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Effects of cellular electromechanical coupling on functional heterogeneity in a one-dimensional tissue model of the myocardium

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ABSTRACT

Based on the experimental evidence, we developed a one-dimensional (1D) model of heterogeneous myocardial tissue consisting of in-series connected cardiomyocytes from distant transmural regions using mathematical models of subendocardial and subepicardial cells. The regional deformation patterns produced by our 1D model are consistent with the transmural regional strain patterns obtained experimentally in the normal heart in vivo. The modelling results suggest that the mechanical load may essentially affect the transmural gradients in the electrical and mechanical properties of interacting myocytes within a tissue, thereby regulating global myocardial output.

1. Introduction

The myocardial architecture plays a critical role in electrical excitation and contraction of the heart ventricles [1,2]. There are two seemingly opposite approaches used to describe this architecture [2]: the ‘cardiac mesh’ approach proposed by Anderson and co-workers [3] and the helical ventricular myocardial band model proposed by Torrent-Guasp and co-workers [4]. The ‘cardiac mesh’ approach suggests that cardiomyocytes are arranged longitudinally and radially, changing their angulations along with myocardial depth [3]. However, in recent work attempting to track the continuity of the aggregated myocytes, as revealed by diffusion tensor magnetic resonance imaging (DT-MRI), the same group noticed that the three-dimensional (3D) cardiac mesh was interconnected to produce highly reproducible tracks (or pathways) that changes smoothly and continuously in terms of the angulations of the long axis of the myocytes relative to the epicardial surfaces and the depth of the walls through the myocardial walls. Anderson's group has written that the tracks can be considered to reflect the chain of transduction of force through the myocardium [5]. Another approach proposed by Torrent-Guasp and co-workers suggests that cardiomyocytes are arranged longitudinally within ventricular myocardial fibres, forming a continuous helical muscle-band that starts at the pulmonary artery and ends at the aorta wrapping the left ventricle (LV) and part of the right ventricle (RV) [4] (Fig. 1A).

Recently, Poveda and co-workers analysed the myocardial architecture for the canine myocardium via an automated method that included the entire myocardium and revealed a continuous helical myocardial fibre arrangement of both the RV and LV, thus supporting the anatomical studies of Torrent-Guasp [2] (Fig. 1A). Gao and co-workers have obtained similar results for the human myocardium [6]. They concluded that ventricular myocardial fibres maintained complete continuity and specific orientations that corresponded to the helical ventricular myocardial band structural hypothesis. Recent computer modelling studies also have taken into account the helical myocardial anatomy [7,8].

Anatomical studies using DT-MRI have revealed that fibre orientation depends on transmural location, with fibre direction being predominantly longitudinal in the subendocardial (ENDO) region; moving into a circumferential direction in the midwall and becoming longitudinal again over the subepicardial (EPI) surface [1] (Fig. 1B).

These experimental findings allow us to assume that there are myofibre pathways tracking longitudinally through the myocardial wall depth from the ENDO to EPI layer and consisting of cardiomyocytes connected in-series along the fibre direction. This myofibre architecture provides for predominant electrical and mechanical propagation pathways through the ventricular wall. Based on this assumption, we developed a one-dimensional (1D) continuous strand model formed from in-series connected, electrically and mechanically coupled cardiomyocytes from distant transmural myocardial regions as a representative model of a single ventricular myofibre. We suggest that cardiomyocytes in our 1D strand model do not penetrate the ventricular wall in the shortest transmural direction (i.e. normal to the epicardial surface of the ventricle); instead, they are arranged along a ‘straightened’ myofibre that is essentially longer than the ventricular wall

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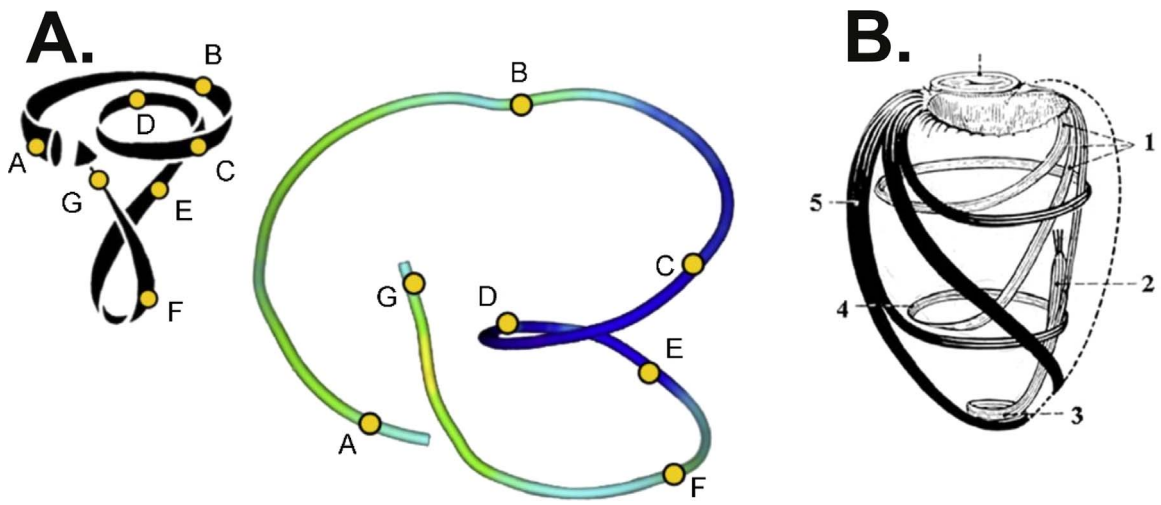

Fig. 1. Myocardial architecture. A. The Torrent-Guasp model of a helical ventricular myocardial band consisting of ventricular myocardial fibres (left) and a tract reconstructed from a single manually picked seed on the diffusion tensor magnetic resonance imaging (DT-MRI) volume (right; with permission from [2]). B. Structure of the left ventricle (LV) wall, with fibre directions continuously changing through the myocardial wall from the subendocardium to subepicardium, where 1: fibres in the subendocardial (ENDO) region, 2: papillary muscle, 3: vortex cordis, 4: circumferential fibres, and 5: fibres in the subepicardial (EPI) region (with permission from [1]).

width.

Recently, we developed detailed, integrative models of cardiomyocytes from the ENDO and EPI ventricular regions that take into account experimental data on specific features of the heterogeneity in the cellular action potential (AP), Ca^{2+} transient and contraction between the ENDO and EPI cells of the guinea pig heart [9]. In the present study, we utilised our cellular ENDO and EPI models in the framework of our 1D model to simulate the effects of regional heterogeneity on the mechanical and electrical activity of cells within the fibre. This heterogeneous strand model was validated against experimental data on regional ventricular mechanics obtained in the normal heart in vivo [10,11].

2. Methods

2.1. One-dimensional tissue model predecessor

The ENDO and EPI single cell models (for more details see the Supplement) were utilised within a recently developed 1D continuous model of a cardiac strand formed from mechanically and electrically coupled cardiomyocytes, connected in series [12]. Shaw and Rudy's assessments allow the cells to be considered as isopotential within myocardial tissue with high accuracy [13]. Considering the tissue strand as a static continuous medium, where each point is identified by the Lagrangian point coordinate x, the excitation propagation is described by a reaction–diffusion equation for the membrane potential $V(x,t)$:

$$\frac{\partial V(x,t)}{\partial t} = D\frac{\partial^2 V(x,t)}{\partial x^2} - \frac{1}{C_m(x)}\sum i_{ion}(x,t), \quad (1)$$

where D is an electrodiffusion coefficient that determines the velocity of excitation propagation through the strand, $C_m(x)$ is the membrane capacity of cell x and $\sum i_{ion}(x,t)$ represents the local transmembrane ionic currents.

As in native tissue, the electrical wave of excitation propagates along a dynamically deforming medium in the 1D strand model. The 1D model integrates both intracellular and intercellular circuits of the electromechanical coupling and mechanoelectric feedback at both the cellular and tissue level [12]. Thus, during the propagation of the electrical signal from the left to the right edge of the strand, the length of each contracting cell continuously changes, providing for the global deformation of the strand and overall force generation.

A special constitutive relation exists between the macro (strand) and micro (cell) geometries determining the links between the strand and cell deformations [12]. Let us consider the current time-dependent position of the cell x within the active tissue. Its displacement $\hat{l}(x,t)$ from the reference position in the unstretched and unexcited strand is determined by the summated deformations of the cells located prior to the cell. So, a key assumption we used in the tissue model is that the local deformation of the strand at any point x in the macrospace ($\frac{\partial \hat{l}(x,t)}{\partial x}$) is equal to the relative deformation of cell x in the microspace $l(x,t)$ [12]:

$$\frac{\partial \hat{l}(x,t)}{\partial x} = l(x,t). \quad (2)$$

An external serial elastic (XSE) element is introduced in the rheological scheme of the strand, and $l_{ex}(t)$ denotes the deviation of the XSE length from its slack length (Fig. 2).

An additional equation to complete the mechanical system is provided by the isometric or isotonic conditions of fibre contraction. The *isometric* mode of contraction is characterised by a fixed length of the strand during the contractile cycle. During the propagation of the electrical signal along the fibre, cells contract, thereby changing their lengths. Isometric conditions for the fibre are achieved when a displacement $\hat{l}(x_F,t)$ of the right edge of the strand (x_F) during an active contraction is balanced by stretching the external passive-elastic XSE element, so that the sum of their deformations remains constant:

$$\hat{l}(x_F,t) + l_{ex}(t) \equiv const. \quad (3)$$

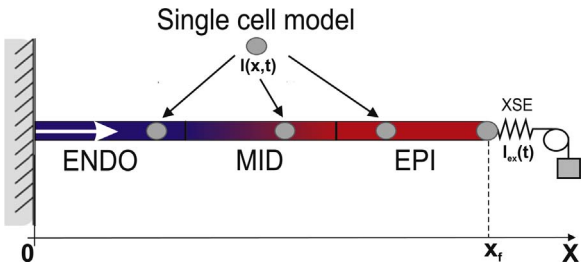

Fig. 2. Scheme of a one-dimensional (1D) model of heterogeneous cardiac strand consisting of cells from subendocardial (ENDO), intermediate (MID) and subepicardial (EPI) regions. The white arrow shows the direction of the excitation wave. Each point x of the continuous medium is a cardiomyocyte (designated by grey circles), which has its own dynamically changing geometry. Variables $l(x,t)$ and $l_{ex}(t)$ define deformations of cell x and external in-series XSE element, respectively, relative to their slack lengths (see text for details).