Heterogeneous Electrical Remodeling of the Failing Heart Modulates the Arrhythmogenic Substrate

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Abstract

Failing hearts undergo electrical and structural remodeling, setting the stage for malignant arrhythmias. Increased dispersion of repolarization has been suggested to underlie increased arrhythmogenesis in human heart failure (HF). Recent experimental studies have shown that transmural dispersion of repolarization (TDR) decreases in failing hearts, while others have observed an increase in similar conditions. In this simulation work, we try to elucidate different mechanism of modulation of the repolarization gradient in failing human hearts and its implication for arrhythmogenesis. The human ventricular action potential (AP) models formulated by O'Hara et al. (ORd) and Grandi et al. (GPB) were modified to simulate the electrical remodeling observed in human heart failure. Several biomarkers (APD_{90}, triangulation (APD_{90}-APD_{50}), Ca^{+2} decay, Ca^{+2} dynamics , systolic Na^{+} and AP-Ca^{+2} Delay) were measured and calculated from individual ventricular cells simulations under different conditions of heterogeneous remodeling, modulating the changes in I_{NCX} and I_{SERCA} in endocardial, midmyocardial and epicardial cells. The results of this study uncover the importance of the existence of M cells and how heterogeneous remodeling can modulate the gradient of AP repolarization and Ca^{2+} handling in failing hearts.

1. Introduction

Heart failure (HF) is a clinical syndrome caused by the inability of the heart to supply blood to the tissues, and has a high variability in its etiology.

Much attention has been paid to the understanding of the arrhythmogenic mechanisms induced by the structural, electrical, and metabolic remodeling of the failing heart. Remodeling of the ventricular myocyte electrophysiology in both human and animal models of HF is well described [1,2]. Action potential (AP) prolongation, altered Ca^{2+} handling, as well as intracellular Na^{+} accumulation have been established as the hallmark characteristics of myocytes and tissues isolated from failing hearts [3-6], and have been observed in isolated myocytes and intact ventricular preparations [2,5,7]. These electrophysiological changes are due to electrical remodeling of several ion channels in failing myocytes.

APD is supposed to be reduced gradually from endocardium to epicardium but experimental studies have detected isolated islands of cells with higher APD, denoted as M cells. The existence of this kind of cells in nonfailing human myocardium has been demonstrated [8], but it is still unclear if they are also located in the failing myocardium.

Increased QT dispersion in HF patients [9,10] suggested the existence of dispersion of repolarization, which may predispose the heart to ventricular arrhythmia. While increased transmural repolarization heterogeneity was not observed in the left ventricle [8] of failing human heart, increased dispersion of repolarization was measured in the failing right ventricle [11]. To elucidate if real dispersion of repolarization is present in failing human hearts more experimental data are required, but modeling is a powerful tool to explore possible explanations.

In this simulation study, a human HF model [12] was used. We introduced heterogeneous remodeling in specific ionic channels, to assess the influence on dispersion of repolarization, excitation-contraction (EC) coupling and on calcium handling gradients.

2. Methods

Simulations were carried out using the human ventricular AP model by O'Hara et al. (ORd) [13] and the Grandi et al. model (GPB) [14]. These models include a detailed description of ionic currents and Ca^{2+} handling of the human ventricular AP. The ORd model, which also includes the specific M cell formulation, allows us to compare between both possible myocardial configurations (with or without M-cells). Thus, these models provide a powerful tool to explore repolarization abnormalities under conditions of disease, such as HF. Both models were modified to represent AP of failing hearts, based on previous works from our group [12,15].

In Figure 1 a representative illustration of AP morphology and calcium transient is showed under normal and failing conditions in both human AP models.

Heterogeneous remodeling of the Na^{+}-Ca^{+2} exchanger (I_{NCX}) and of the activity of the sarcoplasmic reticulum Na^{+} pump (I_{SERCA}) was applied based on experimental available data [16,17]. In failing conditions, a 50% reduction of I_{SERCA} has been measured [18]. This reduction is heterogeneously distributed depending on the myocardial zone [16] and was represented by different factors in the failing model ($ENDO_{ISERCA}$ *0.45, EPI_{ISERCA} *0.75, M_{ISERCA} *0.6). In the same way, an upregulation of the I_{NCX} was measured experimentally in failing conditions [3,19] and was heterogeneously distributed ($ENDO_{INCX}$*1.6, EPI_{INCX}*2, M_{INCX}*1.6)) based on experimental data of [17,20].

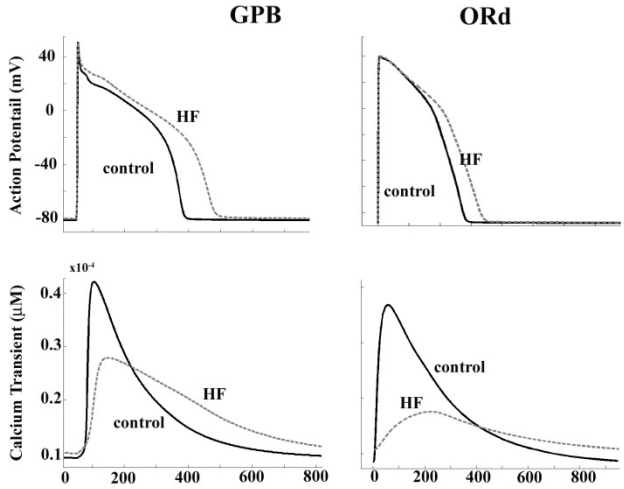

Figure 1. AP (upper panels) and calcium transient (lower panels representation of the HF model (discontinuous line) based on GPB (left) and in ORd (right) models compared to control conditions (solid line).

Biomarkers were measured and calculated from ventricular cellular simulations under different conditions of heterogeneous remodeling and were calculated as follows: APD_{90}, as the time between the maximal upstroke and the ninety percent of the AP amplitude (V_{max} $-V_{rest}$), triangulation as APD_{90}-APD_{50}, Ca^{+2} decay, as the time between the maximal upstroke and the ninety percent of the Ca^{+2} transient amplitude (Ca^{+2}systolic – Ca^{+2}diastolic), and AP-Ca^{+2} delay, as the difference between maximal upstroke of Ca^{+2} transient and AP.

Na^{+} peak was measured as the maximum sodium level reached during AP, and t_{NCX} as the reversal point, the instant in which I_{NCX} changes from inverse mode (Na^{+} extrusion) to forward mode (Ca^{+2} extrusion).

Gradients were calculated as the difference between the maximal and the minimal value of each biomarker in the different types of cells. The baseline gradients (100%) were considered for homogeneous heart failure.

All measurements were analized after achieving steady state conditions, with a BCL of 1000 ms.

3. Results and discussion

Heterogeneous remodeling modified calcium transient dynamics and AP morphology in each kind of failing cell, as showed in Figure 2. We hypothesized that repolarization gradients could be modulated by heterogeneous remodeling and/or the presence of M cells.

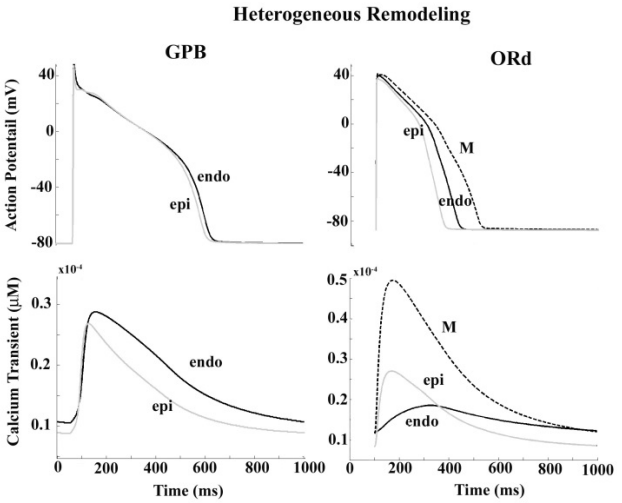

Figure 2. AP (upper panels) and calcium transient (lower panels) representation of the HF model based on GPB (left) and ORd (right) with heterogeneous remodelling of I_{NCX} and I_{SERCA} in endocardial (solid black lines), epicardial (light gray lines) and M cells (discontinuous lines).

The influence of heterogeneous remodeling in the absence of M-cells was measured using GPB model. Table 1 summarizes the simulation results. APD gradient was reduced by 13 % when heterogeneous remodeling was applied in both currents (I_{NCX} and I_{SERCA}). Nevertheless, an increase of 25% was measured if only I_{SERCA} was heterogeneously remodeled (top Table 1). Calcium transient decay gradient was significantly increased when heterogeneous remodeling was applied, suggesting possible differences in contractility depending on the myocardial zone.

GRADIENT (%)	APD_{90}	APD_{90}-APD_{50}	Ca^{+2} Decay
NC	94	127	266
HF	100	100	100
HF INCX	56	73	133
HF ISERCA	125	127	2780
HF INCX ISERCA	87	109	2533

GRADIENT (%)	Ca^{+2} diastolic	Ca^{+2} systolic	Ca^{+2}SR amplitude
NC	100	566	730
HF	100	100	100
HF INCX	400	1000	1600
HF ISERCA	1400	400	3400
HF INCX ISERCA	1700	633	1700
GRADIENT (%)	**Na^{+} peak**	**t_{NCX}**	**AP-Ca^{+2} Delay**
NC	205	200	160
HF	100	100	100
HF INCX	410	50	120
HF ISERCA	378	225	340
HF INCX ISERCA	57	175	200

Table 1. Gradients of different biomarkers under heterogeneous remodeling using the endocardial and epicardial models of GPB.

Intracellular calcium and SR dynamics were strongly modified due to heterogeneous remodeling. The higher increase in sodium level gradient respect to failing conditions was due to I_{NCX} heterogeneous remodeling. The shift in reversal point gradient of I_{NCX} is also regulated through heterogeneous remodeling. To quantify EC coupling, the delay between the AP upstroke and Ca^{+2} transient decay rise was measured.

To elucidate if there were significant changes in the gradients of the selected biomarkers we introduced M – cells in our analysis. In this case, we used ORd model, which includes a formulation for M-cells. Results are summarized in table 2. As can be observed, similar heterogeneous remodeling reduced APD gradient in the presence of M cells. Triangulation gradient was slightly modified but calcium transient decay gradient was significantly increased. In the same line, gradients in calcium dynamics were also increased. However, the gradient in sodium level was slightly modified. If AP-Ca^{2+} delay gradient was evaluated a 12 % of decrease was measured.

Experimental studies [8] measured heterogeneous increased APD in failing hearts, which caused a reduction of APD gradient compared to nonfailing conditions. Similar results were obtained in our simulations when heterogeneous remodeling was applied in both ionic currents (table 1, first data column). However, if M-cells were considered, APD gradient was lower in nonfailing conditions despite ionic remodeling (table 2, first data column).

Other authors [11] have measured increased APD gradient in failing conditions respect to nonfailing hearts, which is achieved in our simulation results when I_{SERCA} heterogeneous remodeling was applied in the absence of M-cells (table 1, first data column), and in every other case if M-cells were present (table 2, first data column).

Experimentally [21] the gradient of AP-Ca^{+2} delay was higher in failing conditions, showing a decreased contractility under such pathological conditions. Our results are in accordance if both currents (I_{NCX} I_{SERCA}) were heterogeneously remodeled without M–cells (table 1, last data column), and in homogeneous or heterogeneous HF in the presence of M-cells (table 2, last data column).

Calcium decay gradient was lower in failing conditions experimentally [21]. Our results were in accordance regardless of the presence or absence of M-cells, and this gradient was increased under heterogeneous remodeling in both configurations.

The presence of M-cells hardly influenced the gradient of I_{NCX} reversal point, which did modify sodium and calcium levels.

GRADIENT (%)	APD_{90}	APD_{90}-APD_{50}	Ca^{+2} Decay
NC	39	24	894
HF	100	100	100
HF INCX	93	102	117
HF ISERCA	99	104	911
HF INCX ISERCA	92	96	929

GRADIENT (%)	Ca^{+2} diastolic	Ca^{+2} systolic	Ca^{+2}SR amplitude
NC	100	413	233
HF	100	100	100
HF INCX	136	113	89
HF ISERCA	136	162	185
HF INCX ISERCA	164	175	182

GRADIENT (%)	Na^{+} peak	t_{NCX}	AP-Ca^{+2} Delay
NC	88	167	19
HF	100	100	100
HF INCX	99	87	108
HF ISERCA	95	99	126
HF INCX ISERCA	94	93	88

Table 2. Gradients of different biomarkers under heterogeneous remodeling, in the presence of M-cells using ORd model.

Summarizing, heterogeneous remodeling in the absence of M-cells could increase gradients in all biomarkers if only I_{SERCA} remodeling was taken into account, compared to failing model results. If heterogeneous remodeling was applied in both currents at

the same time, gradients were also strongly modulated.

In the presence of M-cells APD gradient under heterogeneous remodeling was reduced, and also gradients in calcium dynamics, which also modulate EC. We conclude that heterogeneneous electrical remodeling and the presence of M-cells strongly modulates AP and Ca^{2+} dynamics gradients in the human failing myocardium. Further experiments should be done to confirm the role of the different ion channels implication.

4. Conclusion

The results of this study uncover the importance of the existence of M-cells and how heterogeneous remodeling can modulate the repolarization gradient in failing hearts.

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