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Cellular and Molecular Aspects of Dyssynchrony and Resynchronization

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Synopsis

Dyssynchronous contraction of the ventricle, arising from electrical activation delays, significantly worsens morbidity and mortality in heart failure (HF) patients. Approximately one third of HF patients have cardiac dyssynchrony and are candidates for the pacemaker therapy Cardiac Resynchronization Therapy (CRT), which uses bi-ventricular pacing to recoordinate contraction. The initial understanding of both dyssynchrony and CRT was in terms of global mechanics and hemodynamics, but lack of clinical benefit in a sizable sub-group of recipients who appear otherwise appropriate has challenged this paradigm. Using large animal models and some human data, a framework of complex molecular and cellular mechanisms of cardiac dyssynchrony and CRT is emerging. Heart failure with dyssynchrony exhibits depressed myocyte and myofilament function, calcium handling, survival signaling, interstitial remodeling, altered mitochondrial function, bioenergetics, myocyte structure, and other defects. Many of these are improved by CRT, and in a manner that seems unique to this treatment. Here we review current understanding of these cellular and sub-cellular mechanisms, making the case that these aspects are key to improving CRT utilization, as well as translating its benefits to a wider heart failure population.

Keywords

Dyssynchrony; Cardiac Resynchronization Therapy; animal models; Myocyte; Myofilament

Introduction: Cardiac Dyssynchrony and Resynchronization Therapy

Contraction of the left ventricle is precisely coordinated by the His-Purkinje system, which rapidly conducts electrical excitation to the myocardium. This ensures that fiber shortening

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throughout the muscle wall occurs synchronously and by a similar magnitude to help optimize pump efficiency. Diseases of the conducting system such as a left-bundle branch block (LBBB) leads to a loss of synchrony, and occurs in 30–50% of patients with dilated cardiomyopathy [1, 2]. As a result, regions of the heart stimulated early will contract sooner and at reduced load [3], and rather than generating sufficient pressure to open the aortic valve and eject blood, they impart energy to stretch the later-activated regions. The opposite happens in late-systole, where delayed-contracting regions can stretch earlier stimulated ones [3]. The net transfer of blood internally within the heart results in heterogeneity of myocardial work [4] and a reduction in mechano-energetic performance [5, 6]. In the failing heart, where function is already reduced, dyssynchrony worsens both morbidity and mortality [7].

Pioneering studies in the 1990s [8–10] showed that multisite artificial pacing improved LV function, and this ultimately led to Cardiac Resynchronization Therapy (CRT). CRT involves simultaneous bi-ventricular pre-excitation, and when applied to dyssynchronous hearts, it improves function [10] and chamber efficiency [11, 12], while concomitantly lowering morbidity and mortality [13, 14]. To date, CRT remains the singular therapy for heart failure that simultaneously improves both acute and chronic systolic function, increases cardiac work, and yet also prolongs survival.

CRT has traditionally been viewed as a mechanical tuning of the heart. Its relative simplicity and ease of entry into the clinic led to rapid development, testing, and approval – all performed in human subjects. There was very little basic science on CRT reported prior to its clinical adaption. Recently, however, there have been efforts to “reverse-engineer” CRT, exploring the cellular and molecular mechanisms that are involved. Indeed, dyssynchrony and resynchronization therapy induce a wide range of changes beyond the mechanical effects, many which are unique to both the disease and the treatment [15–19]. Interestingly, in some instances, CRT does not simply reverse the damage done by dyssynchrony, but acts in entirely novel ways to improve function. This review will explore the extensive set of cellular and molecular mechanisms chronically and acutely induced by dyssynchrony and CRT.

Beyond Left Ventricular Mechanics

While there is little doubt that global cardiac mechanics is a major mechanism behind dysfunction of dyssynchrony and recovery with CRT, key issues indicate there is more going on. The first is what is referred to as the “non-responder rate” and the second is the lack of relationship between apparent resynchronization and response.

Current guidelines identify CRT as a class I recommendation for patients with a QRS complex >150 ms (and $EF < 35\%$), and a class IIa recommendation for patients with a QRS complex between >120 and <150 ms [20, 21]. However, of the patients who receive CRT, approximately one-third show no clinical or morphometric response to the therapy [22, 23]. This “non-responder” rate has plagued the field, and despite significant efforts, has remained steady. One of these major efforts was the multi-center PROSPECT trial, which used tissue-Doppler techniques to quantify regional wall motion to determine dyssynchrony and predict

response to CRT. Unfortunately, despite the rigorous study design, there was little predictive capability [24] and the non-responder rate persisted. While efforts continue in this area, alternative hypotheses have emerged to identify responders from other biomarkers. In this regard, understanding the cellular and molecular mechanisms of dyssynchrony and CRT may provide targets that could serve as such biomarkers.

Beyond the non-responder rate, once a patient has been implanted with a CRT device and responds to the therapy, the relationship between the magnitude of resynchronization that occurs and magnitude of chronic improvement is weak at best. For example, in a cohort of patients with Class I indications for CRT, there was a clear lower limit of resynchronization necessary to observe improvement (based on 10% or greater decline in end-systolic volume) [25]. However, if one removes the group of patients who did not resynchronize at all with CRT, there was no correlation between the magnitude of resynchronized wall motion and long-term remodeling (Figure 1). Other studies found similar results using different indices [26]. This suggests there are other important aspects to both dyssynchrony and resynchronization.

Myocyte Function, Calcium Handling, and Beta-Adrenergic Signaling

Experimental access to myocardial tissue in humans is fairly limited to end-stage hearts at time of transplantation, limiting studies of CRT. Thus, the majority of our understanding comes from animal models. Cardiac dyssynchrony can be induced either by right ventricular pacing or from ablation of the left bundle branch, recreating a LBBB. With dog and pigs, it is possible to use existing human pacemaker systems to introduce RV pacing and CRT, superimposed over models of heart failure such as tachypacing [27], pressure overload [28], or volume overload [29]. It is also possible to study dyssynchrony without any underlying HF [30].

Cardiomyocytes isolated from dyssynchronous failing canine hearts exhibit severely reduced peak sarcomere shortening and slowed contractile kinetics [31]. Similarly, whole cell calcium transients and their dynamics are reduced [32–34]. These cellular defects are observed globally [31], rather than being specific to early or late activated territories. CRT significantly reverses most of these abnormalities [31–33] (Figure 2A). Heart failure without dyssynchrony also impairs calcium handling [35] and sarcomere shortening (Figure 2A), so these detriments and their reversal by CRT might be considered a function of heart failure rather than specific to dyssynchrony. However, despite marked improvement in myocyte function in the canine model, global function is far less enhanced [35], whereas dyssynchrony is resolved. The former occurs since the model involves tachycardia pacing that is present whether the heart is dyssynchronous or resynchronized, and prevents significant reversal of HF.

Mechanisms underlying calcium handling have been suggested (Figure 2B), although this remains incompletely understood. Biopsies from humans who responded to CRT showed increased mRNA expression of phospholamban (PLN) [36, 37], sarcoplasmic reticular Ca^{2+} ATPase 2A (Serca2A) [38], and sarcolemmal sodium calcium exchanger (NCX) [37]. In a canine model of dyssynchronous HF, protein expression of PLN and Serca2A decreased

[39] (NCX increased), yet CRT did not improve their expression levels despite enhanced calcium transients [33]. Alternative mechanisms include structural changes to the T-tubules and sarcoplasmic reticulum, where the registration of the ryanodine receptor and membranes where voltage gated channels reside becomes disrupted [34]. This is partially reversed towards normal by CRT (Figure 2C). Another alternative is post-translational protein modifications (such as phosphorylation or oxidation), though specific culprits remain unresolved.

Cardiomyocytes were not just weaker with dyssynchronous HF and stronger with CRT, but they also display differences in response to β -adrenergic stimulation [35]. Healthy cardiac myocytes significantly increase both intracellular calcium transients and sarcomere shortening when stimulated with isoproterenol. Myocytes from dyssynchronous HF, however, displayed very little response to isoproterenol stimulation, whereas CRT restores this to almost normal/healthy levels (Figure 2D) [35]. This mirrors changes observed in CRT patients, who display enhanced responses to cardiac sympathetic stimulation [40, 41], although CRT acutely blunts sympathetic tone [42].

The mechanism for restored β -adrenergic signaling highlights the fact that CRT is not just re-establishing electromechanical synchrony, but engages sub-cellular mechanisms that improve reserve function. HF is characterized by a decline in β -adrenergic stimulation signaling, and this is observed in both synchronous or dyssynchronous forms. β_1 adrenergic receptor plasma membrane density increases with CRT in both humans and canines [31, 43], however, CRT also has a novel impact on β_2 -adrenergic signaling. The latter is illustrated by a greater increase in cAMP after β_2 -adrenergic receptor stimulation (zinterol) in myocytes from CRT-treated hearts (Figure 2E). Inhibitory G-protein G α_i couples to β_2 -adrenergic receptors, and increases in dyssynchronous and synchronous human and canine heart failure [44]. In the latter, augmented G α_i signaling reduced cyclic AMP levels and consequent protein kinase A activation at the SR. Correspondingly, inhibiting G α_i with pertussis toxin (PTX) increased β_2 -adrenergic stimulation. Yet in cells from CRT treated dogs, the resting β_2 -AR stimulation response is near normal, and PTX has no further effect, indicating that CRT effectively de-couples G α_i signaling. CRT achieved this by raising expression of two negative regulators of this G-protein, RGS2 and RGS3 [35]. This did not reverse depression of RGS2/3 expression in dyssynchronous HF, but rather was a specific change observed in response to resynchronization. Human CRT responders also display increased cardiac left ventricular mRNA levels for RGS2/3, but this is lacking in non-responders [35] (Figure 2F).

Another mechanism for altered β -adrenergic signaling involves a shift in parasympathetic modulation by muscarinic acetylcholine receptors (mAChRs). The M2-mAChR couples to G α_i [45] while the M3-mAChR couples to Gq and exerts cardioprotective affects [46]. Dyssynchrony results in an increase in M2-mAChR, and CRT reverses this, while additionally increasing M3-mAChRs [47].

Ion Channels

Heart failure is often associated with prolonged action potential duration (ADP) [48] due to abnormalities of many membrane channels [49–52]. Dyssynchrony introduces marked

heterogeneity in APD, further lengthening APD in the late-activated lateral wall [32, 33]. This can contribute to ventricular arrhythmias, a common cause of death from HF, and in human patients, CRT reduces ventricular arrhythmias [53–58]. Even in dogs without LV dysfunction, dyssynchrony from left bundle branch ablation introduces regional APD heterogeneity [30].

Action potential duration is determined by the magnitude and timing of inward and outward currents in the myocyte. Dyssynchronous HF reduces repolarizing potassium currents, including the inward rectifier K^+ current (I_{K1}), transient outward K^+ current (I_{to}), and delayed rectifier K^+ current (I_K) [33], concordant with less protein expression in corresponding channel proteins: Kir 2.1, Kv4.3 and KChIP2, and KvLQT1, respectively. CRT partially reverses changes in I_{K1} , and I_K (but not I_{to}) and their related proteins [33, 59].

One current whose *increase* is linked to prolongation of APD is the late-sodium current, and this is augmented in HF [60]. Treating cells from dyssynchronous HF dogs with ranolazine, a relatively selective I_{Na-L} inhibitor significantly reduces APD (Figure 3), but has little impact on myocytes from non-failing or CRT dogs [61]. It is known that Ca^{2+} /Calmodulin protein Kinase II (CaMKII) increases I_{Na-L} [62], and dyssynchrony is associated with an increase in CaMKII activity in the late-activated lateral wall, while CRT decreases this activity [61, 63].

Myofilament Function and Structure

Length-dependent cardiac muscle tension is also an important contributor to CRT efficacy [64]. The dynamic properties of the myofilament are carefully controlled during a normal cardiac cycle, but introduction of systolic stretch, as occurs in dyssynchrony, perturbs this [65]. By precisely timing stretch in isolated mouse papillary muscles relative to their electrical stimulation, Tangney et al. developed an *in vitro* model of acute dyssynchrony [66]. They found that time-varying stiffness and force-velocity relationships played only a small role in explaining the tension that a dyssynchronous muscle generated. Instead, the dominant mechanism was transient de-activation [66], where stretching the activated muscle led to cross-bridge detachment [67]. Thus, acute electro-mechanical de-coupling alters myofilament properties.

Chronic dyssynchrony further changes myofilament function, depressing the responsiveness of sarcomere force development to calcium stimulation (Figure 4A) [68]. This is opposite that observed with synchronous heart failure, which increases calcium sensitivity in humans [69] and canines [68, 70], changes thought due to a decline of PKA-phosphorylation of cardiac troponin I (TnI) at serines 22 and 23 [71]. This over-sensitization can result in diastolic dysfunction [72] and arrhythmias [73]. Since reduced TnI phosphorylation is also observed in dyssynchronous HF, something else must explain the *decline* in sensitivity in this setting. To determine this mechanism, we first explored how CRT impacts the myofilament, and found it fully recovers calcium sensitivity (Figure 4B) to normal/healthy levels [74, 75]. The mechanism of improvement involved enhanced phosphorylation of a myofilament protein(s), and from proteomic analysis, a candidate kinase that could explain this was shown to be glycogen synthase kinase β [68], GSK- β (Figure 4A, 4B). This

kinase acted on several proteins in the M-band and Z-disk, regions considered essential for structural scaffolding of the myofilament. This was a novel role for GSK-3 β . Dyssynchrony specifically results in GSK-3 β inactivation, and CRT reverses this. Treating normal or CRT-treated myocytes with activated GSK-3 β had no effect on calcium sensitivity, but restored it in cells from dyssynchronous failing hearts.

In addition to the changes in calcium sensitivity, there is a significant reduction in maximal calcium activated force ($F_{\max}$) with heart failure in both dyssynchronous and synchronous forms, and this too is restored by CRT [68] (Figure 4C, 4D). $F_{\max}$ is conventionally normalized to cellular cross-sectional area since one assumes a larger cell has more myofibers and thus can generate more force. Myocytes in dyssynchronous heart failure are enlarged, and then return to normal size with CRT (Figure 4C, 4D). A similar reduction in myocyte size has been reported in humans after receiving CRT [76]. However, if $F_{\max}$ is *not* normalized to cell cross-sectional area, the force produced in all three groups (healthy, dyssynchronous heart failure, CRT) is similar [68], despite the middle group having much larger cells. This could imply that despite having more myofibers, these are in some way defective. Myocytes from dyssynchronous paced dog hearts exhibit decreased regularity of α -actinin (an integral myofilament Z-disk protein) in both the transverse and longitudinal directions [77]. CRT improves sarcomeric organization, although not entirely restoring it.

Myofilament structure and tethering is also maintained by the cytoskeleton. In myocytes a major intermediate filament that plays this role, colocalizing with the Z-disk, is desmin. Interestingly, in dyssynchronous heart failure, desmin moves away from the Z-disk [78]. Desmin's mechanisms reach beyond myofilament structure in this case, as desmin cleavage products also increase in dyssynchrony and have amyloid-like toxicity for the myocyte. CRT reverses both phenotypes, reducing desmin oligomers and re-associating desmin to the Z-disk [78]. Importantly, desmin cleavage is mediated by its phosphorylation by GSK-3 β , the same kinase involved in regulated Z-disk myofilament calcium sensitivity [68].

Mitochondria, Bioenergetics, and Metabolomics

Changes in energy consumption are a hallmark of heart failure [79], and dyssynchronous heart failure also impacts this, not only at the chamber level, but also in isolated mitochondria. Indeed, molecular metabolic remodeling may be more severe in dyssynchronous HF compared to synchronous HF [80]. Regional disparities in glucose uptake, indicating altered metabolism, occur in the dyssynchronous failing human heart [81, 82], along with diminished substrate metabolism indicated by succinate/glutamate and citrate/glutamate ratios [83]. A pig model of dyssynchronous HF showed a global increase in glucose uptake [84], but regional changes in hibernation, metabolic activity, and energy turnover [85]. CRT normalizes and harmonizes the metabolic fingerprint [11, 83, 86], although it remains distinct from healthy controls.

These findings are further supported by an extensive analysis of the circulating glyco-proteome from the dog model of dyssynchrony. There were 32 glyco-site containing peptides in dyssynchronous HF, and these suggested altered cardiac metabolism; CRT fixed

about 1/3 of these [87]. There remains ongoing debate as to whether a patient's metabolomic profile may also prove a useful biomarker to predict response to CRT [88, 89].

Corresponding to changes in global metabolism, dyssynchrony and CRT also affect mitochondrial function; with increased basal mitochondrial oxygen consumption with dyssynchronous HF over healthy controls or CRT treated hearts [90]. Metabolites that feed into the Krebs cycle are increased in CRT, including pyruvate carboxylase and pyruvate dehydrogenase, and a proteomic analysis revealed 31 mitochondrial proteins altered by CRT, almost half of these involved in the respiratory chain [90].

Cardiac dyssynchrony has also been associated with a decrease in ATPase activity, while CRT increased ATP synthetic capacity to healthy levels [91]. When exposed to reducing conditions, ATPase activity in dyssynchronous HF increased to similar levels as control and CRT myocardium, suggesting an increased oxidative environment in dyssynchronous HF. Cys294 was S-glutathionylated, and CRT suppressed this while favoring S-nitrosylation at the same residue. S-nitrosylation of ATP-synthase α occurs in ischemic preconditioning, and may be cardioprotective [92]. Thus, the S-nitrosylation /S-glutathiolylation balance of appears to be a regulatory mechanism for ATP synthase that is targeted by CRT.

Circulating Indicators of Dyssynchrony and Resynchronization therapy

Several circulating biomarkers have also been explored for their potential to identify patient responsiveness to CRT [93]. For some this may reflect improved heart failure, while for others, a more specific to the restoration of synchrony. One example involves members of extracellular matrix regulating proteins, matrix metalloproteinases (MMPs) that degrade the ECM, and tissue inhibitors of matrix metalloproteinases (TIMPs) that inhibit MMPs. In a prospective study involving 42 patients that received CRT, baseline plasma TIMP-1 levels predicted CRT response (MMP-2 was borderline) at 12 month follow-up [94], as well as long-term mortality [95]. Plasma levels of another ECM regulatory protein, galectin-3, predicted patients who benefited most from CRT, as the highest quartile of pre-CRT serum galectin-3 levels showed a disproportionately larger benefit from CRT [96].

There is variability in these results, however. Other studies using serum found no baseline differences in MMP-1 or TIMP-1 between responders and non-responders, but did find MMP-1 and MMP-9 levels correlated with outcomes [97–99]. Another study showed a decrease in MMP-2 and an increase in TIMP-2 in 27 CRT responders, but had no non-responders to compare them to [100]. Whether these enzymes will provide a useful biomarker to predict CRT response remains unclear, but the studies show ECM remodeling is certainly involved with both dyssynchrony and CRT.

Several other circulating biomarkers show promise as predictors of response prior to CRT. CRT responders displayed lower baseline (pre-CRT) plasma levels of cardiotrophin-1, CT-1, which induces a hypertrophic response, and Tumor necrosis Factor alpha, TNF- α , which can trigger apoptosis, compared to non-reponders [101, 102]. Endothelial progenitor cells (EPCs) are stem cells that can mature into endothelial cells that contribute to neoangiogenesis. They are a heterogeneous population of cells, but two distinct types (CD34⁺CD133⁺KDR⁺ and CD45^{dim}CD34⁺KDR⁺CXCR4⁺) were significantly higher at

baseline in responders than non-responders [103]. Interestingly, CRT super-responders (patients who experience a near normalization of cardiac function with CRT [104]) exhibited still higher levels of both types of EPCs. Thus, it appears that CRT responders (and super-responders) have an increased capacity for vascular remodeling prior to CRT.

Recent evidence has shown that tiny non-coding RNAs (miRNAs) are important regulators of cardiac function [105]. Using a small discovery cohort, and a validation cohort of 40 patients, circulating levels of miR-30d was a predictor of beneficial remodeling 6 months post-CRT [106]. It was independent from, and had better predictive capacity than, any clinical variable. Mechanistically, miR-30d is expressed in myocytes, increased in response to cell stretch, and protects against apoptosis [106]. Another study examined 84 circulating miRNAs, and found dyssynchronous HF patients exhibited a decrease in 24, compared to healthy control patients [107]. Post-CRT, responders saw an increase in 19 circulating miRNAs, while non-responders only saw an increase in six, and even these six increased less than responders [107]. Unfortunately, there were no baseline differences between responders and non-responders, so these could not act as predictive biomarkers. However, these circulating miRNAs that were improved by CRT are known to regulate a variety of cellular functions CRT has been shown to improve, including apoptosis, membrane ion currents, hypertrophic signaling, and fibrosis [108].

There are other circulating markers that mirror the cellular and molecular mechanisms of CRT, but fail to predict response to CRT. Annexin A5 decreases in CRT responders, and is unchanged in non-responders [109]. Annexin A5 is a pro-apoptotic protein [110, 111], and resynchronization has been shown to have anti-apoptotic effects [63, 112]. The neutrophil-to-lymphocyte ratio decreases in responders and increases in non-responders, and while there were no baseline differences, there was a trend ($p=0.20$) towards lower levels in responders [113]. Responses also correlated with changes in G-coupled receptor ligand apelin [37, 114] (rises with CRT), and various glycoproteins [87].

Future Directions

Progress has been made to understand the cellular and molecular mechanisms of cardiac dyssynchrony and resynchronization therapy (Figure 5) and these insights are helping both dissect the key pathways involved and establish better biomarkers for CRT responsiveness. However, to date, no controlled studies have been performed to test these novel biomarkers. Another potential application of these insights is that we may be able to extract a mechanism pertinent to a CRT benefit, and then apply this as its own therapy to patients who have synchronous HF and thus are not suitable for CRT. As currently, the benefits of CRT can only be applied to the subset of HF patients with underlying dyssynchrony [115]. The large animal models used to date have yielded substantial insights, but they have their limitations including cost and lack of genetic control. The only paper to date has reported results from a fairly acute (7–10 days) mouse model of dyssynchrony [116], and methodological development continues to establish robust chronic pacing in mice [117]. As these efforts begin to bear fruit, it should allow unprecedented exploration of the cellular and molecular aspects of regional mechano-signaling in the heart relevant to the mysteries of dyssynchrony and improvements from CRT.

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Key points

- In some instances, CRT does not simply reverse the damage done by dyssynchrony, but acts in entirely novel ways to improve function.
- Progress has been made to understand the cellular and molecular mechanisms of cardiac dyssynchrony and resynchronization therapy and these insights are helping both dissect the key pathways involved and establish better biomarkers for CRT responsiveness.
- It may be possible to extract a mechanism pertinent to a CRT benefit, and then apply this as its own therapy to patients who have synchronous HF and thus are not suitable for CRT.

Figure 1.

Immediate LV resynchronization with cardiac resynchronization therapy (CRT) and change in LV end-systolic volume at 6-month follow-up from Bleeker *et al.* [25] with permission. An acute response to CRT (>20% LV resynchronization) is necessary for a positive chronic response (>10% LV reverse remodelling), but among these “responders” there is almost no relationship between acute and chronic response. Therefore, acute hemodynamic response to CRT has little ability to predict long-term benefit.

Figure 2.

Dyssynchrony reduced baseline cellular function, which is restored by CRT. **(A)** Myocyte sarcomere shortening and corresponding whole cell calcium transients in myocytes taken from control (Con), dyssynchronous heart failure (Dys HF), synchronous heart failure (Sync HF), and CRT. Adapted from Chakir *et al.* [35]. **(B)** Western blots for calcium handling proteins. Arrows show the direction of change in Dys HF and CRT groups as compared to control. Adapted from Aiba *et al.* [33]. **(C)** Three-dimensional reconstructions from confocal microscopic images showing t-tubule structure (blue) and ryanodine receptors (red). Adapted from Sachse *et al.* [34]. **(D)** In response to isoproterenol, Dys HF exhibited a much smaller augmentation in sarcomere shortening and calcium transient amplitude, which was reversed by CRT. **(E)** Cell fluorescence ratio-encoded images from myocytes from Con, Dys HF, and CRT. The CRT myocytes exhibited elevated cyclic AMP generation when stimulated with zinterol (β_2 adrenergic receptor stimulation) **(F)** RGS2/3 can inhibit Gai,

and were significantly up-regulated in CRT. Adapted from K. Chakir, et al. Galphas-biased beta2-adrenergic receptor signaling from restoring synchronous contraction in the failing heart. *Sci Transl Med* 2011;3:100ra88; with permission.

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Figure 3.

Action potential duration and its modulation by the late sodium current. (A) Action potentials from myocytes isolated from the lateral wall in Con, Dys HF, and CRT, exhibiting a significantly longer Action potential duration (APD) in Dys HF that is mostly reversed with CRT. Using ranolazine to block the late sodium current (I_{Na-L}) shortened APD in Dys HF, but had no effect in Con or CRT myocytes. (B) APD duration at 90% repolarization at baseline and after ranolazine. Adapted from T. Aiba, et al. Cardiac resynchronization therapy improves altered Na channel gating in canine model of dyssynchronous heart failure. *Circ Arrhythm Electrophysiol* 2013;6:546–54; with permission.

Figure 4.

Myofilament function is affected by heart failure, dyssynchrony, and CRT in different ways. (A) Compared to healthy myocytes (black) calcium sensitivity is increased in HF (Sync HF, dark red) and decreased in dyssynchronous HF (Dys HF, red). This is due to de-activation of the kinase glycogen synthase kinase 3 β (GSK-3 β) in dyssynchronous HF, but not in synchronous HF (inset). (B) CRT (blue) restores calcium sensitivity to normal levels, via re-activation of GSK-3 β . If Dys HF myocytes are treated with active GSK-3 β , the recovery with CRT is recapitulated. However, treating CRT myocytes with GSK-3 β had no effect, since the myofilament is already re-sensitized via this mechanism (inset). (C) Both Dys HF and Sync HF see a decrease in maximal calcium activated force (F_{max}), and this is due to an increase in myocyte size (inset). (D) CRT restores F_{max} , by reversing the change in cell size (inset). Adapted from J. A. Kirk, et al. Cardiac resynchronization sensitizes the sarcomere to calcium by reactivating GSK-3beta. *J Clin Invest* 2014;124:129–38; with permission.

Figure 5.
Summary of molecular alterations in dyssynchronous HF (Dys HF) and CRT.