ANS model, the fractional factors may be the ones most imperative to further discussion and validation. Therefore we must state that the present summation method, which has been demonstrated to well fit the present study, is not readily applicable to other studies without modification. Moreover, to avoid the treatment of multiple mechanisms involved in CA, the present CA model has been completely constructed empirically, making it far from a deliberate model. Some more-detailed CA models have been recently reported [17–19].

APPENDIX

Mathematical descriptions of the CVS model

(1) Representation of the heart. The basic form of the mathematical model of the heart was derived from [3] where the heart’s four chambers were each represented by a time-variant elastance, which varies over a cardiac cycle according to an exponential charge-discharge waveform with a baseline and an amplitude component. We also made several additional modifications to account for the changes in $E_{max}$ [mmHg/ml] (maximal systolic elastance) and HR (heart rate) in response to the nervous reflex control. Moreover, left-right heart interaction and cardiac volume coupling were also modeled for the purpose of a comprehensive representation of the cardiac hemodynamics.

(1) Basic models: The mathematical representations of the four cardiac chambers can be written in a similar form as follows:

For LV (left ventricle):

$$e_v = \begin{cases} \frac{F \cdot F_v \cdot E_{\max} \cdot (1 - e^{-\frac{t}{\tau}})}{1 - e^{-\frac{t}{\tau}}} + E_{\text{rs}} / F_v, & 0 \leq t < t_1 \\ \left( e_{v_1} - E_{l_v} \right) e^{\frac{t}{\tau}} + E_{\text{rs}} / F_v, & t_1 < t < t_2 \end{cases}$$

And for LA (left atrium):
where \( e_v \) [mmHg·ml⁻¹] and \( e_b \) [mmHg·ml⁻¹] represent the elastances of the left ventricle and atrium, respectively; \( t_s \) [sec], \( t_s \) [s] indicate a cardiac cycle and the moment when systolic elastance reaches the maximal value, respectively; \( t_{ac} \) [s] refers to the time when the atrium begins to contract, \( t_{ar} \) [s] indicates the time when the atrium begins to relax, and \( t_{ao} \) [s] is a constant used to scale the value of systolic elastance when the cardiac cycle changes; \( F_t \) is a scaling factor that characterizes the nonlinear property of the starling law and the dependence of the time-variant elastance on the volume of the left ventricle. \( F_s \) is described by a simple first-order linear function:

\[
F_s = 1 - v_{de}/V_{max},
\]

where \( v_{de} \) [ml] indicates the end diastolic volume of the left ventricle, and \( V_{max} \) [ml] is a volume constant.

For RV (right ventricle):

\[
e_v = \left\{ \begin{array}{ll}
E_s (1 - e^{-v/t_s}) + E_v & 0 \leq t \leq t_s \\
E_s e^{-v/t_s} + E_v/F_s & t_s < t < t_s^t
\end{array} \right.
\]

And for RA (right atrium):

\[
e_v = \left\{ \begin{array}{ll}
E_s (1 - e^{-v/t_{ac}}) + E_v & 0 \leq t \leq t_{ac} \\
E_s e^{-v/t_{ac}} + E_v/F_s & t_{ac} < t < t_{ac} + t_{ac}^t
\end{array} \right.
\]

The parameters in Eqs. 4 and 5 have similar meanings to those in Eqs. 1 and 2.

(II) Left-right ventricular interaction: The left and right ventricles interplay considerably with each other through a so-called “talk pressure” across the interventricular septum. To describe this phenomenon, Maughan et al. [30] proposed a mathematical model that consists of three elastic elements, namely, \( e_v \), \( e_r \), \( e_s \), and \( E_s \) [mmHg·ml⁻¹]. According to the model, blood pressures in the left and right ventricles (\( p_l \) [mmHg], \( p_r \) [mmHg]) can be expressed as follows:

\[
p_l = E_s e_v e_r + E_v + e_v p_r,
\]

and

\[
p_r = E_s e_v e_r + E_v + e_v p_l,
\]

where \( E_s \) [mmHg·ml⁻¹] refers to an elastic element that represents the shift of the septum.

(III) Cardiac volume coupling: Volumetric coupling takes place among all the four cardiac chambers. The coupling was accounted for in the present study by adoption of the model proposed in [3], where pericardial dynamics are represented by a pericardial compartment with an exponential P–V relationship. The pericardial pressure \( p_{pc} \) [mmHg] is controlled by the total cardiac chamber volume in the pericardium according to an exponential relationship. This pressure acts equivalently on all the four cardiac chambers through the free walls of atria and ventricles. The total fluid volume (\( V_{pc} \) [ml]) is calculated by figuring up the total blood volume (\( V_b \) [ml]) contained in the heart and the pericardial fluid volume (\( V_{pc} \) [ml]).

\[
V_{pc} = V_b + V_{pc}, \quad \text{where} \quad V_b = v_v + v_s + v_r + v_c.
\]

Thus the pressure-volume relationship in the pericardium can be represented by an exponential function [3].

\[
p_{pc} = k_{pc} \exp[(V_b - V_{pc})/\phi_{pc}]
\]

where \( V_{pc0} \) [ml] is a volume offset, \( \phi_{pc} \) [ml] is a volume constant, and \( k_{pc} \) [mmHg] is a constant.

(IV) Dependency of systolic duration on heart rate: Systolic duration is not fixed, but changes with heart rate. In the present study, an empirical sigmoidal function [31] was employed to relate the moment of peak systolic elastance to a cardiac cycle. The mathematical description is shown below:

\[
T_s = T_{s_{min}} + \frac{\beta^t}{\left(\beta^t + \theta^t\right)} \cdot \left(T_{s_{max}} - T_{s_{min}}\right)
\]

where \( T_s \) [s] is the moment of peak systolic elastance; \( T_{s_{min}} \) [s] and \( T_{s_{max}} \) [s] are the minimal and maximal val-

Table 1. Coefficients in the heart model.

<table>
<thead>
<tr>
<th>Parameter values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_{iv} = 6.0 ) mmHg·ml⁻¹</td>
</tr>
<tr>
<td>( E_{ir} = 0.07 ) mmHg·ml⁻¹</td>
</tr>
<tr>
<td>( E_{rsv} = 1.2 ) mmHg·ml⁻¹</td>
</tr>
<tr>
<td>( E_{rsv} = 0.04 ) mmHg·ml⁻¹</td>
</tr>
<tr>
<td>( V_{max} = 900 ) ml</td>
</tr>
<tr>
<td>( b_{pv} = 0.000025 ) mmHg·s²·ml⁻²</td>
</tr>
<tr>
<td>( T_{s_{min}} = 0.2259 ) s</td>
</tr>
<tr>
<td>( \phi_{pc} = 40 ) ml</td>
</tr>
</tbody>
</table>
In consideration of the high stiffness of the vessels and the weak oscillation of blood pressures in them, the compliances were assumed as fixed values.

(I) Arteriole and artery: A simple exponential P–V relationship [32] was adopted for artery. The mathematical function is written as

$$p = E_0 e^{\lambda t} \cdot Z$$  \hspace{1cm} (11)

Where $E_0$ [mmHg·ml⁻¹] denotes the zero-volume elastance, $Z$ [ml] refers to the volume constant, and $v$ [ml] indicates the blood volume contained in artery.

(II) Vein: i) At positive transmural pressure, the venous P–V relationship was represented by a mathematical function proposed in [28, 34]:

$$\Delta V = \frac{2 \cdot \Delta P \cdot \arctan \left( \frac{\pi \cdot C \cdot \Delta P_{\text{max}}}{2 \cdot \Delta V_{\text{max}}} \right)}{\pi}$$  \hspace{1cm} (12)

Where $\Delta V$ [ml] represents the change in venous volume corresponding to the change in venous transmural pressure $\Delta P_{\text{trans}}$ [mmHg], where $\Delta P_{\text{trans}} = P_{\text{trans}} - P_{\text{bas}}$, $P_{\text{bas}}$ [mmHg] refers to the baseline venous pressure in normal rest condition. $C_0$ [ml·mmHg⁻¹] indicates the venous compliance at $\Delta P_{\text{trans}} = 0$, and $\Delta V_{\text{max}}$ [ml] denotes the maximal venous volume change.

By simultaneously deriving the differentials about $\Delta P_{\text{trans}}$ on both sides of Eq. 12, a mathematical relationship between venous compliance and transmural pressure can be obtained as

$$C = \frac{d\Delta V}{d\Delta P_{\text{trans}}} = \frac{C_0}{1 + \left( \frac{\pi \cdot C \cdot \Delta P_{\text{max}}}{2 \cdot \Delta V_{\text{max}}} \right)}$$  \hspace{1cm} (13)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Artery $(E_0:Z:R:L)$</th>
<th>Arteriole $(C_0:R:L)$</th>
<th>Capillary $(C_0:R:L)$</th>
<th>Vein $(C_0:R:L;\Delta V_{\text{max}};V_{u,n})$</th>
<th>Vein* $(R:L)$</th>
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</thead>
<tbody>
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<td>$\times$</td>
<td>$\times$</td>
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<td>$\times$</td>
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<td>$\times$</td>
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<td>$\times$</td>
</tr>
<tr>
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<tr>
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<td>0.38:3.12:0.0003</td>
<td>0.60:2.09:0.0005</td>
<td>2.30:0.55:0.0004:62.0:280</td>
<td>0.17:0.0005</td>
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<td>0.93:0.96:0.0005</td>
<td>55.0:0.3:0.0004:1380:1300</td>
<td>0.09:0.0005</td>
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<td>0.35:1.82:0.0003</td>
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<td>0.24:3.52:0.0005</td>
<td>8.60:1.06:0.0004:268:175</td>
<td>0.32:0.0005</td>
</tr>
<tr>
<td>RLB</td>
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<td>0.20.5:2.80:0.0003</td>
<td>0.24:3.52:0.0005</td>
<td>8.60:1.06:0.0004:268:175</td>
<td>0.32:0.0005</td>
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<td>$\times$</td>
<td>3.00:0.003:0.0005:40:0:18</td>
<td>$\times$</td>
</tr>
</tbody>
</table>

Table 2. Values of parameters in the CVS model. Units of the parameters: $E_0$, mmHg·ml⁻¹; Z, ml; R, mmHg·s·ml⁻¹; L, mmHg·s²·ml⁻¹; $C_0$, mmHg⁻¹·ml; $\Delta V_{\text{max}}$, ml; $V_{u,n}$, ml. Note that $R$ and $L$ in Vein* term for each circulation represent the resistance and inertance of the venous system that links the end of the venule bed to the vena cava, respectively.
Although the value of $\alpha$ can be deduced to be 2 by directly transforming Eqs. 12 to 13, in this paper, it was modified to be 1.35 to yield reasonable fits of predictions to experimental data.

Further, when the response time of vascular wall to pressure change is considered, time-variant venous compliance can be calculated according to

$$\frac{dC}{dt} = \frac{C - C^*}{\tau_p}, \quad (14)$$

where $C$ [ml·mmHg$^{-1}$] is a time-variant venous compliance, and $\tau_p$ is a time constant representing the latency of the response of vascular wall to blood pressure, which was set at 5.0 s in the present study.

Moreover, in consideration of the unstressed venous volume ($v_u$ [ml]), a complete mathematical expression of the venous $P$–$V$ relationship is written as

$$v = C \cdot (p - p_0) + v_u, \quad (15)$$

where the value of $p_0$ was set at 0 mmHg in the present study.

ii) At negative transmural pressure, a $P$–$V$ equation proposed in [29] for collapsible tubes was employed, which is written as

$$p = \frac{V}{10C} \left[ 1 - \left( \frac{v}{v_u} \right)^2 \right], \quad (16)$$

where $v_u$ [ml] is the basal value of $v_u$.

Values of the coefficients in the venous compliance model are given in Table 2.

(3) Nonlinear venous resistance. During the Valsalva maneuver, a significant fall in transmural pressure in the vena cava inside the thoracic chamber will result in a significant increase in venous resistance that considerably affects the venous return to the right atrium.

To deduce a function that mathematically represents the dependency of venous resistance on transmural pressure, for the purpose of simplification a segment of flow in a vessel with a circular cross section was taken as an example. According to Poiseuille’s law, the vascular resistance can be calculated by

$$R = \frac{8 \mu l}{\pi r^4}, \quad (17)$$

where $R$ [mmHg·s·ml$^{-1}$] is the vascular resistance, $\mu$ [mmHg·s·cm$^{-1}$] is the viscosity of blood, $l$ [cm] is the length of the vessel, and $r$ is the radius of the vessel. Here, if we assume a constant blood viscosity for a given length we can find that

$$R \propto \frac{1}{r^4} \propto \frac{1}{A^2} \propto \frac{1}{V^2}, \quad (18)$$

where $A$ [cm$^2$] refers to the cross-sectional area of the vessel.

According to Eq. 18, a mathematical function that relates $R$ to $V$ can be written as

$$R = k_R \left( \frac{V}{V_u} \right)^2 + R_0, \quad (19)$$

where $k_R$ [mmHg·s·ml$^{-1}$] is a constant controlling the slope of $R$–$V$ curve, $V_u$ is a constant, and $R_0$ [mmHg·s·ml$^{-1}$] is the basal value of $R$. In the present study, to avoid an unnecessary increase of model complexity, only the resistances of the intrathoracic vena cava segments have been considered nonlinear and calculated according to Eq. 19. The values of the parameters in Eq. 19 are summarized in Table 3.

(4) Inertance. The inertial term is not a hemodynamic parameter that significantly affects the cardiovascular response to the Valsalva maneuver. Nevertheless, its inclusion may favor a more physiologically realistic prediction of the time-dependent transfer of pressure and flow waveforms through the CVS. In the present model, inertial terms have been involved in all vascular compartments.

(5) Intrathoracic pressure. The respiratory effect on hemodynamics was accounted for by defining a periodically varying intrathoracic pressure ($P_{it}$ [mmHg]). The model suggested in [3, 35] was adopted, where the time-dependent $P_{it}$ was characterized as an exponential charge-discharge waveform with a baseline $P_{itb}$ [mmHg] and an amplitude $P_{ita}$ [mmHg]. The duration $T_{it}$ [s], $P_{itb}$, and $P_{ita}$ were set at 5 s, −4.6 mHg, and 3.0 mmHg, respectively, for the normal rest condition. At the onset of the Valsalva maneuver, $P_{it}$ was characterized as an exponentially increasing function of time within the first 2 to 3 heartbeats and then was kept at a constant value throughout the Valsalva maneuver.

(6) Parameter assignment. (I) Cardiopulmonary circulation: Values for parameters involved in the compartments of the heart and the pulmonary circulation have been assigned according to [3].

(ii) Peripheral circulations: Concerning the value assignments for the resistances in the peripheral circulations, the value of the total resistance of each circulation has been reported in [4]. However, insufficient data on the specific resistances of the arterial trees and the vascular networks of arteriole, capillary, and venule are directly available in literature. With this understanding, the estimation of these unknown resistances was done in three steps in this paper. At the first step, arterial resistance on the arterial side of each circulation was roughly calculated according to the law of fluid mechanics based on the anatomic-data-based 3D model of the arterial tree. At the sec-

<table>
<thead>
<tr>
<th>Vein</th>
<th>$k_R$ (mmHg·s·ml$^{-1}$)</th>
<th>$V_u$ (ml)</th>
<th>$R_0$ (mmHg·s·ml$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC1</td>
<td>0.00008</td>
<td>44</td>
<td>0.0017</td>
</tr>
<tr>
<td>VC2</td>
<td>0.00012</td>
<td>58</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

The values in Table 3 are derived from the model described in the text.
ond step, given that the total resistance of each circulation is known [4], the resistances of arteriolar, capillary, and venule beds were estimated according to blood pressure level at each vascular level. At the last step, because arterial resistance is an important determinant of the shape of arterial blood flow waveform, slight adjustments were made for arterial resistances to obtain reasonable fits of predictions to experimental data [20].

Experimental data on invariance at vascular levels detailing the arteriolar, capillary, and venule beds have been merely reported. In fact, data available in literature were usually limited to some big arteries or veins [4, 10, 31]. Although invariance has almost no effect on steady blood flow, it may be a parameter affecting the shape of time-dependent flow waveforms, especially the reversal of arterial flow in early diastole. With this in mind, we first estimated the values of invariance according to the general physiological features of the cardiovascular system and repeatedly adjusted them until acceptable fits of simulated flow waveforms to measurements [20] were obtained. In regard to the vascular compliance models, we distinguished between arteries and other vascular tissues in the present model where the arterial compliances were characterized by zero-volume elastances \(E_0\) and volume constants \(Z\) and other compliances represented by nonlinear capacitors \(C\). The baseline venous compliance of each circulation has been reported in [4, 28]. Whereas for \(E_0\) and \(Z\) in the arterial compliance model, since no direct data was available from the knowledge of previous reports, their values were preliminarily estimated according to the general knowledge of vascular elastic properties at different arterial levels [7] and of blood volume in arterial compartments. Subsequently, the estimated values were adjusted to the yield predictions of blood pressures and blood flows comparable to the experimental measurements reported in [20]. There was also a lack of sufficient experimental data for us to define \(C\) for arteriolar, capillary, and venule beds. In this regard, because \(C\) determines blood volume contained in a vessel and affects the damping of the pulsatile feature of blood flow through a vessel, we were able to base the estimation of these parameters mainly on the blood volume distributions in these vascular beds. Thereafter the estimated values were further optimized to get reasonable fits of predictions of blood flow and pressure waveforms to experimental observations at these vascular levels.

The values of all parameters involved in the CVS model are summarized in Table 2.

Mathematical model of the ANS

(1) Afferent pathways. (I) Aortic and carotid baroreceptors: According to the mathematical model developed by Ursino [10], the frequency discharges of the afferent pathways elicited by the aortic and carotid baroreceptors are described as a serial arrangement of a linear derivative first-order dynamic block and a sigmoidal static characteristic,

\[
\frac{dp}{dt} = \frac{p + \tau_c \frac{dp}{dt}}{\tau_c},
\]

(20) \[
f_a = f_{a,m} + \frac{f_{a,m} \exp[(\tilde{p} - p)/k_p]}{1 + \exp[(\tilde{p} - p)/k_p]},
\]

(21)

where \(\tilde{p}\) [mmHg] is the output of the linear dynamic block; \(p\) is the pulsatile arterial blood pressure; \(\tau_c\) [s] and \(\tau_v\) [s] are two time constants; \(f_{a,m}\) [spike·s\(^{-1}\)] is the frequency of the spikes in the afferent fibers; \(f_{a,m,\min}\) [spikes·s\(^{-1}\)] and \(f_{a,m,\max}\) [spikes·s\(^{-1}\)] are the maximal and minimal values of the afferent frequency discharge, respectively; \(p_a\) [mmHg] is the set-point value of the arterial baroreflex; and \(k_{1,af}\) [mmHg] is a parameter controlling the slope of the \(p_\text{~} - f\) curve, which can be calculated by \(k_{1,af} = (f_{a,m,\max} - f_{a,m,\min})/4G_{1,af}\), where \(G_{1,af}\) [spike·s\(^{-1}\)·mmHg\(^{-1}\)] is the maximal baroreceptor gain.

We presume that afferent pathways of both the carotid sinus and the aortic baroreceptors can be represented by the above mathematical functions; nevertheless, the transmural pressures at the two receptors need to be distinguished according to the following equations:

\[
p_{wa} = p_m - p_a,
\]

(22) \[
p_{wc} = p_m - p_a
\]

(23)

where \(p_{wa}\) [mmHg] and \(p_{wc}\) [mmHg] are the transmural pressures at the aortic and carotid sinus receptors, respectively; \(p_{abs}\) [mmHg] is the absolute arterial blood pressure at the two receptors; \(P_n\) [mmHg] is the intrathoracic pressure; and \(P_h\) [mmHg] is the gravitational stress relative to the heart.

(II) Cardiopulmonary receptor: Mathematical equations describing the afferent discharge of the cardiopulmonary receptors are derived from [5],

\[
\frac{dp}{dt} = \frac{p - \tilde{p}}{\tau_v},
\]

(24) \[
\frac{dp}{dt} = \frac{f_{a,m} \exp[(\tilde{p} - p)/k_p]}{1 + \exp[(\tilde{p} - p)/k_p]}.
\]

(25)

where \(\tilde{p}\) [mmHg] is the output of the linear dynamic block; \(p_v\) is the venous pressure; \(\tau_v\) [s] is a time constant; \(f_{a,v}\) [spike·s\(^{-1}\)] is the frequency of the spikes in the afferent fibers; \(f_{a,v,\max}\) [spike·s\(^{-1}\)] is the maximal value of the afferent frequency discharge; \(p_{nv}\) [mmHg] is the set-point value of the cardiopulmonary baroreflex; and \(k_{dv}\) [mmHg] is a parameter controlling the slope of the \(\tilde{p}_\text{~} - f\) curve, which can be calculated by \(k_{dv} = (f_{a,v,\max} - f_{a,v,\min})/4G_{dv}\), where \(G_{dv}\) [spike·s\(^{-1}\)·mmHg\(^{-1}\)] is the maximal baroreceptor gain.

(2) CNS and efferent pathways. The CNS that functions as an integrating element of the overall nervous reflex system was mathematically modeled by a system of functions
that relate the input signals to the output signals of the CNS, namely, an afferent-effenter discharge relationship. For the purpose of a reasonable representation of the interactions among different receptors, based on the experimental findings that different baroreceptors were summatory and that the pattern of the summation changed remarkably with the intensity of the total afferent signals [36, 37] from baroreceptors, in the present study a weighted summation of the input signals from the aortic and the carotid sinus receptors at the afferent level of the CNS was performed. The contribution of the cardiopulmonary receptors was taken into account by fractionally superposing the efferent discharge elicited by the cardiopulmonary receptors on the efferent pathways of the CNS.

(I) Sympathetic efferent pathways:

\[
f_a = \min\{f_c, (f_c - f_s) \cdot \exp(-k_c \cdot (F_c - f_s)) + F_c \cdot f_s, f_{max}\},
\]

where

\[
f_c = f_s + (f_c - f_s) \cdot \exp(-k_c \cdot f_s) - f_{max} \tag{27}
\]

where \(f_{efs} \text{ [spike·s}^{-1}\] is the relative frequency of spikes in the sympathetic efferent fibers induced by cardiopulmonary afferent input; \(f_{efs,0} \text{ [spike·s}^{-1}\] is a baseline value of \(f_{efs} \text{ in normal condition}; \(f_{esv,E}, f_{esv,S} \text{ [spike·s}^{-1}\] and \(k_{esv} \text{ [s·spike}^{-1}\] are constants; \(f_{efs} \text{ [spike·s}^{-1}\] is the frequency of spikes in the sympathetic efferent fibers; \(f_{esv,E}, f_{esv,S}, f_{efs,max} \text{ [spike·s}^{-1}\] and \(k_{es} \text{ [s·spike}^{-1}\] are constants; and \(F_{aor}, F_{car}\) and \(F_v\) are the fractional factors that reflect the relative contributions of the three baroreceptors to the sympathetic control of different effectors.

\[
f_{efs} = f_{aor} + f_{car} \cdot \exp\left(\frac{f_{aor} - f_{max}}{k_{aor}}\right) + f_{car} \cdot \exp\left(\frac{f_{car} - f_{max}}{k_{car}}\right) + f_{esv} \cdot \exp\left(\frac{f_{esv} - f_{max}}{k_{esv}}\right) \tag{28}
\]

where \(f_{efs} \text{ [spike·s}^{-1}\] is the frequency of spike in the parasympathetic efferent fibers; \(f_{esv,S}, f_{efs,E}, f_{af,car,0}, f_{aor,0} \text{ [spike·s}^{-1}\] and \(k_{es} \text{ [spike·s}^{-1}\] are constants; and \(F_{aor}, F_{car}\) are fractional factors for the aortic and carotid sinus baroreflexes, respectively.

The definition of the fractional factors for the three receptors in the summation model has been based qualitatively on the experimental findings. For instance, it was pointed out that the aortic and carotid sinus baroreceptors might have different relative roles in the control of heart rate, blood pressure, and peripheral vascular resistance [36, 38]. Vatner et al. [38] suggested, based on their studies in awake dogs, that the aortic baroreceptors were more effective in controlling heart rate than the carotid sinus baroreceptors were. Donald and Edis [39] and Edis [40] found that the carotid sinus baroreceptors had a lower threshold and a greater gain and total range than the aortic baroreceptors had in regard to the control of arterial blood pressure. Guo et al. [41] suggested, based on the in vivo experiments in rabbits, that the aortic and carotid sinus baroreceptor-mediated sympathetic control of blood pressure or peripheral vascular resistance was abundant, that the impairment in the control of arterial blood pressure caused by denervation of either baroreceptor could be rapidly compensated for by another intact baroreceptor, and, on the other hand, that the cardiopulmonary receptors had a significant role in heart rate regulation, but contributed negligibly to the regulation of vascular resistance. Following these experimental findings, we specified different fractional factors for the three types of receptors in the summation model to account for their different relative contributions to the control of different effectors.

(3) Effector. (I) Cardiac elastance, vascular resistance, and venous unstressed volume: Cardiac elastance, vascular resistance, and venous unstressed volume respond to sympathetic efferent signals according to a system of functions that include a pure latency, a monotonic logarithmic static function, and a low-pass first-order dynamics [10]. The equations are written as

\[
\sigma_{es}(t) = \frac{G_{es} \cdot \log[f_{efs}(t - D_{es}) - f_{efs,min} + 1]}{\tau_{es}} \tag{29}
\]

\[
\sigma_{es}(t) = 0 \tag{30}
\]

\[
x(t) = \Delta x(t) + x_{0} \tag{31}
\]

where \(x(t)\) represents a generic-controlled parameter for the peak cardiac systolic elastances [mmHg·ml\(^{-1}\)], arterial resistances \(R\ [\text{mmHg·s·ml}^{-1}]\), and unstressed volumes \(V_{u} [\text{ml}]\), and \(\tau_{es} [\text{s}]\) are a pure latency and a time constant related to each individual effector, respectively, and \(\sigma_{es}\) is the output of the static characteristic. \(G_{es}\) is a gain factor, which is positive for \(E\) and \(R\) but negative for \(V_{u}\). \(f_{efs,min}\) is a threshold for sympathetic stimulation.

(II) Cardiac cycle: Although the law of sympathetic-parasympathetic interaction in heart rate regulation has been previously considered complex and nonlinear, Mauro [10] pointed out that it was feasible to assume a linear sympathetic-parasympathetic relationship if heart rate is replaced by cardiac cycle.

Sympathetic stimulation regulates cardiac cycle according to

\[
\sigma_{es}(t) = \frac{G_{es} \cdot \log[f_{efs}(t - D_{es}) - f_{efs,min} + 1]}{\tau_{es}} \tag{32}
\]

\[
\sigma_{es}(t) = 0 \tag{33}
\]
The contribution of parasympathetic stimulation to cardiac cycle regulation is

$$\sigma_T(t) = G_T \cdot f_C^p (t - D_T)$$  \hspace{1cm} (34)$$

Coefficients and constants in the ANS model are summarized in Table 4.

**CA Model**

The CA model comprises a low-pass first-order dynamic equation, a linear equation with a pure latency, and a sigmoidal equation.

$$\frac{dx(t)}{dt} = \frac{-x(t)}{r_x} + \frac{CAB_f - CAB_C}{r_x}$$  \hspace{1cm} (37)$$

$$\Delta R(t) = G_r \cdot x(t - D_r)$$  \hspace{1cm} (38)$$
Table 5. Values of parameters in the CA model.

<table>
<thead>
<tr>
<th>Parameter values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{aut}$ = 1.5 mmHg·s·ml$^{-1}$</td>
</tr>
<tr>
<td>$D_{aut}$ = 3.0 s</td>
</tr>
<tr>
<td>$k_{cerr}$ = 7.6 mmHg</td>
</tr>
</tbody>
</table>

$$
\Delta R(t)_{aut} = \Delta R(t)_{cerr} \frac{\exp\left[\left(\rho_{cerr} - \rho_{aut}\right)/k_{cerr}\right]}{1 + \exp\left[\left(\rho_{cerr} - \rho_{aut}\right)/k_{cerr}\right]} + \frac{\Delta R(t)_{aut}}{2}
$$

$$
R(t)_{aut} = R_{aut} + \Delta R(t)_{aut}
$$

where $x_{aut}$ is a state variable that accounts for the effect of autoregulation; $CABF_{0}$ [ml·s$^{-1}$] is the control $CABF$; $k_{aut}$ and $r_{aut}$ are two constants; $\Delta R_{aut}$ [mmHg·s·ml$^{-1}$] is the variation in arteriolar resistance; and $G_{aut}$ [mmHg·s·ml$^{-1}$] is the gain. $D_{aut}$ [s] is the time of latency; $k_{cerr}$ [mmHg] is a constant; $P_{cerr}$ [mmHg] is the cerebral arteriolar pressure; $P_{cerr}$ is the set point pressure; and $R_{cerr}$ is the basal cerebral resistance. Coefficients in the CA model are given in Table 5.

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