Influence of Activation Time on Hemodynamic Parameters: a Simulation Study

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Abstract Ventricular activation time (AT [ms]) is the time required to activate the ventricle electrically. The influences of AT on hemodynamics are of interest in clinical studies on methods for improving left ventricle (LV) function. However, the cardiovascular system is a dynamic system, in which many parameters are interrelated with each other, and teasing out the causality of the effects of AT within the system experimentally is difficult. In this research, we focused on analyzing the effects of changing AT on hemodynamics using a hemodynamic model by incorporating a cardiac tissue model into an LV geometric model within a circulation model. The cardiac tissue model is constructed by connecting 10 cardiac cellular contraction models in the fiber direction. In our cardiac tissue model, AT is represented by adding a constant delay time, \( \delta_{\text{delay}} \) [ms], to the starting times of calcium transients between adjacent contraction models. Thus, AT becomes \( \delta_{\text{delay}} \times 9 \) [ms]. Simulations were performed under two conditions: normal AT (99 [ms], physiological); and prolonged AT (207 [ms], pathological). AT prolongation caused slight decreases in stroke volume (SV [mL]) and ejection fraction (EF [%]) by 2.10% and 6.00%, respectively, since both LV end-systolic and LV end-diastolic volumes increased by similar amounts. Maximum elastance (\( E_{\max} \) [mmHg/mL]) decreased by 15.4%. The maximum rate of LV pressure rise (max dp/dt [mmHg/ms]) decreased markedly by 43.7% at longer AT. The cellular mechanisms underlying changes in half sarcomere length were analyzed individually in 10 cells. Even though hemodynamic parameters did not change significantly, we concluded that large differences in cell behaviors existed.

Keywords: cardiac tissue model, activation time, hemodynamic parameters, cardiovascular simulation.

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1. Introduction

Animal experiments have long been used to study the mechanisms underlying heart pump function as well as the properties of cardiac cells and the cardiovascular system. Animal experiments provide helpful data to understand these mechanisms and properties, but since many interrelated factors act in the cardiovascular system, controlling for a single factor and distinguishing the direct results of that factor in animal experiments is difficult, which impedes advances in the understanding of the mechanisms underlying cardiac pump function.

For example, contraction of a cardiac cell is triggered by electrical excitation that propagates over the heart tissue, but the relationship between conduction velocity and pump function is not easily analyzed, since many factors are affected if conduction velocity is controlled. In the case of left bundle branch block (LBBB), cardiac function is reported to decrease [1–3], but distinguishing the effects of conduction delay from the effects of left and right ventricular asynchrony is difficult.

To complement animal experiments, simulations with a detailed cardiovascular system model may provide useful information. Computer simulations and analyses of simulation results are therefore gaining importance. Simulations of the heart are studied at many levels, from cellular to organ level. The present research tried to analyze the basic mechanisms underlying cardiac pump function, which involves an excitation delay in cardiac tissue. We therefore identified the relationship between left ventricular (LV) activation time (AT [ms]; the time required for the entire LV wall to be activated) and heart pump function (evaluated from the following hemodynamic parameters: end-systolic LV volume \( V_{l,s}(t_{eg}) \) [mL]), end-diastolic LV volume \( V_{l,d}(t_{eg}) \) [mL]), stroke volume (SV [mL]), ejection fraction (EF [%]), maximum elastance (\( E_{\max} \) [mmHg/mL]), maximum LV pressure (peak \( p_{lv} \) [mmHg]) and maximum rate of LV pressure rise (max dp/dt [mmHg/ms]); and analyzed the underlying mechanisms. Since AT is difficult to measure directly, QRS duration is often used as an index of AT. In the healthy human adults, QRS is reported to be under 100 [ms]. Murkofsky et al. [4] reported that prolonged QRS duration (>120 [ms]) correlates closely with decreased EF in patients. This finding indicates a strong relationship between prolongation of QRS duration and decrease of cardiac function.

As for simulation study, Lu et al. [5] reported a relationship between AT and isometric peak contraction stress using a cardiac tissue model. In their research, simulations were performed under conditions of constant tissue length, and the resulting peak stress decrease was around 3% for an AT of 50 [ms] compared to an AT of 0 [ms]. However, the relationship between contraction stress and AT under physiological changes in cellular length remains unclear.

In this research, the relationship between pump function and AT was evaluated in order to analyze the basic mechanism, using a hemodynamic model by incorporating a cardiac tissue model into an LV geometric model within a circulation model. We used the hemodynamic parameters described above to evaluate pump function.
2. Model and Simulation Method

2.1 Model structure
This research used a human hemodynamic model comprising a circulation model, an LV geometric model, and a cardiac tissue model. The cardiac tissue model was constructed by connecting 10 or 50 cardiac cellular contraction models in the fiber direction.

2.2 Circulation model
A simplified circulation model as proposed by Heldt et al. [6] (Heldt model) was integrated into the hemodynamic model.

In our model, the LV compartment was replaced by the LV geometric model described in Section 2.3. To separate the effects of AT from other factors, the baroreflex model included in the Heldt model was removed. Cardiac cycle length was fixed at 1000 [ms]. In our combined model, we defined preload factor \( K_{rp} \) (= 2.43 or otherwise stated in text) and used this factor to modify venous resistances as follows: \( R_{syp} = K_{rp} \cdot R_{syp0} \), \( R_{sinf} = K_{rp} \cdot R_{sinf0} \) and \( R_{inf} = K_{rp} \cdot R_{inf0} \). Note that \( R_{syp0} \), \( R_{sinf0} \) and \( R_{inf0} \) are the original parameters of the Heldt model parameters.

2.3 LV geometric model
In the hemodynamic model, the following geometric model based on Laplace’s law was used to relate LV pressure (\( \rho_{p}(t) \) [mmHg]), radius (\( R_{lv}(t) \) [cm]), wall thickness (\( h_{lv}(t) \) [mm]) and wall stress (\( F(t) \) [mN/mm²]) [7].

\[
\frac{\rho_{p}(t)}{h_{lv}(t)} = \frac{1.5 \cdot F(t)}{R_{lv}(t)}
\]  

(1)

Since the primary variables in the hemodynamic model are LV pressure (\( \rho_{p} \) [mmHg]), volume (\( V_{lv} \) [mL]), half sarcomere length (\( L \) [\( \mu m \)]) and wall stress (\( F \) [mN/mm²]), we have to provide the relationship between LV radius (\( R_{lv} \) [cm]) and \( V_{lv} \), between \( R_{lv} \) and \( L \), and between LV wall thickness (\( h_{lv} \) [mm]) and \( F \).

We used the following reported data to define mathematical equations for the relationship between \( R_{lv} \) and \( V_{lv} \). Corsi et al. [8] measured the time course of human LV volume, and Sutton et al. [9] measured the time course of human LV internal radius. Combining these data, we obtained a non-linear relationship between LV volume and internal radius. However, since the resolution of these data was insufficient, we used the time course of canine LV volume reported by Rodriguez et al. [10] and the time course of canine LV internal diameter reported by Sabbah et al. [11] to draw a non-linear relationship between LV volume and internal radius. When we linearly scaled end-systolic volume, end-diastolic volume, end-systolic internal diameter and end-diastolic internal diameter from canine data to human data as shown in Fig. 1, we obtained a curve with basic characteristics close to the human data. If we assume that the shape of the LV is close to hemispherical, the relationship between LV volume and internal radius becomes the following equation with \( K_{a} = 3 \).

\[
R_{lv}(t) = \left( \frac{V_{lv}(t) - V_{s}}{K_{h}} \right)^{1/K_{a}}
\]  

(2)

However, since the measured relationship shows disparity from the \( K_{a} = 3 \) curve, we optimized these parameters and obtained \( K_{a} = 3.92 \) (\( R^{2} = 0.95 \)). Note that \( V_{s} \) [mL] denotes LV volume and the same as \( V_{s} \), \( V_{s} \) [mL] is the \( V_{s} \)-intercept of the relationship between \( V_{lv} \) and \( R_{lv} \). \( K_{a} \) and \( K_{h} \) are model parameters that define the non-linear characteristics between \( V_{lv} \) and \( R_{lv} \).

We used the following reported data to define mathematical equations for the relationship between \( R_{lv} \) and \( L \). Rodriguez et al. [10] also measured the time course of canine sarcomere length. By combining this data with the measured canine time course of internal diameter as reported by Sabbah et al. [11], we obtained a non-linear relationship between LV volume and sarcomere length.

We linearly scaled the working range of LV radius from canine (1.55–1.70 [cm]) to human (1.643–2.56 [cm]), but not for half sarcomere length (1.06–1.23 [\( \mu m \)]), which is shown in Fig. 2, since the \textit{in vivo} or \textit{in situ} human sarcomere length has not, to the best of our knowledge, been reported.

\[
L(t) = C_{L} \cdot R_{lv}(t) + L_{0}
\]  

(3)

\( L(t) \) [\( \mu m \)] denotes half sarcomere length and the same as \( L \). \( C_{L} \) [\( \mu m/cm \)] is the proportional constant of the relationship between \( L \) and \( R_{lv} \). \( L_{0} \) [\( \mu m \)] is the \( L \)-intercept of the relationship between \( L \) and \( R_{lv} \).

Next, we considered wall thickness. Yun et al. [12] measured the time course of LV volume, twist angle, and wall thickness, and reported that both volume and twist angle showed relationships with wall thickness. Moreover, wall thickness is known to become maximal at end-systole and minimal at end-diastole. However, wall thickness is not always proportional to LV volume [8, 9], and the quantitative mechanisms underlying wall thickness remains unclear. On the other hand, wall thickness is known to change at isovolumic relaxation phase [13], where cellular contraction stress is decreased. We thus assumed that cellular contraction stress (\( F_{c}(t) \) [mN/mm²]) is linearly related to...
\[
\begin{align*}
\text{Table 1 Parameters in LV geometric model.} \\
V_e [\text{mL}] & \quad K_\theta & \quad K_a & \quad C_l [\mu \text{m/cm}] & \quad L_v [\mu \text{m}] & \quad F_{buld} (\text{mN/mm}^2) & \quad F_{rel} (\text{mN/mm}^2) & \quad h_0 (\text{mm}) & \quad h_0 (\text{mm}) \\
35.0 & \quad 2.33 & \quad 3.92 & \quad 0.163 & \quad 0.782 & \quad 0.465 & \quad 8.14 & \quad 10 & \quad 17
\end{align*}
\]

2.4 Cardiac cellular contraction model

Models of cardiac contraction range from highly simplified models [15, 16] and empirical models [17] to biophysical models [18–20]. Since our aim was to analyze the mechanisms underlying the cardiac tissue with excitation, we used biophysical models. The Rice model [18] has a detailed biophysical representation of sarcomere structure and can reproduce both isotonic and isometric stress and length change, but the isotonic relaxation time course is rather slow, and the characteristics of instantaneous shortening and velocity-dependent stress decrease are not sufficiently realistic, given their importance in our model. The Land model [19] is one of the more sophisticated models, but is a mouse model with different characteristics from human cells. The stress–frequency relationships are also not physiological, which implies poor reproducibility with velocity-dependent stress decrease characteristics. On the other hand, the cardiac cellular contraction model proposed by Negroni and Lascano (NL08) [20] offers good reproducibility in isometric and isotonic contraction, which the effective cross-sectional area is difficult to measure, based on the good reproducibility of velocity-dependent stress decrease characteristics. We thus used the NL08 model as the cardiac cellular contraction model in our hemodynamic model.

Cellular contraction stress \( F_b [\text{mN/mm}^2] \) was calculated from the state transition model of the troponin system and mechanical model of the half sarcomere.

\[
F_b = A_w \cdot (\{TS\}^{Ca^2+} + \{TS\}^1) \cdot (L - X_w) + A_p \cdot (\{TS\}^{Ca^2+} + \{TS\}^1) \cdot (L - X_p) \]  
(5)

where \( A_w \), \( A_p \), \( \{TS\}^{Ca^2+} \), \( \{TS\}^1 \), \( L \), and \( X \) are constants to define the ratio of the contribution of crossbridges in the weak state, power state, and shortening and lengthening of attached crossbridges, respectively. Note that \( \{TS\}^{Ca^2+} \), \( \{TS\}^1 \), \( \{TS\}^{Ca^2+} + \{TS\}^1 \), \( L - X_w \), and \( L - X_p \) are elongations of attached crossbridges in the weak and power states, respectively.

Since characteristics of the end-diastolic pressure volume relationship (EDPVR) are similar in rats [21] and humans [22], by linearly scaling the stress axis with the identical half sarcomere length axis, we used the following mammalian exponential function as a human passive elastic stress \( F_p [\text{mN/mm}^2] \) model showing good agreement with the experimental data [23, 24]. The format of this equation was based on the equation used by Shim et al. [25] and Landesberg et al. [26].

\[
F_p = \begin{cases} 
- K_{PE} \cdot \left( \frac{L}{L_0} \right)^4 & L < L_0 \\
K_{PE} \cdot \left( e^{\left( \frac{L}{L_0} \right)^4} - 1 \right) & \text{otherwise} 
\end{cases} \]  
(6)

Note that \( L_0 [\mu \text{m}] \) is resting half sarcomere length. \( D, K_{PE} [\text{mN/mm}^2] \) and \( K_{PE} [\text{mN/mm}^2] \) are the scale parameters for the heart wall and cardiac cell passive elasticity. Parameter values were manually obtained to reproduce physiological human hemodynamics (Table 2).

Since \( F_p \) is usually measured using a piece of tissue, we can consider that the characteristics of \( F_p \) are compatible with the macroscopic properties. On the other hand, since \( F_b \) is usually measured with a single cell or small piece of ventricular fiber in which the effective cross-sectional area is difficult to measure, measured stress may contain large scale errors. We thus introduced a scale factor, \( K_b \), which is multiplied only to \( F_b \) to adjust cellular contraction stress. \( K_b \) was determined using the method proposed by Utaki et al. [27] which resulted in \( K_b = 6.65 \). Finally, total muscle stress \( F [\text{mN/mm}^2] \) as used in Eq. (1) as wall stress is calculated as follows.

\[
F = K_b \cdot F_b + F_p \]  
(7)

Stimulation time in the NL08 model is controlled by the \( Ca^{2+} \) release equation. The release and uptake of \( Ca^{2+} \) by the sarcoplasmic reticulum \( (Q_{rel} [\mu \text{M/ms}] \) and \( Q_{pump} [\mu \text{M/ms}] \) in the NL08 model are expressed using the following equations.

\[
Q_{rel} = Q_m \cdot (t/t_1)^4 \cdot e^{(t^4/t^4_1)} + Q_{pump,rest} 
\]
(8)

\[
Q_{pump} = K/P/(1 + (K_m/(Ca^{2+}))^2) \]  
(9)

where \( t \) is the time parameter, \( [Ca^{2+}] [\mu \text{M}] \) is the concentration of \( Ca^{2+} \), \( Q_m [\mu \text{M/ms}] \) is the maximum level of \( Ca^{2+} \) release, \( t_1 [\text{ms}] \) is the interval to maximum \( Q_{rel} , Q_{pump,rest} [\mu \text{M/ms}] \) is a parameter to determine \( [Ca^{2+}] \) at rest, \( K_m [\mu \text{M/ms}] \) is maximum value of \( Q_{pump} \) and \( K_m [\mu \text{M}] \) is the value of \( [Ca^{2+}] \) for \( Q_{pump} = K/P/2 \). Parameter values used in Eq. (8) and (9) are shown in Table 3.

The NL08 model is known to have a problem in the filling phase, where contraction stress rapidly decreases when half sarcomere length extends. To improve filling phase characteristics, we modified \( g \) in the crossbridge detachment rate parameters \( g [1/\text{ms}] \) and \( g_d [1/\text{ms}] \) in the NL08 model by introducing the
rest − L + 10 (17)

\[ F_\delta = \frac{K_1}{\gamma} \left( \frac{dx}{dt} > 0 \right) \gamma \left( \text{otherwise} \right) \] (12)

\[ h_{rel} [\mu m] \text{ is steady elongation of attached crossbridges in the weak state.} \]
\[ g = Z_d + Y_d \cdot (1 - e^{-\gamma(h_n - h_u)})^2 \] (10)
\[ \gamma_n = \begin{cases} \gamma \cdot \frac{K_s}{L_c} & (\text{if } dL_c/dt \text{ becomes large}) \\ \gamma & (\text{otherwise}) \end{cases} \]

\[ K_\gamma = 1.0 \text{ (original)} \quad K_\gamma = 85.3 \text{ (modified).} \]

\[ h_{rel} [\mu m] \text{ is used instead of } \gamma \text{ in Eq. (10) and (11) which determines the positive nonlinear cross-bridge detachment rate by the difference between } h_n \text{ and } h_u. \]
\[ \gamma_n \text{ increases if } dL_c/dt \text{ becomes large. However, contraction stress becomes 0 [mN/mm²] after rapid elongation of } L \text{ (Fig. 3 solid line), which does not happen in the real heart, since if this happens, LV pressure becomes negative at this moment. We thus replaced } \gamma \text{ by } \gamma_n \text{ in Eqs. (10) and (11) which is identical to } \gamma \text{ if the cell is contracting; however, by dividing } \gamma \text{ by } K_\gamma, \text{ the value becomes small, which gives better stress transient. By manually adjusting the smoothness of the stress time course, we used 85.3 as the value of } K_\gamma \text{ (Fig. 3 dashed line).} \]

2.5 Cardiac tissue model

Since the heart can be decomposed into several long fiber bundles, we assumed that one fiber bundle surrounding the LV can be considered as a LV wall tissue model with an AT. We thus used a cardiac tissue model constructed by connecting 10 cardiac cellular contraction models in the fiber direction (10-cell model), which represents a fiber bundle surrounding the LV.

Here, the left-most cell in the tissue model is termed cell 1, and the right-most is cell 10. Half sarcomere length, cellular contraction stress, passive elastic stress, and total muscle stress of each cell are represented as \[ L_1-L_{10} [\mu m], \]
\[ F_{p10}-F_{p10} [mN/mm^2], \]
\[ F_{p1}-F_{p10} [mN/mm^2], \]
\[ F_{1}-F_{10} [mN/mm^2], \]
respectively. Cellular contraction stress, passive elastic stress, total muscle stress, and average half sarcomere length of the tissue are represented as \[ L_c [\mu m], \]
\[ F_p [mN/mm^2], \]
\[ F [mN/mm^2], \]
and \[ L_{ave} [\mu m], \]
respectively.

\[ F_p = \frac{F_p}{L_c} \]
\[ F = \frac{F}{L_c} \]
\[ L_{ave} = \frac{L_1 + L_2 + \cdots + L_{10}}{10} \] (13)

Since the serially connected cardiac cells have identical total stresses, the following equation holds.

\[ F = F_1 = F_2 = \cdots = F_{10} \] (14)

According to Eq. (13) and (14), the following system of equations can be derived.

\[ \begin{cases} L_{ave} = (L_1 + L_2 + \cdots + L_{10})/10 = 0 \\
F_1 - F_2 = K_1 \cdot F_{p1} + F_{p1} - (K_1 \cdot F_{p2} + F_{p2}) = 0 \\
F_2 - F_3 = K_1 \cdot F_{p2} + F_{p2} - (K_1 \cdot F_{p3} + F_{p3}) = 0 \\
\vdots \\
F_9 - F_{10} = K_1 \cdot F_{p9} + F_{p9} - (K_1 \cdot F_{p10} + F_{p10}) = 0 \end{cases} \]

ATs can be altered by modifying the time parameter \( t \) in the equation \( Q_{rel} \) (Eq. (8)) by a constant time \( \delta_{delay} [\text{ms}] \).

\[ Q_{rel} = \frac{Q_m \cdot ((t - \delta_{delay} \cdot (i - 1))/t_1)^3}{e^{(t-\delta_{delay} \cdot (i-1))/t_1}} + Q_{pump,rest} \]

Since there are 10 cells in the tissue model, the relationship between AT and \( \delta_{delay} \) becomes the following.

\[ AT = \delta_{delay} \times 9 \] (20)

As mentioned in Section 1, AT is closely related to QRS duration. QRS duration is under 100 [ms] in healthy human adult. On the other hand, under pathological conditions, QRS duration can be longer than 200 [ms] [28]. Here we assumed that LV AT is almost the same as QRS duration and defined two AT conditions by fixing \( \delta_{delay} \) at 11 [ms] and 23 [ms] as follows: normal AT (n.AT) (AT = 99 [ms], a physiological condition) and prolonged AT (p.AT) (AT = 207 [ms], a pathological condition). The length of the average ventricular myocyte is around 100 [\mu m], corresponding to at least 1000 cells in a fiber bundle surrounding the LV. To evaluate the effect of the number of cardiac cells in the tissue model, simulation was performed using a cardiac tissue model comprising 50 cardiac cellular contraction models (50-cell model).

2.6 Simulation method

Simulations were performed with a simBio system [29] in 0.01-ms steps until a steady state was reached, requiring around 100 cardiac cycles. In each step, the non-linear simultaneous equation was solved using the Newton-Raphson method.

3. Simulations

To evaluate the effect of the number of cardiac cells in the tissue...
model, we first performed a simulation with 10-cell and 50-cell models. The simulations were performed under identical conditions. The results showed that the maximum difference in $V_{lv}$ was less than 1.0%, with no significant differences for the other parameters. On the other hand, computational time was 24 times greater for the 50-cell model than for the 10-cell model. We therefore used the 10-cell model in subsequent studies.

We performed simulation with two different ATs and observed the effects of AT prolongation on LV. Numerical values of hemodynamic parameters and parameters used to represent characteristics of the cell and cardiac cycle obtained from this simulation study are listed in Table 4. Time courses of $p_{hi}$ for the two different ATs were superimposed on corresponding traces of aortic pressure ($p_a$) and venous pressure ($p_v$) in Fig. 5(a). We found that $p_{hi}(t_{EG})$ and $p_{hi}(t_{EG})$ changed by only −1.2 [mmHg] and +0.96 [mmHg], respectively. The smaller value of $p_{hi}(t_{EG})$ compared to $p_{hi}(t_{EG})$ made the apparent change seem as large as +16.5%. The time courses of $V_{LV}$ for two different ATs are also plotted in Fig. 5(b). Both $V_{LV}(t_{EG})$ and $V_{LV}(t_{EG})$ were confirmed to increase when AT was prolonged. Since both $V_{LV}(t_{EG})$ and $V_{LV}(t_{EG})$ increased by similar amounts (6.5 [mL] and 5 [mL]), SV did not change markedly. However since $V_{LV}(t_{EG})$ increased with AT prolongation, EF, which was calculated by dividing SV by $V_{LV}(t_{EG})$, obviously became smaller. The difference in $V_{LV}(t_{EG})$ was slightly larger compared to the difference in $V_{LV}(t_{EG})$ for both ATs. The peak value of $p_{hi}$ was unchanged, whereas max dp/dt showed a large decrease after AT prolongation. Simulation results showed that the isovolumic contraction phase is markedly prolonged and onset time of ejection phases is delayed by AT prolongation, which is supposed to be the outcome of decreased dp/dt. The relationship between average LV pressure rise and max dp/dt will be analyzed in a later section. Conversely, duration of ejection phase was shortened by AT prolongation.

From the time courses of $p_{hi}$ and $V_{hi}$, we obtained the PV loops as shown in Fig. 5(c) that have similar properties to the reported human PV loop [30–32]. To evaluate $E_{max}$ from PV loops, it was necessary to obtain values of $p_{hi}(t_{EG})$ and $V_{hi}(t_{EG})$ from at least 2 PV loops. Venous resistances were therefore modified by changing the value of preload factor $K_{rp}$ to 3.375 from 2.43 under two AT conditions. Lines were then drawn through the 2 points of $p_{hi}(t_{EG})$ and $V_{hi}(t_{EG})$ for each AT condition and are shown with PV loops in Fig. 5(c). The slope of the lines was defined as $E_{max}$ and listed in Table 4. In clinical studies, $E_{max}$ obtained from a few points of $p_{hi}(t_{EG})$ and $V_{hi}(t_{EG})$ is often used as a hemodynamic parameter, because it is almost impossible in human subjects to control venous resistances within a wide dynamic range of physiological conditions. In simulation studies, on the other hand, obtaining the relationship of $p_{hi}(t_{EG})$ and $V_{hi}(t_{EG})$ in a wide physiological dynamic range is feasible. As a result, we changed the value of $K_{rp}$ for the 0.675 to 4.86 range, in which $p_{hi}(t_{EG})$ ranged from 90 [mmHg] to 130 [mmHg], and drew the end-systolic pressure-volume relation (ESPVR) curves. The resulting ESPVRs are shown in Fig. 5(d). The slope of ESPVR was not always constant, meaning that $E_{max}$ was not unique for each AT condition and depended on the loading condition of the hemodynamic model. The ranges of $E_{max}$ calculated from the slope of two adjacent plot points for n.AT and p.AT [Fig. 5(d)] were 2.85–4.46 [mmHg/mL] and 2.73–3.33 [mmHg/mL], respectively. A larger variation of $E_{max}$ in n.AT suggested higher non-linearity of n.AT compared to p.AT. These data showed clearly that as AT increased, $V_{hi}$ became larger. As a result, the $V_{hi}$-intercept of the ESPVRs, which was referred to as $V_{hi}$ in previous research, increased as AT was prolonged.

Changes in $E_{max}$, max dp/dt, EF and SV at fixed $K_{rp}$ ($K_{rp} = 2.43$ for max dp/dt, EF and SV; $K_{rp} = 2.43$ and 3.375 for $E_{max}$) with varying AT are plotted in Fig. 6. These parameters depend on load conditions. Although $E_{max}$ seemed to decrease slightly in relationship to AT increase in Fig. 6(a), the curvilinear characteristic of ESPVRs under different loading conditions in Fig. 5(d) should be taken into account. Decrease in max dp/dt was one of the most prominent effects of AT prolongation among all hemodynamic parameters. The reasons are discussed in Section 4.3.

### Table 4  Hemodynamic parameters and parameters used to represent characteristics of the cell and cardiac cycle obtained at AT = 99 [ms] (normal AT: n.AT) and 207 [ms] (prolonged AT: p.AT).

| Parameter                  | n.AT (AT = 99 [ms]) | p.AT (AT = 207 [ms]) |
|----------------------------|---------------------|-----------------------|
| $p_{hi}(t_{EG})$ [mmHg]    | 112.3               | 111.1                 |
| $p_{hi}(t_{EG})$ [mmHg]    | 5.81                | 6.77                  |
| $V_{hi}(t_{EG})$ [mL]      | 47.5                | 54.0                  |
| $V_{hi}(t_{EG})$ [mL]      | 119                 | 124                   |
| $L(t_{ES})$ [μm]           | 1.0323              | 1.0604                |
| $L(t_{ES})$ [μm]           | 1.1886              | 1.1947                |
| $SV$ [mL]                  | 71.4                | 69.9                  |
| EF [%]                    | 60.0                | 56.4                  |
| peak $p_{hi}$ [mmHg]       | 113.6               | 112.1                 |
| max dp/dt [mmHg/ms]        | 6.18                | 3.48                  |
| $E_{max}$ [mmHg/mL]        | 3.58                | 3.03                  |
| Duration of isovolumic contraction phase [ms] | 71.24               | 106.5                |
| Duration of ejection phase [ms] | 281.9               | 265.1                |
| Onset time of ejection phase [ms] | 80.6                | 115                  |
Decreases in values by changing AT from normal 99 [ms] to prolonged 207 [ms] were small for EF (−6%) and almost negligible (−2%) for SV. The decrease in EF was induced by the larger \( V_{lv}(t_{ED}) \) at longer ATs.

Although we also compared EDPVRs for different ATs, no significant differences were identified.

Figure 5: Time courses of \( p_a, p_v, p_{lv}, \) and \( V_{lv} \), PV loops and ESPVRs at different ATs.

4. Discussion

4.1 Effects of AT prolongation on hemodynamic parameters and cardiac cellular parameters

Simulation results revealed that although \( \max dp/dt \) decreased markedly, \( p_{lv8} \) at closure of valves on the aortic and venous sides, corresponding to \( p_{lv}(t_{ES}) \) and \( p_{lv}(t_{ED}) \), respectively, changed by merely −1.2 [mmHg] and 0.96 [mmHg] when AT was prolonged. These changes in \( p_{lv}(t_{ES}) \) and \( p_{lv}(t_{ED}) \) were small, but indispensable for increasing \( V_{lv}(t_{ES}) \) and \( V_{lv}(t_{ED}) \) to a similar extent (6.5 [mL] and 5 [mL], respectively), which, as a result, maintained SV after AT prolongation.

We observed increases in both \( L_{ave}(t_{ES}) \) and \( F_b(t_{ES}) \) at end-systole (time courses of \( L_{ave}(t_{ES}) \) and \( F_b(t_{ES}) \) in Fig. 6) in response to increased cardiac load, induced by decreasing \( K_{rp} \). The mechanisms for the positive shifts of ESPVR (Fig. 5(d)) and ESFLR (Fig. 7) to the right, i.e., expansion of \( V_{lv}(t_{ES}) \) and elongation of \( L_{ave}(t_{ES}) \), after the prolongation of AT were not clarified in detail in this study. In ESFLR, the positive shift in \( L_{ave}(t_{ES}) \) was always accompanied by an upward shift in \( F_b(t_{ES}) \). Differences in curvilinear characteristics between ESPVR and ESFLR were attributable to the non-linear relationship between \( E_{max}, EF, SV \) and \( \max dp/dt \) in relation to AT.

Figure 6: \( E_{max}, EF, SV \) and \( \max dp/dt \) in relation to AT.

Decreases in values by changing AT from normal 99 [ms] to prolonged 207 [ms] were small for EF (−6%) and almost negligible (−2%) for SV. The decrease in EF was induced by the larger \( V_{lv}(t_{ED}) \) at longer ATs.

Although we also compared EDPVRs for different ATs, no significant differences were identified.
4.2 Variable responses of individual cells to AT change

To obtain further insights into mechanisms underlying the effects of AT prolongation, behaviors of each cell in the cardiac tissue model were analyzed as shown in Figs. 8 (AT = 99 [ms]) and 9 (AT = 207 [ms]). In Figs. 8(a) and 9(a), Fb of 10 cells (Fb1−Fb10) are shown individually. Note that all Fs were the same in 10 cells at all times. The onset of Fb was delayed by magnitudes of δdelay values (= 11 [ms] or 23 [ms]) and time courses of the upstroke were delayed in the first few cells of total 10 compartments. The remaining cells subsequently showed increased Fb and reached their peaks sequentially. When the last cell reached the peak Fb in the middle of the ejection phase, 10 Fb gradually converged and the time courses almost coincided. This phenomenon suggested that Fp decreased in the process of cell shortening and almost completely disappeared at the time when all Fb converged. At end-systole where pV balanced with pLV, the valve between aorta and LV was closed (t = 362 [ms] and 380 [ms]). Relaxation of cardiac tissue then proceeded, as represented by a synchronous rapid drop in Fb. At the point where pV, balanced pLV, the valve between the vein and LV was open (t = 490 [ms] and 526 [ms]). Fb was small in the filling phase, and became almost comparable to Fp at end-diastole, and was most effective at end-diastole when the length of individual cells (L1–L10) are shown with the average length (Lav) in Figs. 8(b) and 9(b). Cell 1 started to contract in response to Ca2+ signals without delay, which in turn extended the remaining cells at a resting Ca2+ concentration within the tissue model. We defined the period from the time when Cell 1 started to contract until the time when L10 became shorter than the initial length as the early contraction phase (0−177.1 [ms] in Fig. 8, and 0–276.2 [ms] in Fig. 9). In the early contraction phase, Ls of the cells to be activated were extended to the maximum. During the isovolumic contraction phase (9.370−80.61 [ms] in Fig. 8, and 8.880–115.4 [ms] in Fig. 9), since Lav was unchanged, shortening of L in cells contracted earlier was compensated by elongation of L in cells contracted later. During the isovolumic relaxation phase (362.5–490.0 [ms] in Fig. 8, and 380.5–526.6 [ms] in Fig. 9), on the other hand, preceding elongation of the first few cells compensated for shortening of L in the remaining cells contracting later. To clarify why Fb in all 10 cells gradually converged toward end-systole and synchronized despite large variations in L during ejection and isovolumic relaxation phases, the concentration of crossbridges in the power state (TSp1−TSp10 [μM]) and crossbridge elongation in power state (h1−h10 [μm]) for each cell are shown in Figs. 8(c), (d) and 9(c), (d). These parameters were used in calculating Fb in Eq. (5). Note that parameters for crossbridges in the weak state in Fb equation (TSw1−TSw10 [μM] and hw1−hw10 [μm]) for each cell are not shown because of their similar trends as TSp1−TSp10 and h1−h10 and have relatively small contributions to Fb. According to the equation which gives h velocity in the original NL08 paper (Eq. (10) in [20]), h, is basically related to the first- and second-order derivatives of L. Thus, at the period when L shortening is accelerating, h, becomes small, and vice versa. Since the changes of Ls in Fig. 8(b) and Fig. 9(b) have similar trends, the changes to h, is shown in Fig. 8(d) and Fig. 9(d) are basically similar. Initial slowing of the upstroke in TS, in cells activated earlier was the cause of the delayed upstroke of Fb in Figs. 8(a) and 9(a), and attributable to increases in detachment parameters, g, and g, calculated from Eqs. (10) and (11). During the relaxation phase, Ts, in the first few cells activated earlier were too low to generate cellular contraction stress. Therefore, those cells were extended and increased h, to balance the stresses generated by other cells. The characteristic increases in L and h, of the few cells activated earlier during isovolumic relaxation phase were caused by the mechanism explained above. It was revealed that the significant drop in Fb and Fp in the later phase of isovolumic relaxation at AT = 207 [ms] (Fig. 9(a)) occurred because L1 and L2 were sufficiently extended to generate effective Fp1 and Fp2, which were not shown but was clear from exaggerated increases in L1 and L2 (Fig. 9(b)). Since dissecting cellular parameters from living human or animal tissue is almost impossible, these results may suggest fundamental characteristics of constituting cells through understanding of a mathematical contraction model.

Since we could not find any experimental data corresponding to these simulation results, the results are theoretical predictions that are derived from the physiological characteristics of cardiac cells and circulation system.

4.3 Comparing simulation results with other reports

In Table 4, we can see that max dp/dt decreases markedly from the physiological AT of 99 [ms] to the prolonged AT of 207 [ms], and ejection time was delayed accompanying the increase in AT. Decreased max dp/dt and delayed ejecting time in LBBB are known [3, 33, 34], which may partly correspond to the simulation results. The physiological range of max dp/dt is around 0.85−2.0 [mmHg/ms] [35], but the value was 6.178 [mmHg/ms] in our model. From the LV pressure time course shown in Fig. 5(a), the pressure rise before the ejection phase seems slightly high, which deviates from the clinical data. This may be due to the problem of reproducibility of cardiac contraction stress time course of the NL08 model. Thus, direct evaluation or comparison between the max dp/dt value obtained from our model and clinical data is not possible. However, since the effect of this difference on total hemodynamics is not overly large and the difference in the shape of the pressure rise between AT = 99 [ms] data and AT = 207 [ms] data is quite small, we consider that the relative difference still reflects basic characteristics of the phenomena. Takeshita et al. [3] reported the max dp/dt difference between normal and LBBB conditions in a patient who showed a 1.00 [mmHg/ms] to 0.48 [mmHg/ms] drop. Their relative difference in max dp/dt be-
between normal and LBBB conditions is close to our simulation results, suggesting that the model may reflect to some extent the effect of AT on cardiac pump function.

While max dp/dt decreased by 43.7%, EF and SV decreased by only 6.00% and 2.10%, respectively, when AT increased from 99 [ms] to 207 [ms]. Moreover, the PV loops (Fig. 5(c)) showed that the hemodynamics were preserved even if AT was prolonged to 207 [ms]. These results suggest that the parameters directly relating to cardiac output, such as EF and SV, may be robust to AT prolongation, while max dp/dt is predisposed to decrease mark-
the duration of isovolumic contraction phase is the major dete-
rmining factor for max dp/dt. Since this study is still in the pre-
liminary stage, we did not consider AT and contraction in the right
ventricle (RV) in the hemodynamic model used in our study. In other
words, simulations were performed while excluding the effects of RV
contraction and inter-ventricular asynchrony (inter VA). Differences there-
fore exist between our simulation results and experimental results us-
ing real hearts. We used QRS duration as the index of AT and
evaluated influences of AT alteration on hemodynamic parame-
ters. However, in real hearts, cardiac function can be changed by
alteration of inter VA even if QRS duration is unchanged, as re-
ported by Verbeeck et al. [39], representing a situation that cannot be
simulated by our model. Comparing our results with their re-
port, although SV decreased only a little by AT prolongation in
our results, SV decreased markedly under prolonged QRS dura-
tion with increased inter VA in their results. The cause of this dif-
ference may be the influence of synchrony between LV and RV. On the
other hand, other data from their report suggested that max dp/dt in-
creased when intra-ventricular asynchrony was large, corresponding to the
significant increase in max dp/dt at longer AT in our study. In addition, they also reported no signifi-
cant differences in end-diastolic pressure and end-diastolic vol-
ume between normal and prolonged QRS durations. In our simu-
lation, no significant differences in ED PVR were seen even when
AT increased from 99 [ms] to 207 [ms], which may correspond to
their experimental results.

In clinical data and conscious-condition animal ex-
periments, preload and afterload conditions are controlled by the au-
tonomic nervous system, which may affect hemodynamic param-
eters. In our simulation model, preload and afterload conditions
are controlled manually, so direct comparison between experi-
mental data and our simulation data might show deviations. How-
ever, since the changes in hemodynamic parameters are relatively
small in terms of physiological preload and afterload conditions,
the results can be considered to have meaningful differences.

5. Conclusion

In this research, we aimed to analyze the relationship between AT
and hemodynamics using a human hemodynamic model by incor-
porating a cardiac tissue model into an LV geometric model with-
in a circulation model, and also tried to analyze the underlying
mechanism of the relationship. As a result of the simulations, we
found that \( E_{max} \), EF and SV only decreased by 15.4%, 6.00% and
2.10%, respectively, when physiological AT (99 [ms]) was pro-
longed to 207 [ms], while max dp/dt decreased markedly by 43.7%.
The cellular mechanisms underlying changes in half sar-
comere length were analyzed individually in 10 cells. Our analy-
sis showed that the 10 cells were excited asynchronously and
changed their half sarcomere lengths individually to generate
equivalent \( F \) with different balance between \( F_s \) and \( F_p \). Thus,
even though hemodynamic parameters did not change signifi-
cantly, large differences in cell behaviors were identified.

In this research, AT was altered by changing constant exci-
tation delays among cardiac cells (\( \delta_{d_{exc}} \)) in the cardiac tis-
eue model. As future work, we are interested in integrating a cardiac
cell model that includes modern ion channel models and an exci-
tion contraction coupling model. This kind of model should
prove useful for evaluating the influence of gap junction current
on contraction stress. We are also interested in integrating cardiac
cell models that can evaluate energy consumption.

Conflict of Interest

We have no conflicts of interest relationship with any companies
or commercial organizations based on the definitions of the Japa-
nese Society for Medical and Biological Engineering.

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