

# Simulation of Cellular Remodeling: from Cardiac Myofiber to Whole Heart

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## Article Info

### Article Notes

Received: May 01, 2018

Accepted: July 06, 2018

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### Keywords:

Cardiac myofiber

Heart failure

Mathematical model

Cardiac electrophysiology

## ABSTRACT

Heart failure is characterized as any heart condition resulting from impairment of the heart's ability to pump blood, with high prevalence in both aged and diseased hearts. Numerous population-based studies have shown that, in patients with impaired left ventricular systolic function, additional structural and functional cardiovascular abnormalities are often found, making it difficult to understand the underlying pathophysiological processes. Advances in experimental and modeling tools have led to the identification of many cellular mechanisms that contribute to cardiac failure. Still, the mechanism by which cardiac myofiber adaptation ultimately leads to failure remains unclear. Several human cell, tissue, and organ models are used to model heart failure. In this mini review, several available human models are summarized with a focus on the simulation of cellular remodeling: from membrane excitation at the level of the single cell to contraction of the ventricle.

Despite substantial progress in experimental and modeling tools, the understanding of the underlying pathophysiological processes in cardiac tissue is still limited due to the difficulty in direct measurements of the mechanical and electrical processes within the contracting heart. Multiple models of individual muscle cells (cardiac myofibers or myocytes) have been established to clarify the nature and pathogenesis of heart diseases. These models, which simulate cellular electrical, and mechanical activity, can be integrated into organ level cardiac models to study the contribution of interrelated cellular mechanisms to global myocardial function in both normal and disease conditions.

One of the most common heart disease conditions is heart failure (HF), which reduces the ability of the heart to pump blood<sup>1</sup>. Because HF is highly prevalent in both aged and diseased hearts<sup>2</sup>, it has become the subject of numerous models at the single-cell<sup>3-6</sup>, tissue<sup>7-9</sup>, and whole-heart levels<sup>10-14</sup>. Each of these models has different experimental data basis, accuracy, ability to account for underlying physiology and computational efficiency. Despite considerable development of these models, the great challenge remains to describe the mechanisms of HF in humans due to the limited availability of human data.

## Simulation of Cellular Remodeling in the Failing Myocyte

The electrophysiological remodeling under HF condition is associated with action potential (AP) prolongation and altered calcium ( $Ca^{2+}$ ) handling in animal models and humans<sup>15</sup>. Several human electrophysiological models are capable of simulating these events by changing the maximal conductances or scaling factors of particular ion currents<sup>4-7</sup>. For example, in these models, the density of the transient outward potassium current ( $I_{to}$ ), which contributes significantly to AP prolongation<sup>16</sup>, is reduced by 33-60%. The reduction of the inward rectifier potassium current ( $I_{K1}$ ) in the models ( $\downarrow$ 25-50%) contributes

to the reduced resting membrane potential, which has been reported in human studies<sup>16,17</sup>. Few models consider the downregulation (↓40-50%) of a slow component of the delayed rectifier potassium current ( $I_{Ks}$ ) as an important contributor to the late phase of repolarization. Altered calcium ( $Ca^{2+}$ ) handling in the electrophysiological models is commonly simulated by sarcolemmal sodium-calcium exchanger ( $I_{NaCa}$ ) upregulation (↑36-200%) and sarcoplasmic reticulum  $Ca^{2+}$  (SERCA) pump downregulation (↓40-50%), as is observed in human HF<sup>18,19</sup>.

If the objective of a particular research requires remodeling of three transmural cell types—epicardial (epi-), mid-myocardial (M cells), and endocardial cells (endo-cells)—there is another group of models<sup>3,4,20-22</sup> that have been developed based on existing electrophysiological models of undiseased human ventricular cells: the Ten Tusscher-Noble-Noble-Panfilov (TNNP) model<sup>23,24</sup>, the O’Hara-Virág-Varró-Rudy (OVVR) model<sup>25</sup>, and the Grandi-Pasqualini-Bers (GPB) model (for epi- and endo-cells only)<sup>26</sup>. Transmural remodeling can be incorporated using the mentioned alterations of the transmembrane currents for each cell type. Table 1 contains several characteristics of these models (i.e., the sources of experimental data of the remodeled currents and exchangers, ventricular cell type, the number of variables and integration time step, and the models on which they are based).

The consequences of AP prolongation include elevated intracellular  $Ca^{2+}$ ,<sup>27</sup> which, in turn, increases contractility as a compensatory response of the heart to an increased

load<sup>15</sup>. On the other hand, chronic elevation in intracellular  $Ca^{2+}$  resulting from AP prolongation may lead to the maladaptive expression of genes encoding  $Ca^{2+}$ -handling proteins [e.g., SERCA, ryanodine receptor (RyR2)]<sup>19</sup>. In both cases, the muscle contractile process, which involves the interaction of myofilaments (actin and myosin) in the presence of  $Ca^{2+}$ , is compromised by impaired  $Ca^{2+}$  handling.

To simulate a disturbance in excitation-contraction coupling, the changes related to HF can be incorporated into the cellular myofilament models. Notably, the investigators of one study by Adeniran *et al.*<sup>11</sup> have examined the cellular mechanisms influencing myocardial  $Ca^{2+}$  homeostasis in HF with preserved ejection fraction using an electromechanical single cell model in the 3D multiscale model of the human left ventricle. The authors altered passive forces arising from titin and collagen in the myofilament model<sup>28</sup>, which represent the active tension generation within each myocyte, thereby influencing the contractile force. The study also includes simulations of structural remodeling of the left ventricular wall. The results of this study emphasize the reduction in sodium-calcium exchange ( $I_{NaCa}$ ) activity as a dominant factor leading to impaired  $Ca^{2+}$  handling and diastolic dysfunction in patients with HF-preserved ejection fraction. Additionally, the results indicate the role of impaired  $Ca^{2+}$  homeostasis in abnormalities of left ventricle contraction and relaxation.

### Whole-Heart Simulation of Heart Failure

There are several multiscale electromechanical models aimed at investigating the effects of HF-induced intracellular remodeling on global ventricular function.

**Table 1:** Electrophysiological models of failing human ventricular myocytes

Study	Cardona et al. <sup>β</sup>	Trenor et al. <sup>β</sup>	Elshrif et al. <sup>β0</sup>	Walmsley et al. <sup>β1</sup>	Lu et al. <sup>β2</sup>
<b>Model based on</b>	modified GPB model	modified GPB model	modified OVVR model	modified OVVR model	modified TNNP model
<b>Cell type</b>	not specified	Endo <sup>a</sup>	Epi <sup>b</sup> , Endo, M <sup>c</sup>	Endo	M
<b>Number of variables</b>	38	38	41	41	17
<b>Integration time step</b>	not specified	not specified	0.02 ms (0.001 ms for calcium equations)	not specified	0.01 ms
<b>Experimental data basis</b>	$I_{NaL}$ (A) <sup>d</sup> , $I_{to}$ (A&H), $I_{K1}$ (A&H), SERCA(H) $I_{NaCa}$ (A), $I_{NaK}$ (H), $I_{leak}$ (H), EC <sub>50SR</sub> (H), $I_{Cab}$ (H), $I_{Nab}$ (model fit)	$I_{NaL}$ (H) <sup>e</sup> , $I_{to}$ (H), $I_{K1}$ (H), SERCA(H) $I_{NaCa}$ (H), $I_{NaK}$ (H), $I_{Cab}$ (H), $I_{leak}$ (model fit), EC <sub>50SR</sub> (A)	$I_{Na}$ (H), $I_{NaL}$ (H), $I_{to}$ (H), $I_{K1}$ (H), $I_{Kr}$ (A&H), $I_{Ks}$ (A&H), SERCA(H), $I_{NaCa}$ (H), $I_{NaK}$ (H)	$I_{CaL}$ (H), $I_{to}$ (H), $I_{Kr}$ (H), $I_{Ks}$ (H), SERCA(H), $I_{NaCa}$ (H)	$I_{Na}$ (A), $I_{to}$ (H), $I_{K1}$ (H), $I_{Ks}$ (A), SERCA(H), $I_{NaCa}$ (H), $I_{NaK}$ (H), $I_{bCa}$ (model fit), RyR2 (H)

<sup>a</sup> Endo-endocardial cell; <sup>b</sup> Epi - epicardial cell; <sup>c</sup> M - midmyocardial cell

<sup>d</sup> (A) experiments on failing animal cardiomyocytes

<sup>e</sup> (H) experiments on failing human ventricular myocytes

Each model uses different microscopic and macroscopic anatomy representation and different levels of biophysical detail of the subcellular/cellular models. Common features among the whole-heart models are the electrical and mechanical components and their coupling by intracellular  $Ca^{2+}$  released during electrical activation. The models differ, however, regarding geometrical structure, which is usually selected based on the objectives of the particular research. The investigator's choice thus lies between simplified 3D geometries such as elliptical geometries<sup>11,14</sup> and anatomically accurate geometries<sup>10,12,13</sup>.

In one study<sup>14</sup>, the 3D model structure represents the left ventricle with one layer of myocardial fibers (mid-myocardium, as a significant contractile layer). Notably, this 3D fiber-based model of the contracting ventricle uses a non-continuum approach to represent the myocardium. In this model, each individual fiber can be controlled, and blood elements are included to represent the resistance of intraventricular blood to ventricular contraction. In this configuration, each blood element is connected to a nodal point on the inner ventricle at one end and the center of volume of the intraventricular space at the other end. In contrast, in most other models, blood is represented as boundary conditions on the ventricles, and hence, blood pressure or flow parameters are inputs, rather than outputs, of the simulations.

Other models use the segmentation of the heart wall to account for the transmural heterogeneity (epi-, M, endo- layers)<sup>11-13</sup> based on experimental data<sup>29,30</sup>. In anatomically accurate models, anatomical details were obtained by individual heart geometries using magnetic resonance (MR) imaging data<sup>12,13</sup>. The models used a rule-based approach<sup>30-32</sup> to generate the myocardial fiber and sheet directions. The model of *Moreno and coworkers*<sup>12</sup> incorporated ionic conductivity changes to the normal values from the TNNP model<sup>24</sup>, including a Markovian representation of the cardiac sodium channel ( $I_{Na}$ ), to model HF in 3D human ventricular models. The image-based computational model of the human ventricles<sup>33</sup> served as a geometrical basis for the evaluation of the conditions under which the anti-arrhythmic drugs flecainide and lidocaine will prevent or exacerbate arrhythmia. The simulation results demonstrated that reentrant arrhythmias could be initiated even if an ectopic stimulus occurs outside of the "vulnerable window" for flecainide, but not for lidocaine. This is due to lidocaine-blocked sodium channels which showed faster recovery from drug blockage. These results have important implications for the modeling approaches toward the pharmacologic treatment of cardiac arrhythmias.

The study by *Sanchez-Alonso et al.*<sup>13</sup> examined microdomain-specific remodeling of L-type  $Ca^{2+}$  channels in HF within the 3D human left ventricle model<sup>33</sup> by analyzing the resulting early afterdepolarizations (EADs). For this purpose, the human ventricular cell electrophysiological

OVVR model<sup>25</sup> was extended by adding Markovian representation of the L-type  $Ca^{2+}$  current, implementing HF ion channel remodeling based on Elshrifet al.<sup>20</sup>. Simulations of EADs in control and in failing endo- and epicardial cells in this model revealed the development of EADs only in failing endo cells and, subsequently, an endocardial EAD trigger formation in whole-heart simulations in HF. The authors concluded that HF-induced L-type  $Ca^{2+}$  channel remodeling and subcellular changes can lead to the occurrence of arrhythmogenic triggers or arrhythmias at the organ level.

Both studies<sup>12,13</sup> used image-based individual geometries<sup>33</sup> for the evaluation of the cellular and tissue models under HF. The main advantage of MR imaging data includes the fiber and laminar sheet structure information for individual ventricular geometry, which is of critical importance when modeling diseased hearts. In addition, MR imaging data acquisition procedure is considerably less time- and resource-intensive compared to histological sectioning. Despite these advantages, most MRI-based whole-heart models do not include the representation of the spatially varied structural remodeling that occurs as a result of HF.

## Conclusions

The efforts towards simulation of cellular remodeling associated with HF in the papers reviewed above show significant progress both at cardiac myofiber level and whole-heart level. The development of advanced, high quality experimental methods is a challenging, but necessary step towards further extension of multiscale models. While cellular remodeling process predicted through simulation studies is valuable, particularly for the understanding of the complex pathophysiological factors that underlie HF, reconstructions of structural remodeling from MR images provide a framework in which predictions can be reliably ascertained. However, this approach has not yet been widely adopted due to the complexity and large computational requirements of the models.

## Conflicts of interests

The author has no potential conflicts of interests to disclose.

## Sources of funding

None.

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