An Integrative Model of the Cardiovascular System Coupling Heart Cellular Mechanics with Arterial Network Hemodynamics

Young-Tae Kim,1* Jeong Sang Lee,2* Chan-Hyun Youn,3 Jae-Sung Choi,2 and Eun Bo Shim1

1Department of Mechanical and Biomedical Engineering, Kangwon National University, Chunchon; 2Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine and SMG-SNU Boramae Hospital, Seoul; 3Department of Information and Communications Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea

*Young-Tae Kim and Jeong Sang Lee contributed equally to this study.

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Address for Correspondence:
Eun Bo Shim, PhD
Department of Mechanical and Biomedical Engineering, Kangwon National University, 1 Kangwondaehak-gil, Chunchon 200-701, Korea
Tel: +82.33-250-6318, Fax: +82.33-257-6595
E-mail: ebshim@kangwon.ac.kr

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INTRODUCTION

There have been a number of recent studies examining the relationship between arterial wall stiffening and cardiac cellular overload (1, 2). However, despite substantial progress in understanding this issue, the detailed mechanisms underlying this relationship remain unclear. Therefore, a novel approach is required to delineate the causal relationship between arterial stiffness and heart hypertrophy. The use of computer simulations with mathematical models is an alternative method and has been widely used for the analysis of cardiovascular system dynamics (3-6).

Lumped models of the cardiovascular system are very simple and can be easily coupled with the nervous system for long-term simulation (7). However, the model cannot accurately predict microscopic phenomena in cells or tissues. To overcome this limitation, we proposed a cell-system integrated model of the cardiovascular system that included cardiac cells, the Laplace heart, and the vascular system (8-10). However, the cell-system model uses relatively a simple lumped model for the arterial system and lacks detailed information regarding arterial pressures and pulse wave velocity (PWV). On the other hand, mathematical models focusing on arterial hemodynamics have been proposed by several groups (11-13). These models have the ability to represent the spatial distribution of arterial hemodynamics and PWV. However, the time-varying capacitance heart model (14) was incorporated into these models by which the relationship between heart cellular mechanics and arterial hemodynamics could not be analyzed.

In this study, the arterial network model of Ozawa et al. (11) was incorporated into our previous cell-system model (8) to delineate the physiological relationship between arterial pressure and left ventricular hypertrophy (LVH). To verify the present method, we calculated the effects of arterial stiffness, arterial hemodynamics, and pulse wave velocity on cardiac cellular mechanics, and compared the results with experimental and...
clinical observations. Using this methodology, the physiological effects of arterial stiffness variation on LVH were assessed in an integrated manner.

MATERIALS AND METHODS

To simulate heart mechanics and arterial pulse waves at a multiscale level, we developed an integrative mathematical model that combined cell excitation-contraction coupling with heart mechanics, system circulation, and hemodynamics of the arterial network. In our previous studies (8, 10), we combined the ventricular cell model with the Negroni and Lascano model (NL model) (15) and eventually with system circulation. Here, we used the same approach for the atrial and ventricular models, but with the addition of arterial network branches (Fig. 1).

As described in our previous report (10), the present computational approach to cardiac cells is based on the electrophysiological models of human atrial and ventricular myocytes proposed by Nygren et al. (16) and ten Tusscher et al. (17) (TNNP model), respectively. In addition, these cellular electrophysiological models were combined with the NL model of cross-bridge dynamics (CBD) for contraction (18). Cross-bridge dynamics in the NL model are described by a four-state system consisting of free troponin (T), Ca$^{2+}$-bound troponin (TCa), Ca$^{2+}$-bound troponin with attached cross-bridges (TCa*), and troponin with attached cross-bridges ($T^*$). The total force ($F$) of a single muscle unit is given by the following relationship:

\[ F = F_b + F_p \]  

where $F_b$ is the equivalent cross-bridge force generated by the contribution of all cross-bridges attached in parallel within the muscle unit and $F_p$ is the force developed by the elastic element of the muscle unit. The cross-bridge force generated in (a) is presented as follows, according to the NL paper (15):

\[ F_b = A \cdot ([TCa^*] + [T^*]) \cdot h \]  

where $A$ is the model parameter and $h$ is the cross-bridge elongation length. The related parameters in the NL models are presented in Table 1.

The forces obtained from the cell-NL models were converted into atrial and ventricular pressures by applying Laplace’s law to the atrial and ventricular models. In our previous report, we referred to this type of heart model as a biological Laplace heart (BLH) (9). The NL, as well as the spherical atrial and ventricle models, were explained in detail in our previous reports (8, 9).

We used a lumped parameter model to simulate a cardiovascular system. With the exception of the heart and arterial compartments, the hemodynamic elements were the same as those described by Heldt et al. (19). The entire model is shown in Fig.

![Fig. 1. Schematic of the integrative cell-system simulation model designed for effective multiscale numerical analysis from cellular to tissue mechanics. BLH, biological Laplace heart.](image-url)

Table 1. Equations and parameter values for the cross-bridge dynamics model

| Heart chamber | Forces | Equations & parameter values | References |
|---------------|--------|------------------------------|------------|
| Left ventricle | CBCF | $F_b = A([TCa^*] + [T^*])h$ | Negroni and Lascano (15) |
|               |       | $A = 1,800 \text{ mN/mm}^2/\mu\text{m} / \mu\text{M}$ | Negroni and Lascano (15) |
|               | Cellular passive elastic reaction force | $F_p = E(e(D(L/Le-1)), (L > Le)$ | Landesberg and Sideman (29) |
|               |       | $E = 2 \mu\text{M/s}, D = 10$ | Landesberg and Sideman (29) |
|               |       | $F_p = -B(1-L/Le), (L < Le)$ | Landesberg and Sideman (29) |
| Left atrium   | CBCF | $F_b = A([TCa^*] + [T^*])h$ | Negroni and Lascano (15) |
|               |       | $A = 450 \text{ mN/mm}^2/\mu\text{m} / \mu\text{M}$ | Beyar and Sideman (30) |
|               | Cellular passive elastic reaction force | $F_p = E(dL/Le-1), (L > Le)$ | Landesberg and Sideman (29) |
|               |       | $E = 1.0 \mu\text{M/s}, D = 20$ | Landesberg and Sideman (29) |
|               |       | $F_p = -B(1-L/Le), (L < Le)$ | Landesberg and Sideman (29) |

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The peripheral circulation is divided into the upper body, renal, splanchnic, and lower extremity sections; the intrathoracic superior, inferior vena cava, and extrathoracic vena cava are identified separately. The model thus consists of compartments, each of which is represented by a linear resistance (R) and compliance (C) that can be either linear, nonlinear, or time-varying. The NL model and Laplace’s law were applied to calculate heart mechanics. All of the related parameters in the systemic circulation model are presented in Table 2.

The arterial network model proposed by Ozawa et al. (11) was incorporated into the current cell-system model system as shown in Fig. 2. Model of Ozawa et al. was based on the numerical solution of one-dimensional equations for fluid and vessel wall motion in a geometrically accurate branching network of the arterial system (28 elements), including energy losses at bifurcations. Blood flow and pulse wave propagation in each element were described by one-dimensional Navier-Stokes equations with axial velocity, fluid pressure, and vessel cross-sectional area as variables (14). These equations were solved using the finite difference method on one-dimensional meshes for each element of the arterial network branches (14). Rebound of arterial waves from terminal or bifurcation branches were numerically implemented through boundary conditions. As similar to Ozawa et al. (11), we used the method of characteristics for the boundary conditions. Detailed specifications of the four large arteries in the arterial network are shown in Table 3. The
Table 2. Lumped parameter values for the cardiovascular system model

| Locations      | Elements       | Parameter values | References |
|----------------|----------------|------------------|------------|
| Left atrium    | Outflow resistance | \( R_{p} = 0.0025\) PRU ( = mmHg/s/mL) | Ursino and Innocenti (31) |
|                | Inflow resistance | \( R_{p} = 0.006\) PRU | Ursino and Innocenti (31) |
| Left ventricle | Outflow resistance | \( R_{p} = 0.004\) PRU | |
| Aorta          | Outflow resistance | \( R_{p} = 0.03\) PRU | |
|                | Compliance      | 0.03 mL/mmHg     |            |
| Periperal resistance | \( R_{p1} \) | 3.9 PRU          |            |
|                | \( R_{p2} \) | 0.23 PRU         |            |
|                | \( R_{p3} \) | 0.06 PRU         |            |
|                | \( R_{p4} \) | 0.01 PRU         |            |
|                | \( R_{p5} \) | 0.003 PRU        | Heldt et al. (19) |
|                | \( R_{p6} \) | 0.015 PRU        |            |
|                | \( R_{p7} \) | 0.01 PRU         |            |
|                | \( R_{p8} \) | 4.1 PRU          |            |
|                | \( R_{p9} \) | 0.3 PRU          |            |
|                | \( R_{p10} \) | 3.0 PRU          |            |
|                | \( R_{p11} \) | 0.18 PRU         |            |
|                | \( R_{p12} \) | 3.6 PRU          |            |
|                | \( R_{p13} \) | 0.3 PRU          |            |

PRU, peripheral resistance unit (mmHg/s/mL); up, upper body; sup, superior vena cava; pv, pulmonary vein; ro, right ventricular outflow; inf, inferior vena cava; ab, abdominal vena cava; kid, kidney; sp, splanchnic; ll, lower limbs.

Table 3. Material properties and dimensions of the four large arteries

| Element number | Artery name       | Length (cm) | Proximal area (cm²) | Distal area (cm²) | Elastic modulus (10⁶ dyn/cm²) |
|----------------|-------------------|-------------|---------------------|------------------|-----------------------------|
| 1              | Ascending aorta   | 5.5         | 6.605               | 3.941            | 4.0                         |
| 2              | Thoracic aorta    | 18.5        | 3.597               | 2.835            | 4.0                         |
| 3              | Abdominal aorta   | 4.3         | 2.378               | 2.378            | 4.0                         |
| 4              | Abdominal aorta   | 9.6         | 1.021               | 1.021            | 4.0                         |

To assess the feasibility of our cell-system-arterial network model, we plotted the sequential events from the cell level to that of the arterial pulse (Fig. 3) and reconstructed the shapes of the original action potential and Ca²⁺ transient. The action potential showed the characteristic spike notch dome shape of ventricular cells (Fig. 3A). Fig. 3B shows the transient increase in free calcium concentration within the cytoplasm. The force of muscle contraction develops rapidly in response to the Ca²⁺ in free calcium concentration within the cytoplasm. The force generated by cross-bridges, thick dotted line: passive elastic force at the ventricular myocyte. (D) Cardiac volume. (E) Blood pressure in the left atrium and left ventricle, respectively. (F) Pressure pulse waves at three arterial positions (ascending aorta, common iliac artery, and anterior tibial artery).

**RESULTS**

To assess the feasibility of our cell-system-arterial network model, we plotted the sequential events from the cell level to that of the arterial pulse (Fig. 3) and reconstructed the shapes of the original action potential and Ca²⁺ transient. The action potential showed the characteristic spike notch dome shape of ventricular cells (Fig. 3A). Fig. 3B shows the transient increase in free calcium concentration within the cytoplasm. The force of muscle contraction develops rapidly in response to the Ca²⁺ transient in cells (Fig. 3C). Two components comprise this force: that generated by cross-bridges and elastic force. The LV active force showed a peak value of approximately 28 mN/mm² (kPa). Fig. 3D shows the volume variation in the left atrium (LA) and LV relative to time. The ejection fraction of the left ventricle was nearly 0.58. The LA contracts prior to ventricular contraction. The timeline of the pressure changes observed in the aorta, atrium, and ventricle are shown in Fig. 3E. Here, the heart rate was assumed to be 72 bpm (beats/min). Pressure pulse waves at three arterial positions (ascending aorta, common iliac artery, and anterior tibial artery) are plotted in Fig. 3F and show increased pulse pressures and a smoothed dicrotic notch in the distal portion of the arterial branches.

To verify our model, the major hemodynamic variables generated by the model are compared with standard values in Table 4. The computed blood pressure is within the range considered to be physiologically normal within the general population. The total length of the four arteries was 37.9 cm, and the length of the thoracic aorta was about half (48.8%) of the total length, with a mean diameter of 2 cm. In the normal case, wall stiffness values for the arterial elements were identical to those described in the Model of Ozawa et al. (11). To couple the arterial network model with BLH, we regarded the left ventricular (LV) pressure as the boundary condition of the arterial network model and the aortic flow rate as the input condition of the BLH model.

To investigate the effects of arterial wall stiffening on heart cellular mechanics and cardiovascular system dynamics, we performed a parametric study with respect to arterial wall stiffness, increasing arterial wall elasticity of the model by 1, 2, 3, and 4 times the normal value. However, this variation in arterial elasticity was assumed only in large arteries because the wall stiffness of small arteries remains nearly unchanged (21). Here, PWV was calculated from the distance and traveling time of the pressure wave between the ascending aorta (1st element of the arterial network in Fig. 2) and the abdominal aorta (4th element of the arterial network in Fig. 2).
stroke volume was approximately 73 mL. The cardiac output, which was obtained by multiplying the stroke volume with a heart rate of 72 bpm, was 5,256 mL/min. The computed value of the PWV in the aorta was within the range 4.4 to 8.5 m/sec, which is consistent with an experimental study in humans (22).

Fig. 4 shows the variation in pressure waves within the aorta according to arterial stiffness. Compared with the baseline value of arterial elasticity ($E_n = 4 \times 10^6 \text{ dyne/cm}^2$), with increases in arterial stiffness, the time delay of the pressure wave between the ascending and abdominal aortas decreased, whereas the difference in peak aortic pressures increased. As shown in Fig. 4A and B, increase of arterial stiffness by 2 times of normal value increased peak aortic pressure by nearly 8% (from 112.5 mmHg to 121.5 mmHg). However, the increased value is relatively small compared with in vivo experimental observation (23). Interestingly, in reverse to the present cases, acute rise in blood pressure can increase in vivo arterial stiffness demonstrated by Stewart et al. (24). The relation between arterial stiffness and cardiac output is shown in Table 5.

At the cellular level, the cross-bridge elongation (CBEL) decreased sharply during contraction below the steady-state value ($= 5 \text{ nm}$) and then immediately reverted to the back to the steady-state value (Fig. 5A). Shortening of the CBEL below the steady-state value during contraction played a critical role in active force generation, as the calcium-bound troponin concentration was high during this period (Fig. 5B). This shortening of the elongation during contraction was accompanied by a decrease in the half sarcomere length (HSL) (Fig. 5C). The active force was generated by the product of the CBEL and the concentration of calcium-bound troponin (Fig. 5D).

There was no change in the amount of troponin bound to the cross-bridge with increasing arterial thickness (solid, thick, and thin dotted lines in Fig. 5B), whereas CBEL increased (Fig. 5A). Accordingly, the HSL and LV peak pressure (Fig. 5E) increased with arterial stiffness. According to increased stiffness, it is remarkable that the changes of CBEL and half sarcomere length during ventricular relaxation were relatively small compared with those during ventricular contraction.

The peak cellular stress observed with increases in arterial stiffness is shown in Fig. 6A. As shown in the Fig. 6, there was an initial steep increase in the peak cellular stress followed by a saturated pattern at higher arterial stiffness values. On the other hand, the variation in PWV was nearly linear with increasing arterial stiffness (Fig. 6B). Systolic blood pressures (SBP) in the ascending aorta and brachial artery also changed consistent with peak cellular stress (Fig. 6C). Interestingly, variation in aortic SBP was more prominent than that in the brachial arterial with respect to increasing arterial stiffness. Fig. 6D presents the relationship between PWV and peak cellular stress, showing a saturated pattern for higher values of PWV.

**DISCUSSION**

A major objective of the present study was to integrate cellular processes with systemic and arterial hemodynamics by which propagation of the arterial pulse wave is related to heart me-
Fig. 5. Simulated results of the inotropic state of the left ventricular BLH in the cell-system model. (A) Cross-bridge elongation length (CBEL), (B) Concentration of cross-bridge-attached troponin ([TCa*]+[T*]), (C) Half sarcomere length, (D) Cross-bridge-generated contraction force (CBCF), (E) LV pressure according to arterial stiffness. Here, $E_n$ represents the normal stiffness value of the large arteries.

Fig. 6. Simulation results of the (A) peak cellular stress of the ventricle, (B) pulse wave velocity (PWV) change, (C) brachial and central systolic blood pressures (SBP) with respect to arterial stiffness, and (D) peak cellular stress with respect to PWV.
chanics in the human circulatory system. Here, the arterial net-
work model proposed by Ozawa et al. (11) could couple blood
hemodynamics and pulse waves in detailed arteries with LV
mechanics and systemic circulation. Our discussion of the
computational results focuses on three main aspects: the plau-
sibility of the integrative method of a cell-system-arterial net-
work to simulate heart mechanics and cardiovascular hemody-
namics, a parametric study focusing on arterial stiffness to de-
lineate the relationship between arterial hemodynamics and
cardiac cellular mechanics.

In the cell-system-arterial network model, electrophysiologi-
cal variables such as the action potential, calcium concentra-
tion, and generated cellular forces in the cellular models were
determined for atrial and ventricular cells (Fig. 3A-C). Compu-
tational results for the cardiovascular system dynamics were
consistent with published results of pressure and volume varia-
tions in the LA and LV (Fig. 3D, E). Arterial pulse wave propaga-
tion along the arterial network also showed a pattern similar to
previous clinical observations (Fig. 3E, 4). In conclusion, all se-
quential events from the cell to arterial pulse waves were well
reproduced and consistent with the existing data, demonstrat-
ing the plausibility of the present method as an integrative
analysis tool for evaluating heart mechanics and arterial hemo-
dynamics.

Atherosclerosis is a symptom of aging that causes serious
health problems. Specifically, it increases cardiac cellular stress,
which eventually stimulates heart hypertrophy (23, 24). Roman
et al. (25) investigated the effects of central blood pressure (BP)
on left ventricular hypertrophy (LVH), and showed that systolic
BP in the central artery (or the ascending aorta) is more impor-
tant in stimulating LVH and inducing conformational changes
and remodeling of the heart. With respect to medical terminol-
ogy, central BP represents the BP in the large arteries, such as
the ascending, descending, and abdominal aortas. Wang et al.
(26) also reported that central systolic pressure is more critical
than other blood pressures in predicting cardiovascular dises-
es. However, theoretical approaches to explain the detailed
physiological mechanism underlying these effects have not
been reported. Therefore, we proposed an integrative cell-sys-
tem-arterial network model to delineate the relationships be-
 tween heart cellular stress, LVH, and arterial stiffness.

Using this model, we performed a parametric study to evalu-
ate the effects of stiffened arteries on heart cellular mechanics
by increasing the vascular wall stiffness of the largest arteries in
the model. Cross-bridge-generated contraction force (CBCF)
(Fig. 5D), LV peak pressure (Fig. 5E), and PWV (Fig. 6B) in-
creased, whereas HSL decreased with increasing arterial stiff-
ness. Peak cellular stress and SBP in the brachial and central ar-
terries also increased, but were saturated at higher values of ar-
terial stiffness (Fig. 6A). As shown in Fig. 6C, central arterial
stiffness could more affect SBP, which is because the half of

This study developed a cell-system-arterial network coupled
model of the cardiovascular system. Although results were rea-
sonable, the study has several limitations. First, we did not con-
sider other effects, such as autonomic nerve control or changes
in the resistance of the peripheral vessels involved in the arteri-
al stiffening process. Therefore, we elucidated only the mechani-
isms involved in arterial stiffness perturbation, cellular con-
tractility, and vascular hemodynamics. Second, the heart has a
complex muscle layer with fiber anisotropy and heterogeneous
muscle thickness. In addition, different parts of the ventricles
are activated at different times. However, in this study, the ven-
tricle was assumed to be a Laplace heart to reduce the com-
plexity of the coupled cell-circulation hemodynamics method.
Besides, in this study we didn’t consider long-term compensa-
tory mechanism of blood pressure through renal excretory sys-
tem. Nevertheless, these limitations were not expected to mark-
edly alter the main findings of this study.

Despite its limitations, our model can simulate the sequen-
tial events of the cardiovascular system from cells to the sys-
temic circulation. Consequently, the model can be applied to
perioperative intensive care in heart, lung and liver surgery
which requires accurate evaluation of the pulmonary preload
and systemic afterload. Along with clinical data, a computer
model of the cardiovascular system can be a useful tool allowing
clinicians to estimate critical information about patients’
cardiovascular system, such as blood pressure, and the arterial
pulse wave. In addition, clinicians can use the model to predict
the cardiovascular changes induced in patients by treatment in
intensive care units. For example, Kashif et al. (28) showed that
a simulation method combined with clinical measurements
can provide information about patients in intensive care. We
expect that our model could play a similar role in estimating
patient-specific data for grave patients. In the future, this will be
delineated by combining the model with clinical data.
DISCLOSURE

The authors have no conflicts of interest to disclose.

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