Reduced Myofilament Contraction in Human Heart Failure. Insights From Electromechanical Simulations

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Abstract

Intracellular Ca^{2+} is the main activator of myofilament contraction and the altered Ca^{2+} handling observed in failing cells has been established as the leading cause of reduced inotropy in heart failure. Electrophysiological studies usually quantify Ca^{2+} transients to estimate contractile effects. However, heart failure remodeling of myofilaments also occurs, modifying the correlation between Ca^{2+} and force. The aim of this study was to analyze myofilament tension generated by action potentials in human heart failure.

In a ventricular electromechanical we investigated cellular contraction force associated with intracellular Ca^{2+} in heart failure by implementing the characteristic electrophysiological, β-adrenergic, and mechanical changes. Despite the inotropic myofilament remodeling induced by heart failure, the maximal active tension in failing cells was one third of the force generated in normal cells. With isoproterenol, β-adrenergic stimulation increased systolic Ca^{2+}, which enhanced myofilament tension by up to 150%, but failing cells also showed a smaller contraction force compared to normal. We observed that contractility was very sensitive to changes in intracellular Ca^{2+}, confirming that increasing Ca^{2+} peak would improve contraction in heart failure.

1. Introduction

The diminished cardiac output in heart failure (HF) due to reduced ejection fraction has been related to altered Ca^{2+} handling because its active role in myofilament activation and force generation [1]. Electromechanical modeling allows the quantification of myocyte contraction force and the analysis of mechanoelectrical feedback on action potential and Ca^{2+} cycling. Apart from myofilament contraction modelling, stretch-activated channels (SACs) are also considered for its role in modulating electrophysiology.

The aim of cardiac computational models is to study pathologies such as HF, which allow the obtention of information about action potential, Ca^{2+} transient and force altogether. Human electromechanical simulations have already been performed by using the action potential model coupled to myofilament mechanics in human cardiomyocytes [2–4], and in this work we additionally introduced HF remodeling. One of the goals of this study was to implement changes in myofilament dynamics induced by HF to reproduce the reduced contraction observed in failing cells [5]. The β-adrenergic system was also integrated in the study because the inotropic response of myocytes under β-stimulation is altered in HF and PKA phosphorylates myofilament proteins.

2. Methods

2.1. Cellular models

The human electromechanical model used in this study combined the action potential model in ventricular cells by O'Hara et al. [6] with the myofilament contraction model developed by Land et al. [7]. SACs were introduced in the model as K-selective channels and non-specific cationic channels with maximal current at stretch (λ) of 1.1 [4]. Additionally, β-adrenergic signaling [8] was integrated in the electrophysiological model as described in [9]. Simulations were performed in single epicardial myocytes until achieving steady state at a pacing rate of 1 Hz. β-adrenergic stimulation was applied with a saturated dose of isoproterenol (iso). Regarding HF remodeling, electrophysiological changes were introduced as previously defined in [10], while β-adrenergic remodeling, specified in Table 1, was based on an unpublished work, currently under review [11].

2.2. Mechanoelectrical effects

Human experimental data about myofilament remodeling highlight changes in Ca^{2+} sensitivity to troponin C (TnC). In Land et al. [7] cardiac contraction model, TnC dynamics are modeled with a simple cooperative binding equation, in which Ca^{2+} sensitivity is represented by the half-activating binding affinity parameter ($K_{Ca\text{-}Tn}$), set to 0.805 μM after a fitting process. $K_{Ca\text{-}Tn}$ varies with sarcomere length (length-dependent

 ISSN: 2325-887X DOI: 10.22489/CinC.2020.056

activation), modulating force. Since failing myocytes and PKA-phosphorylation also modify $K_{Ca\text{-}Tn}$ value, the analysis of this parameter variation between 20% to 200% its baseline value was performed to study the impact on Ca^{2+} transient, tension and APD_{90}. As in experiments, simulations consisted of isometric twitches, but we set λ=1 to avoid SACs effect and length-dependent variation of maximal force.

Table 1. β-adrenergic remodeled parameters in HF.

Parameter	% of control value
β1-AR	82%
β2-AR cav	45%
GRK	209%
PDE4	78%
Inh1	75%

The mechanoelectrical effect of SACs was studied, initially, in isometric twitches. The maximal effect of the total current generated by these channels at λ=1.1 was analyzed on action potential and Ca^{2+} transient.

2.3. Mechanical contraction in cardiomyocytes

To simulate sarcomere length variation at the cellular level, we applied λ as a sinusoidal waveform, representing lengthening, shortening, and no stretching during the cardiac cycle.

Table 2 summarizes the myofilament remodeling in failing myocytes and the modulation exerted by PKA-phosphorylation in response to β-adrenergic stimulation, based on the literature and adjustments to obtain an acceptable force of contraction (see Section 3 for details). Apart from Ca^{2+} sensitivity, phosphorylation of different myofilament proteins modifies rate constants involved in crossbridge attachment and detachment (k_{ws}) and titin-based passive tension (T_p). The length-dependent activation was maintained in HF but with reduced $K_{Ca\text{-}Tn}$ [12].

Table 2. Mechanical-related changes in myocyte model.

Parameter	% of control value	Reference
HF remodeling		
$K_{Ca\text{-}Tn}$	60%	[12,13]
PKA-phosphorylation		
$K_{Ca\text{-}Tn}$	100%*	[12]
k_{ws}	200%	[14]
T_p	50%	[15]

* Different to the initial model formulation.

3. Results and Discussion

The first analysis consisted in studying the effect of Ca^{2+} sensitivity to myofilament binding on electrophysiology and contraction force. From the isometric twitches we measured peak Ca^{2+} and tension.

Since TnC acts as a Ca^{2+} buffer, $K_{Ca\text{-}Tn}$ increase (reduced Ca^{2+} sensitivity) reduced Ca-TnC binding and free intracellular Ca^{2+} was more elevated, as illustrated in Figure 1A. Reduced Ca-TnC binding affected tension development and Figure 1B shows that tension decreased with increasing $K_{Ca\text{-}Tn}$ despite the observed increase in $[Ca^{2+}]_i$. It changed up to ±50% of the reference value. Due to excitation-contraction coupling, changes in intracellular Ca^{2+} can alter ionic currents and change membrane potential. However, we measured APD_{90}, and only small changes (< 5%) were registered, while Ca^{2+} peak variability oscillated between 70%-150% the control value.

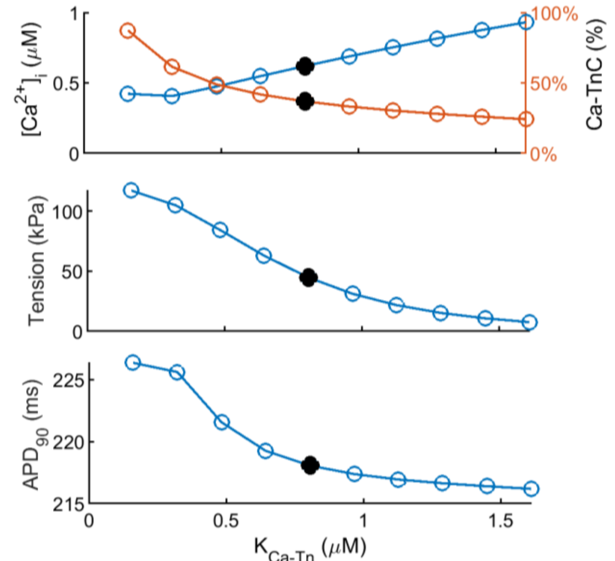

Figure 1. Effect of Ca^{2+} binding sensitivity to TnC ($K_{Ca\text{-}Tn}$) on A) Maximal free intracellular Ca^{2+} (left) and Ca^{2+} bound to TnC (right), B) Maximal myocyte active tension and C) APD90, in isometric twitches with resting sarcomere length (λ=1). Black dots represent reference value.

The effect of SACs reproduced well the AP shortening due to the K-selective current under stretch, while the non-specific cationic current contributed to increase $[Ca^{2+}]_i$, as displayed in Figure 2.

Since the response to SACs is slow and only occurs under stretch conditions, the final simulations, combining electrophysiology, β-adrenergic stimulation, myofilament force, mechanical stimulus, and heart failure conditions were performed with variable λ (Figure 3A).

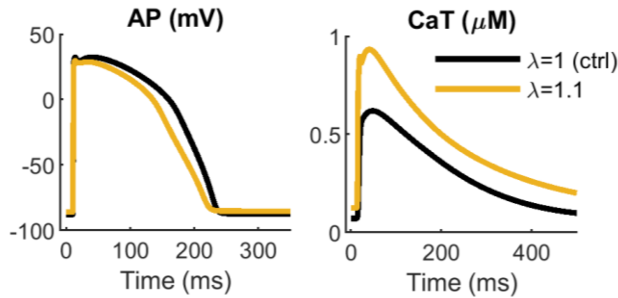

Figure 2. Effect of I_{SAC} on action potential and Ca^{2+} transient.

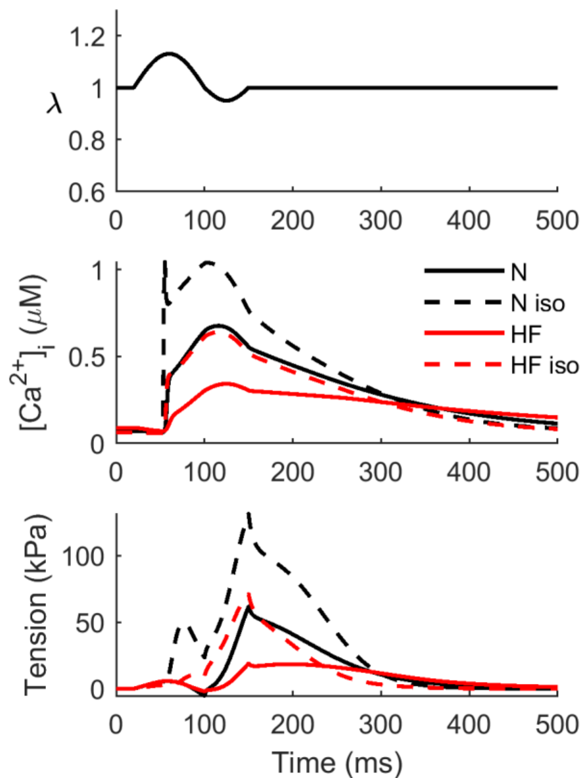

Figure 3. Ca^{2+} transient and mechanical force in myocytes under dynamic stretch in normal (N) and failing conditions (HF), and after β-stimulation (iso).

The depressed Ca^{2+} transient in HF illustrated in Figure 3 (solid red line) shows a common failing/healthy peak ratio of 0.5. The altered Ca^{2+} dynamics reduced systolic intracellular Ca^{2+} to values that could not generate physiological mechanical force. However, reduced myofilament phosphorylation induced by HF remodeling enhanced Ca^{2+} binding affinity to TnC leading to a more inotropic effect. After this, HF tension peak reached 30% of the maximal force in healthy myocytes.

β-adrenergic stimulation mediates PKA phosphorylation of ionic and myofilament proteins, modulating their activity. It is known to have an inotropic effect, although the response of failing myocytes is usually aberrant. We obtained that Ca^{2+} peak increased by 50% in normal myocytes following iso application, which was translated to more than twofold initial tension peak. This occurred because of PKA modulation of ionic mechanisms, mainly PLB and I_{CaL}, which enhanced Ca^{2+} transient amplitude [9]. Troponin was found to be in maximal phosphorylation state before PKA application and did not change Ca^{2+} sensitivity [12]. In HF, Ca^{2+} transient and tension also increased with iso although only half of the normal mechanical force was obtained, in agreement with [16]. The positive modulation of $K_{Ca\text{-}Tn}$ induced by HF remodeling was reversed by troponin PKA-phosphorylation and Ca^{2+} affinity to TnC was as in healthy myocytes.

The modulation of crossbridge kinetics only affected the rate of force relaxation, and passive tension, which had a small contribution compared to the active component (< 10%) did not affect total force differences.

Stiffness increase in HF is usually associated to HF with preserved ejected fraction, but it can also occur together with systolic HF. However, myocardial tissue can be less compliant due to enhanced myofilament passive force or due to extracellular properties of cardiac tissue. Due to the controversies found about passive tension remodeling in HF [13,15] we did not apply any modification.

Dynamical stretch showed a reduced impact of SACs because the cell was under stretch less than 10% of the cardiac cycle. The impact on action potential was negligible compared to the characteristic APD prolongation in HF or APD shortening following β-adrenergic stimulation.

When introducing cellular models into whole-organ simulations, the quantified ejection fraction was under the physiological range, and it could be improved by increasing the maximal active tension parameter [3]. Although we did not modify this parameter, tension waveforms and values obtained in the present cellular simulations were useful to compare the relative differences between conditions such as HF or β-stimulation and healthy myocytes. And differences in Ca^{2+} transients were found amplified when quantifying the force.

4. Conclusion

We have observed that myofilament contractility is mainly regulated with the phosphorylation level of troponin, which modulates Ca^{2+} binding to the myofilament and therefore contraction. However, when the phosphorylation level is elevated, as in HF with β-adrenergic stimulation, targeting ionic proteins involved in Ca^{2+} dynamics could be a better mechanism to improve inotropy in HF.

Acknowledgments

This work was partially supported by the "Plan Estatal de Investigación Científica y Técnica y de Innovación 2017-2020" from the Ministerio de Ciencia e Innovación y Universidades (PID2019-104356RB-C41/AEI/10.13039/501100011033) and by the Dirección general de Política Científica de la Generalitat Valenciana (PROMETEO/2020/043). MTM is being funded by "Programa de Ayudas de Investigación y Desarrollo (PAID-01-17)" from the Universitat Politècnica de València.

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