Excitation Contraction Coupling in Hypertrophy and Failing Heart Cells

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Abstract. The contraction of the heart is dependent on a process named the excitation-contraction coupling (E-C coupling). In hypertrophy and failing heart models, the expression, phosphorylation and function of key calcium handling proteins involved in E-C coupling are altered. It’s important to figure out the relationship changes between calcium channel activity and calcium release from sarcoplasmic reticulum (SR). This review will therefore focus on novel components of E-C coupling dysfunction in hypertrophy and failing heart, such as L-type Ca2+ channel (LCC), ryanodine receptor type-2 channel (RyR2) and SR Ca ATPase (SERCA), and how these molecular modifications altered excitation-contraction coupling. A lot of literature was well read and sorted. Recent findings in E-C coupling during hypertrophy and heart failure were focused on. Most importantly, the electrophysiological and signal pathway data was carefully analyzed. This review summarizes key principles and highlights novel aspects of E-C coupling changes during hypertrophy and heart failure models. Although LCC activity changed little, the loss of notch in action potential, reduced Ca2+ transient amplitude and desynchronized Ca2+ sparks resulted in a decreased contraction strength in hypertrophy and heart failure models. What’s more, L-type Ca2+ current becomes ineffective in triggering RyR2 Ca2+ release from SR and the SR uptake is reduced in some models. It has great meanings in understanding the E-C coupling changes during different heart diseases. Theses novel changes suggest potential therapeutic approaches for certain types of hypertrophy and heart failure.

1 Introduction

As we all knew, heart is one of the most important organs in our body. The weighted of a human heart is around 300g and it is about the size of a fist. The main function of heart is pumping blood to the whole body and it is a bag made of muscle cells called the cardiac muscle. The cardiac muscle is not like other muscle cells in body cause it is myogenic [1]. It can naturally contract and relax by its own and no need to receive an impulse from the nerve system to start working. Theoretically speaking, if the heart is putting in an environment which is warm, oxygenated and nutrients are abundant, it is able to beat rhythmically. However, the individual heart cell cannot contract under its own natural rhythms, the whole heart should follow the rules of the cardiac cycle [2]. If the cardiac cycle is disordered then the heart will lose the ability to work as a pump. The cycle starting from a muscle wall from right atrium called the sinoatrial node. It contracts each time faster than other parts in the heart and sets up an electrical excitation wave which can spread efficiently through the whole atrial walls. Then the rest of the cardiac muscle responds to this wave and the whole atria contracts. The excitation wave sweeps onwards and reaches the atrioventricular node which is another patch of the cells to delay the impulse and let it travels down to the ventricle. The electrical wave is now on the septum of the heart along fibers named Purkinje tissue. When it reaches to the bottom of the heart, it turns upwards to let the whole cardiac muscle in ventricle wall contracts. This is the whole journey of the electrical excitation wave going through the muscle in our heart.

To further understand the relationship between the electrical wave and the contraction of the muscle in the heart, scientists focus on the E-C coupling and its property changes in hypertrophy and heart failure. E-C coupling refers to the process by which cardiac myocyte translates electrical excitation into mechanical contraction and Ca2+ plays a crucial role during it [3]. The SR is the source for most of the Ca2+ and it is released by the process known as the calcium-induced calcium release. Ca2+ binds to the troponin and triggers the sliding of the thin and thick filaments, shortening the sarcomere [4]. Normally the heart requires to maintain its function by controlling the level of the intercellular Ca2+, high in the systole and low in the diastole. For example, in the process of ventricular systole, the level of Ca2+ increases and filaments slip to cause muscular wall contracts. The atrioventricular valves are pushing shut to avoid blood flowing backwards and causes the pressure to pump blood out of the heart. To put it simply, depending on the number of successfully combined Ca2+ with troponin and also their binding strength, the force that forces heart to pump will increase as the number increases.
To be precisely on processing the intercellular Ca\textsuperscript{2+} cycling, the relationship between various channels and pumps should be included. So scientist started to consider it into two parts, the structural coupling and the functional coupling [3]: (1) structural coupling: all the transporters within the dyad link the SR and transverse tubule (TT) together, this will create the shortest approach for Ca\textsuperscript{2+} to release. (2) functional coupling: to balance the amount of influx and eflux Ca\textsuperscript{2+} across every membrane stay the same and under steady state in every beats. The whole process will be optimized by not only the combination of different Ca\textsuperscript{2+} channels and transporters, but also their strict location and spatial positioning.

Different heart diseases models have given useful insight into the E-C coupling changes. Failing E-C coupling could come from altered properties and interactions among Ca\textsuperscript{2+} channels. Specifically on the expression, phosphorylation and function changes. To figure out the problem we have sorted and analyzed the electrophysiological and signal pathway data in different hypertrophy and heart failure models. The changed action potential timecourse, LCC activity, RyR included signal pathway and SR calcium load and uptake are all discussed. Much research in this file focused on the pathomechanisms involved in hypertrophy and heart failure may develop targeted therapeutic approaches for patients with heart failure.

2 The novel components of E-C coupling dysfunction in hypertrophy and failing heart

2.1 Myocardial function in heart failure

E-C coupling is related to the close association between the SR network and the TT membranes. The L-type Ca\textsuperscript{2+} channels located in TT membrane will be stimulated by the action potential depolarization and caused the resulting entry of small amount of Ca\textsuperscript{2+} which will trigger a large amount of Ca\textsuperscript{2+} increased in the dyadic space (an area surrounded by the SR and the TT). This process mentioned above is called the calcium-induced calcium release. The process should be given under the basis of the closed connection between the junctional SR and the t-tubules membrane, so the RyR2 can be closer to the L-type Ca\textsuperscript{2+} channels (from the t-tubules) [5, 6], nearly approximated to 15 nm [7], forming the cardiac dyad which is the basic principle of starting the ventricle systole upon Ca\textsuperscript{2+} transient. After the Ca\textsuperscript{2+} releases into the cytosol, the increase of Ca\textsuperscript{2+} needs to be remove out as the resting state. If it is unbalanced, then it will transiently occur in the dyad causing the changes of the Ca transient and disordering the frequency of amplitude or pausing stimulation. If the stimulation is finding stop in the ventricular muscle, the Ca\textsuperscript{2+} will leak out from the SR [8] and make its content low. To let the Ca\textsuperscript{2+} transient back into the resting sate, SR Ca\textsuperscript{2+} content increases. This will ensure the Ca eflux finally balances the influx and back in a steady state [9, 10]. This balance theory is not only suitable for the surface membrane but also applied to organelles such as mitochondria.

In hypertrophy and heart failure the mass of heart increased. Hypertrophy can divided into two kinds (Figure 1): (1) physiological cardiac hypertrophy: normally it’s known as the ‘athlete's heart’. The cause of this hypertrophy is because of the standing exercise training and it is reversible. No fibrosis or apoptosis is apparent and given as normal cardiac morphology or even enhanced cardiac function. (2) pathological cardiac hypertrophy: it is usually accompanied by an increase in interstitial fibrosis and massive cell death leading to cardiac dysfunction [11]. The most obvious pathologic feature is lowering the times and speed of contraction and relaxation, which can be easily found in ventricular myocytes from a failing human hearts [12]. This change is graded in terms of different degree of cardiac insufficiency and is associated with impaired Ca\textsuperscript{2+} processing. In dilated human cardiomyopathy, diastolic Ca\textsuperscript{2+} transients are prolonged due to a reduced ability to restore low resting Ca\textsuperscript{2+} levels. Therefore, increased resting or end-diastolic Ca\textsuperscript{2+} can lead to Ca\textsuperscript{2+} overload. Dysfunction of Ca\textsuperscript{2+} removal from cytosol is an early manifestation of pressure overload hypertrophy, which impairs cardiac diastolic function [13].

2.2 Triggers of calcium release :T-type Ca\textsuperscript{2+} current (\textit{I\text{CaT}}) and L-type Ca\textsuperscript{2+} current (\textit{I\text{Cal}})

In cardiac cells we can only discover two types of I\textit{Ca} which are L- and T-type I\textit{Ca}. [14, 15]. T-type Ca\textsuperscript{2+} channels have been found in a variety of excitatory and non-excitatory cells [16], and they may represent a heterogeneous subgroup of Ca\textsuperscript{2+} channels with significant differences in functional properties [17]. While the cardiac L-type Ca\textsuperscript{2+} channels is known as the site of operating I\textit{Cal} and it is a trigger for Ca\textsuperscript{2+} to release and refill into the SR again which play a crucial role in the E-C coupling [18]. These two channels shared similar name but with distinct electrophysiological and pharmacological properties. During the voltage-clamp depolarisation testing, I\textit{CaT} is characterized by rapid decay and slow inactivation rate, while I\textit{Cal} lasts longer and has a faster inactivation rate. The T- and L- channels can also distinguished by the threshold of activation and their voltage-dependence of availability for opening. Usually I\textit{Cal} is strong-voltage-activated whereas I\textit{CaT} is activated by low depolarizations, for example I\textit{Cal} needed at depolarization ≥30mV but I\textit{CaT} stimulated in a more negative result around -60mV [18]. However scientists still don’t know well about the T-type Ca\textsuperscript{2+} channels so here will directly talk about its expression in diseased heart cells. In addition to a possible contribution to the automaticity of adult heart tissue, I\textit{CaT} appears to be associated with hypertrophy. When isolated from a normal adult feline left ventricle, the presence of I\textit{CaT} was completely undetectable in long-term conditions of pressure-induced ventricular hypertrophy [19]. Similar case, a genetically determined cardiac myopathic Syrian hamster suffered an ascensive
and ultimately fatal congestive HF. Its ICaT had a 2 to 3 fold higher density than in a normal heart cells but its ICaL remained unchanged and this caused the inactivation kinetics [20]. All these changes suggest that ICaT is involved in the pathogenesis of Ca2+ overload and cardiomyopathy arrhythmia.

On the other hand, about the L-type Ca2+ channels scientists obtained many groups of various animals modules and tried to find out the different changes of ICaL in HF [21-28]. In addition to species dependence, there are many reasons for the obvious heterogeneity of model differences, the importance of hypertrophy, the degree of hemodynamic pressure and the stage of heart failure. There may also be varying degrees of hypertrophy or failure between cells in the same heart tissue. But the overall trend has been found out not affected by HF at all. Obviously, it has no significant effect on the electrophysiological properties of ICaL.

The deterioration of calcium induced calcium release process in hypertrophy/heart failure is thought to be the principal cause of the pump dysfunction. In heart failure non-uniform release of Ca2+ sparks will lead to a slower rate of rise of the Ca2+ transient which will probably cause disordered binding of Ca2+ to troponin C and slower myocyte contraction [29, 30]. (Figure 2A) The reduction of ventricular myocyte contractility in the hypertrophied/failing is closely correlated with the abnormal Ca2+ homeostasis. The cellular basis defects in excitation-contraction coupling, Ca2+ release and uptake events are all considered.

At the cellular level, the contractile power during E-C coupling is governed by a mechanism known as calcium induced calcium release [31]. In this process, Ca2+ influx through L-type Ca2+ channels on the cell surface membrane (including TT) activates ryanodine receptor Ca2+ release from the SR to generate cell-wide Ca2+ transients [32]. Besides L-type Ca2+ channels and RyR2, Ca2+ cycling proteins, e.g., sarcoplasmic reticulum Ca2+ pumps, N+,Ca2+ exchangers, and their regulatory mechanisms, are also important in determining the amplitude and kinetics of Ca2+ transients [32]. All these mechanisms have been studied in a wide variety of hypertrophy and heart failure models [32] [33, 34]. Most studies support the idea that the L-type Ca2+ channel activity does not change much during hypertrophy and heart failure. However, the Ca2+ transients triggered by comparable L-type Ca2+ channel currents are decreased in amplitude and/or slowed in kinetics in most models of decompensated hypertrophy (DHT) and heart failure [26] (Figure 2B). These studies lead to the notion that the Ca2+ influx through L-type Ca2+ channels becomes less effective in triggering RyR2 Ca release [26].

A study recently using the patch-clamp methods under the confocal microscopy showed that although ICaL density and SR Ca2+ release channels are normal in experimental rat models of hypertension induced cardiac hypertrophy and HF, but the Ca2+ channel fails to activate SR Ca2+ release [26]. This experiments support the idea that Ca2+ signaling between the surface membrane and the SR is abnormal in heart failure which means that calcium current of L-type Ca2+ channel is a less effective trigger of SR Ca2+ release in hypertrophied and failing myocytes [26]. The decreased excitation-contraction coupling gain could be rescued by exposure to β-agonists in hypertrophied but not failing myocytes, and experiments support that the reduced size of the Ca2+ transition in failing rat myocytes results from a decrease in the SR Ca2+ release rather than a reduction in SR Ca2+ loading as show in failing human ventricular myocytes. Meanwhile, other studies found that SR Ca2+ loading is decreased. SR Ca2+ loading is decreased in the failing myocytes. The density and location of Ca2+ regulatory proteins are changed between the non-failing and failing myocytes. The mainly reason for lower peak systolic calcium current of the early action potential plateau phase in the failing myocyte is that SR Ca2+ release is smaller and Ca2+ efflux through the forward-mode Ni2+-Ca2+ exchangers is bigger than normal. Defective excitation-contraction coupling can also reduce the SR Ca2+ release in the failing myocyte. While during the late phase of the action potential plateau calcium current is bigger in the failing myocyte which is mainly caused by the prolonged action potential duration triggers reverse-mode Ni2+-Ca2+ exchangers and reduced SR uptake. Fully recovery of diastolic Ca2+ in failing myocytes need the repolarization of the membrane potential.

2.3 Other putative triggers of Ca2+ release

Defects in excitation-contraction coupling gain can’t totally explain the fact that Ca2+ transient in failing human myocytes only become significantly different compared to the control group when the heart rate increases in some disease models, so a more likely contributors to the associated reduction in SR Ca2+ release in failing human myocytes is mainly caused by a frequency-dependent decrease in the size of calcium current of L-type Ca2+ channel and abnormal SR Ca2+ loading [35-37] (Figure 3). Recent studies suggest that RyR2 phosphorylation level in human heart failure is abnormal which can change the open probability of the calcium release channel. It is solid to say that in hypertrophic and heart failure, the function of the RyR2 is abnormal.

RyR2 is disordered with the increased Ca2+ leak from SR, causing the reduction of Ca2+ content in SR in heart failure (Figure 4) [38, 39]. RyR2 is proposed to be regulated by both protein kinases protein kinase A, Ca2+-calmodulin-dependent kinase II, protein phosphatase PP1 and PP2A [40, 41].

These results proved that SR Ca2+ leak threshold is lowered in heart failure. The increase Ca2+ leak from SR in heart failure is caused by altered RyR2 gating properties, which is proposed to be regulated by hyperphosphorylation from cAMP-dependent protein kinase A [42, 43], CaMK [44-47] and dephosphorylation from PP1 [42, 48]. In heart failure the function of RyR2 undergoes obvious changes. Usually the RyR2 is closed in diastole and allow Ca2+ remain stayed in SR. However in heart failure, the probability of this channel open increased and caused a strong increase in spontaneous and asynchronous Diastolic Ca2+ release events from the...
SR, measured as the Ca\(^{2+}\) spark. One Ca\(^{2+}\) spark can generate by a cluster of four RyR2, together forming a Ca\(^{2+}\) releasing unit [49]. In addition, it has been observed that the release of Ca\(^{2+}\) from SR is not synchronized in time in heart failure, which may be related to the release of a certain amount of Ca\(^{2+}\) ions, resulting in a decrease in contractility [50]. Ca\(^{2+}\) waves can be observed in cardiomyocytes, [51] that is, a spontaneous increase in cytoplasmic Ca\(^{2+}\). Spread throughout the cell. Although it has been proven that they are caused by Ca\(^{2+}\) sparks, the threshold SR Ca\(^{2+}\) content required to initiate them has been discussed [51]. Moreover, although a method of propagating Ca\(^{2+}\) waves through Ca\(^{2+}\) sparks has also been proposed, there is a differential activation of Ca\(^{2+}\) dependent ion channels [52]. What is important is that, in any case, another important aspect that disrupts the function of RyR2 is the instantaneous inward current (ITI) generated by the power supply NCX due to the RyR2 Ca\(^{2+}\) flux extruded by the exchange with Na\(^+\). By inducing delayed depolarization (DAD), these can trigger arrhythmia and sudden cardiac death [49, 53], and appear to be involved in atrial fibrillation [54, 55].

Some researchers believe protein kinase A hyperphosphorlation on RyR2 leads to increased Ca\(^{2+}\) leak from SR. They proposed that RyR2 phosphorylation by protein kinase A caused FKBP12.6 dissociation and altered RyR2 gating [42], which is similar to the result induced by displacement from FKBP12.6 to FK-506 or rapamycin [56, 57]. However protein kinase A-mediated phosphorylation of RyR2 may not affect RyR2 activities in all animals [58]. Whereas, others, proposing that calmodulin modulation changing the gating properties of RyR2, thought the prevention of calmodulin binding to CaMBD in the RyR2 causes Ca\(^{2+}\) leak during the diastole process in heart failure [44-47, 59]. The detailed mechanism is still not clear and requires additional study.

3 The variation of key calcium handling proteins and the analysis of electrophysiological pathway data

![Figure 1. Physiological, pathological and heart failure occurs in different condition [60]. Physiological hypertrophy occurs during pregnancy or in response to chronic exercise training, is reversible and characterized by normal cardiac morphology and function. In contrast, pathological hypertrophy that occurs in settings of disease is detrimental for cardiac structure and function and can lead to heart failure. Developmental hypertrophy is associated with the normal growth of the heart after birth until adulthood. RV: right ventricle, LV: left ventricle. Normal/ physiological heart growth is shown in green, pathological heart growth is shown in red.](https://example.com/figure1.png)

![Figure 2. Human action potential (AP) waveform on E-C coupling(Cooper et al., 2010). (A) Human AP profiles of non-failing (N) and failing (F) human myocytes (upper traces), and nifedipine sensitive ICa (middle traces), and indo-1 fluorescence (lower traces). (B) Comparison of ICa not with phase of the N and F Aps.](https://example.com/figure2.png)

The main participants in the coupling between sarcolemma and SR are shown in Figure 3. They first include all L-type Ca\(^{2+}\) channels (No. 1), Na\(^+\)-Ca\(^{2+}\) exchangers (No. 2), and possibly VSRM (No. 3). Since the Na + -Ca\(^{2+}\) exchanger is up-regulated, the reduced
gain is unlikely to be due to changes in the function of the protein. However, there may be multiple reasons why the L-type Ca\textsuperscript{2+} channel and RyR cannot communicate effectively. First, it is reported that the structure of the T tube changes during heart failure. Secondly, it has also been observed that the number of ryanodine receptors is reduced compared to L-type Ca\textsuperscript{2+} channels. Third, it has been proposed to increase the distance between the two proteins. Fourth, it is said that increased phosphorylation of lysine receptors can change EC coupling and cause basal Ca\textsuperscript{2+} leakage in SR.

Figure 3. Illustration of alterations in excitation-contraction coupling in heart failure (Sjaastad et al., 2003) [61]. Cellular structures basis of calcium homeostasis are showed. Calcium release and uptake functions are altered in heart failure.

Each Ca\textsuperscript{2+} channel and transporter is composed of pore-forming proteins and various auxiliary subunits, which regulate the amount of Ca\textsuperscript{2+} that moves through the pore. These channels and switches have been extensively reviewed elsewhere. One of the most intensively studied multi-protein complexes may be the RyR2 macromolecular complex. Various RyR2 interacting proteins directly regulate RyR2 channel activity by binding to pore subunits.

Figure 4. Phosphorylation of Ryanodine receptor 2 [62]. CaM indicates calmodulin; CaMKII, Ca\textsuperscript{2+}/calmodulin-dependent protein kinase II; CASQ2, calsequestrin-2; FKBPI2.6, FK506-binding protein-12.6; JCTN, junctin; JPH2, junctophilin-2; PKA, protein kinase A; PM, plasma membrane; PP, protein phosphatase; SR, sarcoplasmic reticulum; TECRL, trans-2,3-enoyl-CoA reductase-like protein; and TRDN; triadin.

4 Conclusion

In summary, L-type Ca\textsuperscript{2+} channel activity changed little during hypertrophy and heart failure, but a reduction in Ca\textsuperscript{2+} transient amplitude and kinetics triggered by current were found by comparing L-type Ca\textsuperscript{2+} channels in different models. In heart failure, desynchronized Ca\textsuperscript{2+} sparks slows the rate of Ca\textsuperscript{2+} transient rise, which may cause Ca\textsuperscript{2+} binding to troponin C to be disrupted and slow contraction of cardiomyocytes, and Ca\textsuperscript{2+} influx through L-type Ca\textsuperscript{2+} channels becomes ineffective upon triggering the release of Ca\textsuperscript{2+} from the RyR2. Scientists also found abnormal Ca\textsuperscript{2+} signaling between the surface membrane and the SR in heart failure. During the late stage of an action potential, the calcium current in failing cardiomyocytes is greater, mainly due to prolonged action potential duration triggering the antipattern of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchangers and reducing SR uptake.

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