

Increase in Late Sodium Current and Cellular Uncoupling Exacerbates Transmural Dispersion of Repolarization in Heart Failure

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Abstract

Failing hearts undergo electrical and structural remodeling, setting the stage for malignant arrhythmias. Specifically, failing hearts show enhanced late Na⁺ current (I_{NaL}) and cellular uncoupling. In the present study, the effects of these changes on transmural dispersion of repolarization (TDR), on action potential duration (APD) gradient and on the safety factor for conduction (SF) were simulated. The human ventricular action potential model formulated by O'Hara et al. was modified to simulate the electrical remodeling observed in human heart failure (HF). The electrical activity of ID ventricular tissue was measured under several conditions, with enhanced and blocked I_{NaL} and homogeneous intercellular uncoupling. Computer simulations showed that homogeneous electrical remodeling of failing ventricular tissue increased TDR in 69% and APD gradient in 36%. A two-fold increase in I_{NaL} and in homogeneous uncoupling further increased TDR 174% and APD gradient 204% with respect to normal conditions (NC). 90% block of I_{NaL} reduced TDR and APD gradient values in all the conditions simulated. Finally, HF remodeling provoked a reduction of SF with respect to NC, indicating a less safe conduction under HF conditions.

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 ventricular myocyte electrophysiology in both human and animal models of HF is well described [1,2]. Action potential (AP) prolongation, altered Ca²⁺ 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 the remodeling of several ion channels in failing myocytes. Particularly, the late sodium current (I_{NaL}) becomes determinant in the evolution of the electrical signal [8-10] and in the prolongation of the AP duration (APD). Experimental studies have shown that I_{NaL} is involved in the occurrence of early after depolarizations (EADs) in myocytes [9], and life-threatening arrhythmias, such as *Torsade de Pointes* (TdP) [11].

In addition to electrical remodeling, structural changes also affect the failing heart. Indeed, fibrosis and cellular uncoupling have been observed in the setting of HF [12,13]. The loss of gap junctions between myocardial cells in HF conditions [14,15], and thus the increase in cellular uncoupling alters AP propagation, modifying propagation wavefront and conduction velocity (CV) and setting the stage for arrhythmogenesis.

In the present study, the impact of HF electrical remodeling and cellular uncoupling on several biomarkers for arrhythmogenesis has been analyzed. Specifically, changes in transmural dispersion of repolarization (TDR), APD gradient and safety factor (SF) for conduction during HF have been evaluated using a computational model. Indeed, TDR and APD gradient have been suggested to play an important role in the genesis of polymorphic ventricular tachycardia in different animal models of HF [16]. Also the SF has been used as an indicator for safe AP conduction, which represents a crucial factor in arrhythmogenesis [17].

2. Methods

Simulations were carried out using the human ventricular AP model by O'Hara et al. (ORd) [15]. This model is one of the latest and most detailed mathematical models for ionic currents and Ca²⁺ handling of the human ventricular AP. Thus, this model provides a powerful tool to explore repolarization abnormalities under conditions

of disease, such as HF. At the tissue level, simulations were conducted considering a fiber of 165 cells composed by endocardial, M, and epicardial cells as described in [15] and shown in Figure 1. Stimuli were applied to the endocardial edge of the fiber and were 1.5 times the stimulation threshold in amplitude and 2 ms in duration.

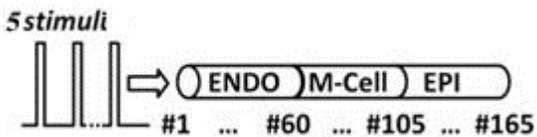


Figure 1. 1D transmural tissue composed by 60 endocardial cells, 45 M-cells and 60 epicardial cells. Stimulation was applied to the endocardial edge of the fiber.

We modified the ORd model to reproduce HF conditions, based on a previous work from our group [10], and on experimental studies [1,3,9,18]. The main changes produced in ORd model to establish the HF model are summarized in Table 1. Normal conditions (NC) of the healthy tissue were established as in ORd model. In order to evaluate the influence of the I_{NaL} we increased its conductance two-fold compared to nonfailing cells and decreased it ten-fold compared to nonfailing cells in different simulations. In the same way, to assess the importance of cellular uncoupling in the signal propagation, we increased two-fold the gap junction resistance compared to nonfailing cells. Combinations of both effects were also simulated.

Ionic feature modified	% of change with respect to ORd
I_{NaL}	↑ 180
τ_{hL}	↑ 180
I_{to}	↓ 60
I_{K1}	↓ 32
I_{NaK}	↓ 58
I_{Nab}	= 0
I_{Cab}	↑ 153
I_{NCX}	↑ 175
J_{SERCA}	↓ 50
I_{leak}	↑ 130
CaMKa	↑ 150
Khalf	↓ 20

Table1. Changes in ionic properties applied in the HF model, expressed as percentages of change with respect to ORd values.

TDR and APD gradient were measured after achieving steady-state, and were computed as the difference between maximum and minimum repolarization time (RT) and APD values, respectively, in the ventricular myocytes consisting of endocardial, M and epicardial cells. Steady-state action potential duration was computed at 90% of repolarization (APD_{90}). The SF was also evaluated following Romero et al. formulation [17], quantifying the source-sink relationship as an indicator of safety in wave conduction.

$$SF = \frac{\int_A I_{cdt} + \int_A I_{outdt}}{\int_A I_{indt}} \quad A|t \in [t_{1\%}, t_{Vmax}]$$

The SF expresses the relationship between the quantity of charge which enters into the cell, and the quantity of charge that is able to be transmitted to the next cell. If the safety factor is less than '1' a block in the transmission of the electrical signal may occur.

3. Results and discussion

Computer simulations showed that homogeneous electrical remodeling of failing ventricular tissue increased TDR in 69% from 29.2 ms under normal conditions (NC) to 49.3 ms.

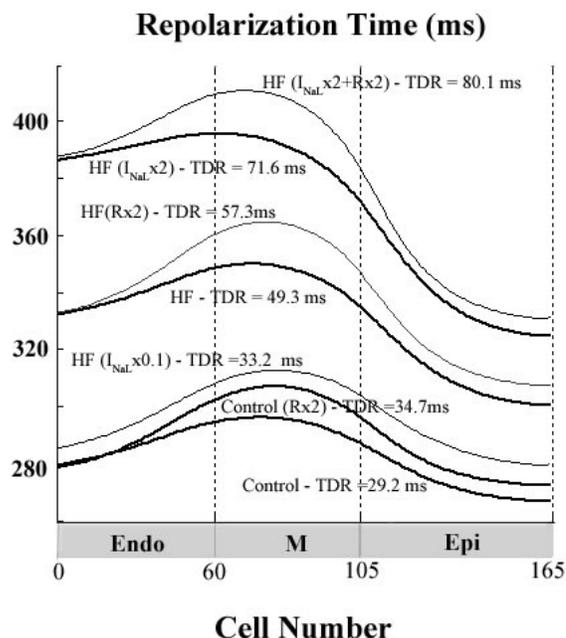


Figure 2. 1D Repolarization time measured along the fiber. TDR shows the difference between the maximum and minimum repolarization times in the different cells of the fiber.

A two-fold increase in I_{NaL} in HF conditions further increased TDR to 145% of the HF value, and when I_{NaL} was decreased, (multiplied by a factor of 0.1), TDR underwent a decrease of 32.6%.

When cellular uncoupling was increased in the ORD fiber model, TDR went up from 29.2 ms to 34.7 ms, an increase of 19%. If cellular uncoupling was applied in the HF model, TDR reached 57.3 ms, an increase of 96% with respect to NC, and 16% with respect to HF conditions. Results are shown in Figure 2.

In the same way, if the effects of cellular uncoupling and I_{NaL} increase were added, TDR suffered an increase of 174% with respect to NC value and 63% with respect to HF. The higher value of TDR implies significant higher differences in the repolarization times between cells, establishing the substrate to develop malignant arrhythmias. As HF progresses, cells inside the tissue begin to uncouple from each other, hampering the propagation of the signal. Our results show a strong increase in TDR when the degree of uncoupling is increased, even in NC.

Moreover, the importance of I_{NaL} is reflected in the decline of TDR value with respect to HF, when I_{NaL} is reduced ten-fold. If the effects of an upregulation of I_{NaL} and the degree of uncoupling were added, TDR increased strongly.

The same trend as in TDR measurements was observed in APD gradients. In HF conditions the heterogeneity in AP duration was bigger than in NC. An elevation of the intercellular resistance produced a higher degree of APD heterogeneity, and the influence of I_{NaL} provoked the same pattern of changes. It is important to highlight the strong influence of I_{NaL} on APD in HF conditions as demonstrated in [10] and on its gradient along the fiber. When I_{NaL} was multiplied by a factor of two, the APD gradient is 101 ms, while if I_{NaL} was reduced (ten-fold), the APD gradient yielded only 58 ms. These results can be observed in Table 2.

SIMULATION	TDR (ms)	APD gradient (ms)
NC	29	52
NC Rx2	35	60
HF	49	76
HF Rx2	58	88
HF $I_{NaL} \times 2$	71	101
HF $I_{NaL} \times 0.1$	36	58
HF $I_{NaL} \times 2$ R x 2	80	112

Table 2. TDR and APD gradient results under different conditions.

Several experimental and theoretical studies have shown that heterogeneities in electrophysiological properties in the ventricular tissue, such as CV, membrane excitability and refractoriness, set the stage for reentrant arrhythmias in pathological situations such as HF [19,20]. It is well known that the alteration of these properties may lead to unidirectional block, which is essential for reentry generation. In order to assess the wave propagation along the fiber we also calculated the SF. The main results are represented in Figure 3. As it can be observed, the SF in HF conditions was always smaller than in NC, due to structural and electrical remodelling. In NC, SF values oscillated between 1.39 and 1.41 while in failing cells SF was around 1.37-1.39. These values were measured in the central cells of each part of the myocardium. When the degree of uncoupling was increased, an increase of the SF was produced along the fiber, both in NC (1.46-1.48) and HF (1.44-1.46).

Furthermore, if the degree of coupling was increased, which is traduced in a higher value of intracellular conductivity, the safety in the electrical propagation was reduced. Similar results were obtained in [17].

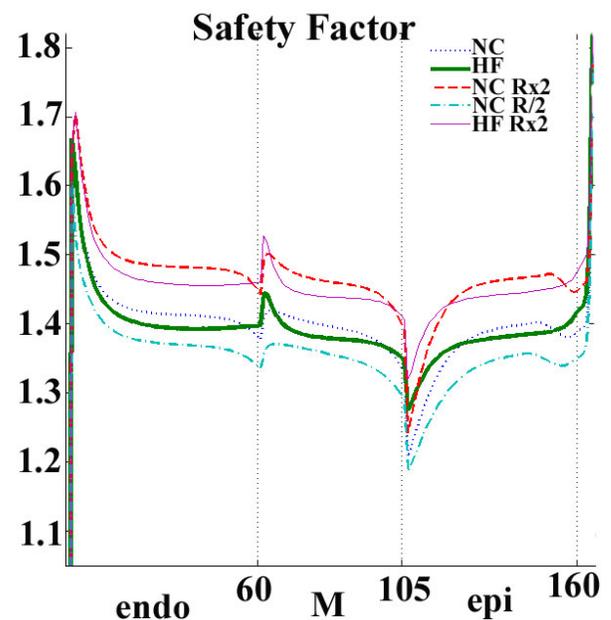


Figure 3. Safety factor calculated along the fiber under different conditions.

4. Conclusion

The results of this study uncover the importance of I_{NaL} and cellular uncoupling in modulating TDR, APD gradient and conduction safety in HF. I_{NaL} can be considered as a pharmacological target in HF to prevent arrhythmias.

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