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Review

A new integrated method for analyzing heart mechanics using a cell–hemodynamics–autonomic nerve control coupled model of the cardiovascular system

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Abstract

A model of the cardiovascular system coupling cell, hemodynamics, and autonomic nerve control function is proposed for analyzing heart mechanics. We developed a comprehensive cardiovascular model with multi-physics and multi-scale characteristics that simulates the physiological events from membrane excitation of a cardiac cell to contraction of the human heart and systemic blood circulation and ultimately to autonomic nerve control. A lumped parameter model is used to compute the systemic and pulmonary circulations interacting with the cardiac cell mechanism. For autonomic control of the cardiovascular system, we used the approach suggested by Heldt et al. [2002. Computational modeling of cardiovascular response to orthostatic stress. J. Appl. Physiol. 92, 1239–1254] (Heldt model), including baroreflex and cardiopulmonary reflexes. We assumed sympathetic and parasympathetic pathways for the nerve control system. The cardiac muscle response to these reflex control systems was implemented using the activation-level changes in the L-type calcium channel and sarcoplasmic/endoplasmic reticulum calcium ATPase function based on experimental observations. Using this model, we delineated the cellular mechanism of heart contractility mediated by nerve control function. To verify the integrated method, we simulated a 10% hemorrhage, which involves cardiac cell mechanics, circulatory hemodynamics, and nerve control function. The computed and experimental results were compared. Using this methodology, the state of cardiac contractility, influenced by diverse properties such as the afterload and nerve control systems, is easily assessed in an integrated manner.

Keywords: Cardiovascular hemodynamics; Autonomic nerve control (ANC); A cell-system-ANC coupled model

Contents

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1. Introduction

The physiomic approach has emerged as a promising tool for biomedical science. In particular, the heart physiome (Nickerson et al., 2006) is a leading target for this approach and several studies have been conducted. As reviewed by Noble (2002), a variety of computational modeling studies have covered everything from a cardiac cell electrophysiology model to a heart organ model. Models of heart cells including the sinoatrial node, Purkinje fibers, atrial cells, and ventricular cells have been studied for four decades (Noble and Rudy, 2001). Clancy and Rudy (2002) linked the electrophysiological simulation of LQT3 syndrome to genetics. Mechanoelectric feedback is also an important target of heart modeling. Kohl and Sachs (2001) demonstrated that the contraction of the cardiac cell influences its electrical properties. A cardiac tissue model for electric wave propagation was developed to simulate cardiac electrophysiology using bidomain or monodomain methods (Henriquez, 1993; Panfilov and Holden, 1993). At the organ level, Usyk et al. (2002) used the finite element method (FEM) to couple ventricular contraction mechanics with electric excitation. Recently, Kerckhoffs et al. (2007) have coupled a finite element model of a ventricle with a closed circulation, and Watanabe et al. (2004) performed a multi-scale simulation that included fluid–solid interaction. Smith et al. (2000) reconstructed the anatomical structure of the coronary vasculature and resolved the blood flow coupled with ventricular contraction. These previous studies, however, did not consider the fluid–structure interaction in the ventricular wall coupled with the blood circulation of the cardiovascular system, although cardiac mechanics are closely related to valvular and vascular hemodynamics. Moreover, heart and vascular mechanics, including wall motion and the hemodynamics of the cardiovascular system, are greatly influenced by the autonomic nerve system. Therefore, an integrated approach is needed to simulate the comprehensive characteristics of the heart and cardiovascular system, requiring a multi-scale, multi-physics model that incorporates everything from cells to systemic circulation and autonomic nerve control.

From a physiological perspective, autonomic nerve control of the heart and cardiovascular system is very important. In particular, the variation in the heart rate and heart contractility with autonomic nerve control is critical for an individual's optimal performance and even survival. To maintain blood pressure homeostasis, the terminal neurons of autonomous nerves liberate their primary messengers or neurotransmitters, mainly norepinephrine and acetylcholine, which travel across the synaptic junction to the external cell membrane of the heart. The beta-adrenergic receptors activated by the neurotransmitters enhance contractility and the heart rate. Recently, Saucerman and McCulloch (2004) developed a computational model of the beta-adrenergic signaling network and its regulation of rat ventricular myocyte excitation–contraction coupling. These cellular-level changes in physiological properties due to the autonomous nerve system are provoked by blood pressure homeostasis. Due to the complicated interaction between the cellular properties and blood pressure homeostasis at the level of the systemic circulation, it is necessary to combine cellular mechanism with systemic circulation. To our knowledge, however, the interaction between cellular mechanism and autonomic nerve control has not been elucidated. Previously, we combined the model of ten Tusscher et al. (2004; TNNP model) of the ventricular cell with the NL model