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A mathematical model of human heart including the effects of heart contractility varying with heart rate changes

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ABSTRACT

Incorporating the intrinsic variability of heart contractility varying with heart rate into the mathematical model of human heart would be useful for addressing the dynamical behaviors of human cardiovascular system, but models with such features were rarely reported. This study focused on the development and evaluation of a mathematical model of the whole heart, including the effects of heart contractility varying with heart rate changes. This model was developed based on a paradigm and model presented by Ottesen and Densielsen, which was used to model ventricular contraction. A piece-wise function together with expressions for time-related parameters were constructed for modeling atrial contraction. Atrial and ventricular parts of the whole heart model were evaluated by comparing with models from literature, and then the whole heart model were assessed through coupling with a simple model of the systemic circulation system and the pulmonary circulation system. The results indicated that both atrial and ventricular parts of the whole heart model could reasonably reflect their contractility varying with heart rate changes, and the whole heart model could exhibit major features of human heart. Results of the parameters variation studies revealed the correlations between the parameters in the whole heart model and performances (including the maximum pressure and the stroke volume) of every chamber. These results would be useful for helping users to adjust parameters in special applications.

1. Introduction

Numerical simulation of physiological and pathological changes in the human cardiovascular system had became an active research area in the past decades. Various models had been proposed to study the dynamics of the cardiovascular system (Snyder and Rideout, 1969; Heldt et al., 2002; Liang et al., 2009; Wang et al., 2013). Among these studies, lumped parameter models were usually used to study the global responses of the whole circulation system (Snyder and Rideout, 1969; Melchior et al., 1992; Ursino, 1998; Pennati et al., 1997; Sun et al., 1997; Heldt et al., 2002; Ellwein et al., 2008). Mathematical models of the heart played critical roles in investigating the global responses of human cardiovascular system. Due to their important roles in pumping blood into the circulation system, ventricular models had been paid more attention than atrial models in most modeling studies (Suga et al., 1973; Melchioret al., 1992; Drzewiecki et al., 1996; Pennati et al., 1997; Heldt et al., 2002; Ottesen and Danielsen, 2003). Models of the whole heart were also developed and used in some studies, while only a few of them included arbitrary heart rate (Sun et al., 1997; Ursino, 1998; Vollkron et al., 2002; Liang et al., 2009; Muller and Toro, 2014).

There were mainly three ways to include arbitrary heart rate. Heldt et al. (2002) used 'Bazett formula' to determine the systolic time interval, which linked the systolic time interval of the present beat to duration of cardiac cycle that preceded it, meanwhile the length of the present cardiac cycle was determined by means of an integral pulse frequency modulation model of the sinoatrial node. Ottesen and Danielsen (2003) presented a different paradigm for modeling ventricular contraction with heart rate changes through using a polynomial expression of the activity function, which contained more features and would generate results in good agreement with experimental data from Regen et al. (1993) and Mulier (1994). Liang and Liu (2006) used a constant time parameter to scale the value of systolic elastance when the cardiac cycle changes. Ottesen's paradigm was chosen in this study for building the whole heart model with consideration of contractility varying with heart rate changes.

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Modeling atrial contraction with heart rate changes was also valuable for analyzing the global responses of human cardiovascular system with closed loop regulation, because atrial contraction played an increasingly significant role in ventricular filling as heart rate increases Mohrman and Heller (2010). In the past decades, atrial contraction was usually neglected or described as a linear capacitor in published cardiovascular system models. Only a few of them contained atrial contraction (Liang and Liu, 2006; Liang et al., 2009; Olufsen et al., 2005). Olufsen et al. (2005) adopted Ottesen's paradigm and model for modeling both left ventricle and left atrium in their modeling investigation, but detailed discussions on modeling atrial contraction with consideration of contractility varying with heart rate changes were not presented.

In this study, a mathematical model of the whole heart including the effects of contractility varying with heart rate changes was established and evaluated. The paradigm and model reported by Ottesen and Danielsen (2003) was chosen for modeling ventricular contraction with heart rate changes. A mathematical piece-wise function together with expressions for time-related parameters were constructed for describing activation of atrial contraction, based on the same paradigm as that of the ventricle. A mathematical model of the whole heart, including the right and left atriums and ventricles, were built and evaluated through coupling with a simple model of the systemic circulation and the pulmonary circulation. Parameters variation studies were carried out for evaluating the influences of the parameters in the model of each chamber on the maximum pressure and the stroke volume of every chamber. Improvements and limitations of this mathematical model were finally discussed.

2. Methods

2.1. Modeling ventricular contraction

The isovolumic ventricular pressure was described as a function of ventricular volume and heart rate, which was demonstrated to be able to exhibit the major features of an ejecting heart when it was coupled to a simple windkessel model of arterial tree (Ottesen and Danielsen, 2003),

$$p(t,V,H) = a(V-b)^2 + (cV-d)\cdot f(t,H) \tag{1}$$

where p is pressure, mmHg; t is time, s; V is ventricular volume, ml; H denotes the heart rate, rpm; $a(V-b)^2$ denotes the isovolumic minimum pressure, in which a relates to ventricular elastance during relaxation and b represents ventricular volume for zero diastolic pressure; $cV-d$ represents peak developed pressure, in which c and d relate to the volume-dependent and volume-independent components of developed pressure respectively; $f(t,H)$ is a continuous activation function.

The activation function, $f(t,H)$, played a critical role in the performance of Eq. (1). There were several types of activation functions, including Muliers approach, polynomial expression, gamma distribution, combined exponential, product of Hill functions, etc., which were comparatively studied in investigations of Ottesen and Danielsen (2003). A polynomial expression of activation function was chosen to build the ventricular model in this study, as shown in Eq. (2),

$$f(t,H) = p_p \cdot \begin{cases} \frac{t^n(\beta-t)^m}{n^n m^m[\beta/(m+n)]^{m+n}} & 0 \leqslant t \leqslant \beta(H) \\ 0 & \beta(H) < t < T_0 \end{cases} \tag{2}$$

where $n^n m^m[\beta/(m+n)]^{m+n}$ is a normalizing factor; p_p is a scaling factor for considering variation of the peak value of $f(t,H)$ when heart rate changes (Ottesen and Danielsen, 2003); the parameter β represents time for end of the active force generation; the parameters m and n characterize contraction and relaxation respectively; T_0 is the total time of one cardiac cycle, which can be calculated by 60.0/H.

Experimental data from Regen et al. (1993) showed that time for peak pressure t_p could be described as a decreasing sigmoidal function of heart rate H, while p_p could be described as an increasing sigmoidal function of heart rate H. These sigmoidal functions could be expressed using the Hill function (Ottesen and Danielsen, 2003),

$$t_p(H) = t_{p,\min} + \frac{\theta^v}{H^v+\theta^v}(t_{p,\max} - t_{p,\min}) \tag{3}$$

$$p_p(H) = p_{p,\min} + \frac{H^\eta}{H^\eta+\phi^\eta}(p_{p,\max} - p_{p,\min}) \tag{4}$$

where θ represents the median and v the steepness of the Eq. (3), $t_{p,\min}$ and $t_{p,\max}$ denote the minimum and maximum values of t_p respectively; Similarly, ϕ is the median and η the steepness of the Eq. (4), $p_{p,\min}$ and $p_{p,\max}$ represent the minimum and maximum values of p_p respectively. The change of t_p with heart rate can be introduced into the isovolumic pressure model by modifying the parameter β such that it become a function of heart rate H,

$$\beta_v(H) = \frac{n+m}{n}t_p(H) - \alpha_v\frac{m}{n} \tag{5}$$

where α represents time for onset of contraction, and the subscript v denotes the ventricle. The value of α_v is always set to be 0 in this study, which means a cardiac cycle is defined to begin at the onset of ventricular contraction.

Parameters in this ventricular model were adapted from investigations of Ottesen and Danielsen (2003) and Olufsen et al. (2005), as listed in Table.1.

2.2. Modeling atrial contraction

The atrial model was established using similar functions as that of the ventricle. Actually, Eq. (2) could also be used to describe the atrial myocardium activation. If so, the expressions of the ventricular activation function and the atrial activation function were difficult to be arranged in the same cardiac cycle, because the time for onset of contraction were different for ventricle and atrium. These expressions were preferred to be set in the same cardiac cycle for convenience. A piece-wise type of activation function of atrial contraction in the study of Liang et al. (2009) was used as reference to construct the atrial activation function in this study, and the result was shown as following,

$$f(t,H) = p_p \cdot \begin{cases} \frac{(t+T_0-\alpha)^n(\beta-t-T_0)^m}{n^n m^m[(\beta-\alpha)/(m+n)]^{m+n}} & 0 < t \leqslant \beta(H) - T_0 \\ 0 & \beta(H) - T_0 < t \leqslant \alpha \\ \frac{(t-\alpha)^n(\beta-t)^m}{n^n m^m[(\beta-\alpha)/(m+n)]^{m+n}} & \alpha < t \leqslant T_0 \end{cases} \tag{6}$$

As there would be overlap between time histories of the atrial and ventricular activation, value of time for end of the activation (i.e., β) in Eq. (6) would be larger than the value of T_0, which meant that an atrial activation would cross two cardiac cycles according to the definition of cardiac cycle in this paper. The part of atrial activation curve beyond this cardiac cycle was translated into this cycle according to its periodicity and became the first expression in Eq. (6).p_p in Eq. (6) were also calculated by Eq. (4), and β in the atrial model could also be calculated by Eq. (5). However, it was difficult to obtain matched $t_{p,\min}$ and $t_{p,\max}$ for both the atrial model and the ventricular model. A different method for calculating time-related parameters in the atrial model was presented as following,

$$\beta_a(H) - \alpha_a = k_2 \cdot [\beta_v(H) - \alpha_v] \tag{7}$$

where the subscript a denotes atrium, and k_2 is a constant. The Eq. (7) was constructed based on an assumption that the time duration

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