Journal of Theoretical Biology 397 (2016) 103–114

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

The dual effect of ephaptic coupling on cardiac conduction with heterogeneous expression of connexin 43

Ning Wei [a], Yoichiro Mori [a], Elena G. Tolkacheva [b,*]

[a] School of Mathematics, University of Minnesota, 206 Church St. SE, Minneapolis, MN 55455, United States
[b] Department of Biomedical Engineering, University of Minnesota, 312 Church St. SE, 6-128 Nils Hasselmo Hall, Minneapolis, MN 55455, United States

HIGHLIGHTS

- We explored the interplay of heterogeneous Cx43 expression and ephaptic coupling on cardiac conduction.
- The presence of ephaptic coupling leads to alternating conduction, instability of planar fronts and SAP.
- Ephaptic coupling can either prevent or promote CB depending on Cx43KO content.

ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form
25 January 2016
Accepted 19 February 2016
Available online 9 March 2016

Keywords:
Heterogeneous connexin 43
Bidomain model
Alternating conduction
Small amplitude action potential
Instability of planar fronts
Conduction block

ABSTRACT

Decreased and heterogeneous expression of connexin 43 (Cx43) are common features in animal heart failure models. Ephpatic coupling, which relies on the presence of junctional cleft space between the ends of adjacent cells, has been suggested to play a more active role in mediating intercellular electrical communication when gap junctions are reduced. To better understand the interplay of Cx43 expression and ephaptic coupling on cardiac conduction during heart failure, we performed numerical simulations on our model when Cx43 expression is reduced and heterogeneous. Under severely reduced Cx43 expression, we identified three new phenomena in the presence of ephaptic coupling: alternating conduction, in which ephaptic and gap junction-mediated mechanisms alternate; instability of planar fronts; and small amplitude action potential (SAP), which has a smaller potential amplitude than the normal action potential. In the presence of heterogeneous Cx43 expression, ephaptic coupling can either prevent or promote conduction block (CB) depending on the Cx43 knockout (Cx43KO) content. When Cx43KO content is relatively high, ephaptic coupling reduces the probabilities of CB. However, ephaptic coupling promotes CB when Cx43KO and wild type cells are mixed in roughly equal proportion, which can be attributed to an increase in current-to-load mismatch.

1. Introduction

Cardiac cells communicate electrically to coordinate the muscular contraction of the heart to pump blood. Gap junctions are low-resistance pathways that mediate the electrical impulses between myocytes. Gap junctional coupling is one of the key factors that guarantees the velocity and reliability of cardiac conduction (Shaw and Rudy, 1997; Vaidya et al., 2001; Beauchamp et al., 2004, 2012).

Ventricular myocytes are connected electrically through gap junction channels formed mainly by connexin 43 (Cx43) and, to a smaller extent, Cx45 (Davis et al., 1995). Growing experimental and theoretical evidence suggests that heterogeneity of Cx43 can lead to altered patterns of conduction, re-entrant arrhythmias and sudden death (Danik et al., 2004; Gutstein et al., 2001; Jongsma and Wilders, 2000; Kanno and Saffitz, 2001; Prudat and Kucera, 2014). For example, in Danik et al. (2004), authors investigated susceptibility to arrhythmias in a genetically engineered murine model to express progressively decreasing levels of Cx43. Lethal tachyarrhythmias were initiated if cardiac Cx43 abundance was decreased in a heterogeneous fashion to 18% of the control level. In Gutstein et al. (2001), authors designed a murine model of heterogeneous gap junction channel expression, which results in conduction defects as well as markedly depressed contractile function. Additionally, in Prudat and Kucera (2014), authors showed that velocity and stability of conduction behave in a nonlinear manner when cardiomyocytes expressing different amounts of Cx43 are combined. In particular, conduction became very heterogeneous and was susceptible to block in the co-

* Corresponding author. Tel.: +1 612 626 2719.
E-mail address: talkacal@umn.edu (E.G. Tolkacheva).

http://dx.doi.org/10.1016/j.jtbi.2016.02.029
0022-5193/

culturing of Cx43 knockout (Cx43KO) and wild type (WT) cells, while block was never observed in monogenotypic preparations.

It is widely accepted that gap junctional coupling is the primary mechanism responsible for electrical communication between cardiac cells (Rohr, 2004). However, recent experimental observation has raised the question of whether conduction can be sustained in the absence of gap junctions (Danik et al., 2004; Yao et al., 2003). For instance, in Yao et al. (2003), intercellular conductance measured by dual whole cell voltage clamp in pairs of adult rat ventricular myocytes with genetic Cx43 ablation was dramatically reduced from 588 nS to 10 nS. However, impulse propagation was reduced by only 50% in tissue composed of the same cells.

One possible explanation of this intriguing observation is ephaptic coupling, first proposed in Sperelakis and Mann (1977) and further elaborated in Sperelakis and McConnell (2002). In it, neighboring cells are electrically coupled through a narrow cleft space that is resistively connected to the extracellular space. It is further assumed that Na^+ channels are preferentially localized to the cleft space, as shown by experiments in Cohen (1996), Maier et al. (2002), Kucera et al. (2002), and Sperelakis and McConnell (2002). When an action potential reaches one cell, the Na^+ current flows into the cell from extracellular bath via the cleft, and the potential in the cleft space drops. Once the cleft potential becomes sufficiently negative, it depolarizes the membrane of the adjacent cell to the threshold, and that cell then produces an action potential. Several theoretical studies investigated the possible role of ephaptic coupling in cardiac signal propagation (Kucera et al., 2002; Mori et al., 2008; Veeraraghavan et al., 2014b; Hand and Peskin, 2010; Copene and Keener, 2008). In Kucera et al. (2002) and Hand and Peskin (2010), the authors assessed the hypothesis that conduction could be modulated by the preferential localization of Na^+ channels in the cleft space, which causes a large negative potential in the cleft and influences conduction in two opposite ways, depending on the strength of gap junctional coupling. In particular, for normal and moderately reduced gap junctional coupling, localization of Na^+ channels to the cleft space forces Na^+ current to go through the large resistance between cleft and extracellular space, which slowed down the conduction. In contrast, for greatly reduced gap junctional coupling, the negative cleft potential induced by Na^+ current in the prejunctional membrane leads to a suprathreshold depolarization of the postjunctional membrane, which facilitated and accelerated conduction. In Mori et al. (2008), the authors identified a mode of conduction in which the ephaptic and gap-junction-mediated mechanisms alternate. Authors of Copene and Keener (2008) explored the feasibility of ephaptic mechanism in the absence of gap junctions, which is highly parameter dependent.

Decreased and heterogeneous expression of Cx43 are common features in animal heart failure models (Wang and Gerdes, 1999; Huang et al., 1999; Yoshida et al., 2011). Emerging evidence suggests a more active role for ephaptic coupling in mediating intercellular electrical communication when gap junctions are reduced in a homogeneous manner (Yao et al., 2003; Kucera et al., 2002; Hand and Peskin, 2010; Lin and Keener, 2014). However, the interplay between heterogeneous Cx43 expression and ephaptic coupling on cardiac conduction has not been investigated yet. In this paper, we aim to explore the effects of ephaptic coupling on cardiac impulse propagation via numerical simulations when Cx43 expression is reduced and heterogeneous.

2. Materials and methods

2.1. Mathematical model

2.1.1. Bidomain model with ephaptic coupling

A two dimensional (2D) bidomain model (Fig. 1A) of electrical conduction was modified to incorporate ephaptic coupling (Hand and Peskin, 2010; Copene and Keener, 2008), which relies on the presence of a junctional cleft space between the ends of adjacent cells. Each cell is assumed to be cylindrical in shape with radius r and length L. The cells are connected by gap junctions to form an $M \times N$ rectangular lattice. At each lattice point (i,j), we associated intracellular potential $\phi_i^{(i,j)}$ and extracellular potential $\phi_e^{(i,j)}$. The cleft lies in between cells (i,j) and $(i,j+1)$. We then defined a cleft potential $\phi_c^{(i,j+\frac{1}{2})}$ at location $(i,j+\frac{1}{2})$. We called the space, which lies in the extracellular space and stays adjacent to the cleft, the extracellular-cleft space. The potential in the extracellular-cleft space is denoted by $\phi_{ec}^{(i,j+\frac{1}{2})}$. Note that Fig. 1A shows the lattice view of the model, whereas Fig. 1B shows the connection between lattices. In particular, Fig. 1B shows a circuit diagram for two adjacent cells that are ephaptically coupled through a common cleft space in the presence of end-to-end gap junctions (GJ_{end}), side-to-side gap junctions (GJ_{side}) and resistive connections between extracellular spaces (R_{ee}) are not shown here. Cleft space was modelled as a single narrow compartment with resistive connections (R_c) to the extracellular space; resistive connections between extracellular space and the extracellular-cleft space are denoted by R_{ec}. Intracellular and extracellular spaces of each cell are separated by the cell side membrane; intracellular and cleft spaces are separated by the cell end membrane. Both side and end membranes allow the free flow of ionic and capacitive currents. Ephaptic coupling is maintained by the active end membranes that are connected by a shared cleft potential. In order to save on computational cost, we treated intracellular and extracellular spaces of each cell to be isopotential.

As can be seen from Fig. 1, four different compartments, namely intracellular, extracellular, cleft, and extracellular-cleft spaces, were modelled separately. Current conservation in each compartment provides the following equations, with parameters listed in Table 1.

- Intracellular space ($\phi_i^{(i,j)}$; $1 \le i \le M$, $2 \le j \le N-1$):

$$GJ_{\text{end}}\left(\phi_i^{(i,j)}-\phi_i^{(i,j-1)}\right)+GJ_{\text{end}}\left(\phi_i^{(i,j)}-\phi_i^{(i,j+1)}\right)+GJ_{\text{side}}\left(\phi_i^{(i,j)}-\phi_i^{(i-1,j)}\right)+GJ_{\text{side}}\left(\phi_i^{(i,j)}-\phi_i^{(i+1,j)}\right)+A_{\text{end}}C_m\frac{\partial\left(\phi_i^{(i,j)}-\phi_c^{\left(i,j-\frac{1}{2}\right)}\right)}{\partial t}+A_{\text{end}}C_m\frac{\partial\left(\phi_i^{(i,j)}-\phi_c^{\left(i,j+\frac{1}{2}\right)}\right)}{\partial t}+I_{\text{end}}+A_{\text{side}}C_m\frac{\partial\left(\phi_i^{(i,j)}-\phi_e^{(i,j)}\right)}{\partial t}+I_{\text{side}}=0, \tag{2.1}$$

where $A_{\text{end}}=\pi r^2$ and $A_{\text{side}}=2\pi rL$ denote the cross-sectional and side areas of a cell, respectively; $GJ_{\text{end}}=A_{\text{end}}g_{\text{end}}$ and $GJ_{\text{side}}=\frac{A_{\text{side}}}{2}g_{\text{side}}$ denote end-to-end and side-to-side gap junctional conductance, respectively; $\phi_i^{(i,j)}$, $\phi_i^{(i,j-1)}$ and $\phi_i^{(i,j+1)}$ denote the intracellular potentials of cells (i,j), $(i,j-1)$ and $(i,j+1)$, respectively; $\phi_i^{(i-1,j)}$ and $\phi_i^{(i+1,j)}$ denote the intracellular potentials of cells $(i-1,j)$ and $(i+1,j)$, respectively; $\phi_c^{(i,j-\frac{1}{2})}$ and $\phi_c^{(i,j+\frac{1}{2})}$ denote cleft potentials at locations $(i,j-\frac{1}{2})$ and $(i,j+\frac{1}{2})$, respectively; C_m represents the membrane capacitance per area; I_{end} and I_{side} denote the outward ionic current of the end and side