

Pathobiology of cardiac dyssynchrony and resynchronization

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Cardiac resynchronization therapy (CRT) represents the major new advance for treatment of heart failure since the start of the new millennium. With this therapy, failing hearts with discoordinate contraction due to conduction delay are subjected to biventricular stimulation to “resynchronize” contraction and improve chamber function. Remarkably, CRT was mostly developed and tested in patients first, and the speed at which the concept was translated to an approved clinical therapy was unusually quick. To date, CRT is the only heart failure treatment that can both acutely and chronically improve the systolic pump performance of the failing human heart yet also enhance long-term survival. This situation underscores the importance of understanding how CRT works at the molecular and cellular levels, as these insights might shed light on new approaches to treating heart failure more generally. Over the past 7 years, my laboratory and others at Johns Hopkins have developed novel animal models for addressing this

question, and new results are revealing intriguing insights into the mechanisms of CRT. This review, presented on the occasion of the Fourth Annual Douglas P. Zipes Lecture at the 2009 Scientific Sessions of the Heart Rhythm Society, highlights these advances and new directions in CRT research.

KEYWORDS Animal model; Apoptosis; Beta-adrenergic receptor; Calcium; Cardiac resynchronization therapy; Dyssynchrony; Heart failure; Ion channel; Molecular biology; Myocyte; Excitation–contraction coupling; Stress response kinase

ABBREVIATIONS CRT = cardiac resynchronization therapy; CHF = congestive heart failure; **dys-HF** = dyssynchronous heart failure; RGS = regulator of G-protein signaling

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Introduction

Congestive heart failure (CHF) is the leading cause of morbidity and mortality in adults throughout western societies.^{1–3} At least half of patients have dilated cardiomyopathy (reduced ejection fraction), and many of these individuals develop left ventricular dyssynchrony associated with conduction delay. The presence of dyssynchrony markedly worsens CHF morbidity and mortality independent of traditional risk factors.^{4–7} Dyssynchrony generates marked regional heterogeneity of both function and loading, effectively dividing the heart into early and late contracting zones. The early-activated territory is relatively unloaded, its work being wasted first by prestretching a still quiescent opposing wall and then by being stretched itself in late systole as the delayed territory contracts. Stress in the latter region is correspondingly greater⁸ and chamber function inefficient.⁹ Depending on the metric used, current estimates of the prevalence of dyssynchrony vary from 25% to 30% of CHF patients (based on QRS widening) to >60% based on tissue Doppler or magnetic resonance imaging measures of dyssynchrony.^{10,11} To treat dyssynchronous heart failure cardiac resynchronization therapy (CRT) was developed in

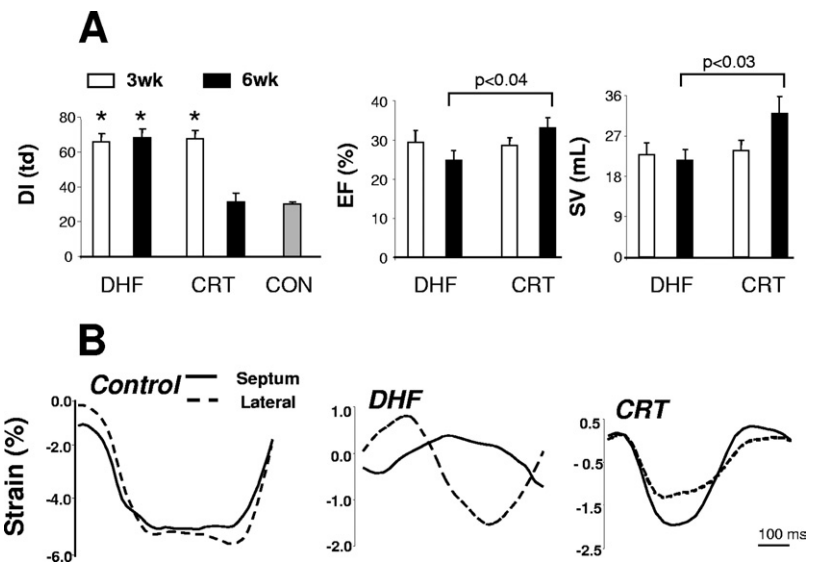
the mid 1990s after investigators found that biventricular (or left ventricular only) preexcitation could restore mechanical synchrony and improve acute left ventricular mechanics,¹² energetic efficiency,¹³ and regional metabolism.¹⁴ Subsequent large-scale clinical trials demonstrated benefits of improving symptoms and lowering rehospitalization rates and mortality in selected patients.^{15–17}

Despite the overall success of CRT, problems with the therapy remain. Nearly one third of seemingly appropriate recipients do not benefit clinically from CRT, and our ability to identify nonresponders before the fact remains poor. We have presumed that dyssynchrony—first measured electrophysiologically and more recently using various imaging metrics to examine wall-motion timing—is the key property to be identified, but is this correct? Mechanical dyssynchrony seems important, yet our measures have not predicted response well,¹⁸ and even improvement in dyssynchrony after CRT is initiated weakly predicts chronic response.¹⁹ We all recognize that having a low ejection fraction does not predict whether the patient will be able to play golf, will be able to conduct normal daily activities, or will be virtually bedridden; there is a lot more to the disease than is apparent from wall motion. Regional dyssynchrony may act the same way, so we need to look under the hood.

The ability of CRT to both acutely and chronically improve systolic pump function yet also prolong survival is unique among heart failure treatments to date. No existing drugs can achieve this effect. Positive inotropes not only fail to prolong survival but often have worsened arrhythmia and mortality,

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Figure 1 Development of a canine model of cardiac dyssynchrony and resynchronization. In this model, both dyssynchronous heart failure (DHF) and resynchronized heart failure [cardiac resynchronization therapy (CRT)] groups are exposed first to tachypacing for 3 weeks (in the presence of a preestablished left bundle branch block). This protocol is continued for an additional 3 weeks in DHF hearts but is switched to rapid biventricular pacing in CRT hearts. **A:** Left ventricular dyssynchrony (DI, **left**) is assessed by the variance in timing delay in systolic motion using tissue Doppler. This is similar in both groups at 3 weeks and declines to control levels (synchrony) only in the CRT group. Slight improvements in ejection fraction (EF, **middle**) and stroke volume (SV, **right**) are greater in the CRT group than in the DHF group at 6 weeks. **B:** Myocardial strain patterns (tissue Doppler images) obtained in the anterior and lateral wall (tissue Doppler) for a normal control, DHF heart, and CRT heart. With DHF, major disparities in the timing of shortening and reciprocal shortening/stretch in each region are ameliorated by CRT. (Adapted from Chakir K, Daya SK, Aiba T, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. *Circulation* 2009;119:1231–1240.)



and agents such as beta-blockers work chronically but do not acutely enhance pump function. How is this effect achieved? Is it all due to improving chamber level mechanics and efficiency, or is something more going on? Is dyssynchronous heart failure (dys-HF) simply a worse form of disease, or does it have unique aspects that play a role when CRT is effective? How does CRT influence basic cellular and molecular properties, and are the changes purely regional in nature or are they global? Despite more than a decade of clinical experience with CRT, such basic mechanistic questions have been largely unanswered until recently. In this regard, CRT is somewhat unusual as a heart failure therapy because it moved from bedside to bench rather than the other way around. Only recently have new animal models been developed that are beginning to reveal how potent CRT is at the molecular and cellular levels and are helping to define unique features of dys-HF.

Developing an animal model

To initiate analysis of how dyssynchrony affects the failing heart and what CRT does about it, we developed a large animal model. Leveraging decades of research in the canine rapid pacing model of dilated HF, we modified the model in two ways. First, we doubled the time course to 6 weeks, allowing for a 3-week period during which dyssynchronous rapid pacing (atrial pacing superimposed on a left bundle branch block) was implemented, followed by 3 weeks of the same (dys-HF) or biventricular rapid pacing (CRT). Both models involved 6 weeks of rapid tachypacing, which generated similar heart failure with reduced function, dilation and elevated filling pressures. However, as in humans, dogs treated with biventricular rapid pacing during weeks 4 to 6 had a slight improvement in ejection fraction and stroke volume, whereas in dogs with continued dys-HF, both ejection fraction and stroke volume declined. The difference after 6 weeks was significant (Figure 1A). Furthermore, we showed evidence for resynchronization based on standard tissue Doppler parameters (Figure 1B). Thus, we have two conditions: both involve the same underlying rapid pacing model, but the pattern of contraction is

altered midway through in one instance. It is worth keeping this in mind, as the changes observed with the CRT model are all the more remarkable given how little was altered. This is not a regionally ischemic model or a common form of human heart failure, but it does provide a platform to selectively alter dyssynchrony versus resynchronization of contraction in the setting of depressed dilated HF.

Molecular polarization and the impact of CRT

Initial molecular insights into dys-HF were provided in a brief report by Spragg et al,²⁰ who examined the effects of dys-HF at 3 weeks. Their study revealed that selective down-regulation (calcium handling proteins, connexin43) and up-regulation (mitogen-activated protein kinases) of key proteins involved in stress remodeling, contraction, and conduction occurred in the lateral wall only. This regional molecular change was not observed in synchronous CHF. In a more recent study by Chakir et al²¹ using the 6-week model, the dys-HF ventricle showed regional amplification of lateral stress kinase and cytokine stimulation, whereas these changes were reversed in the CRT ventricle, and expression/activity again was homogeneous (Figure 2). This is just the tip of the iceberg. Using genome-wide analysis, we recently reported >3,000 genes that were differentially altered between anterior and lateral walls, with most changes occurring in the anterior wall that broadly recapitulated a fetal gene pattern.²² Importantly, CRT reverses this geographically disparate gene expression, rendering patterns similar to those of normal controls, although absolute expression levels remain characteristic of CHF. Thus, the dys-HF ventricle is strikingly heterogeneous at the molecular and protein expression/activation level and is not just *worse* heart failure. This molecular substrate may be important, if not essential, for CRT to truly benefit the heart.

Human gene expression data are scant, but some results have been reported. The inability to biopsy from different targeted regions has prevented examination of heterogeneity, but evidence that reduced expression of calcium handling proteins, beta-1 receptors and elevated tumor necrosis factor- α

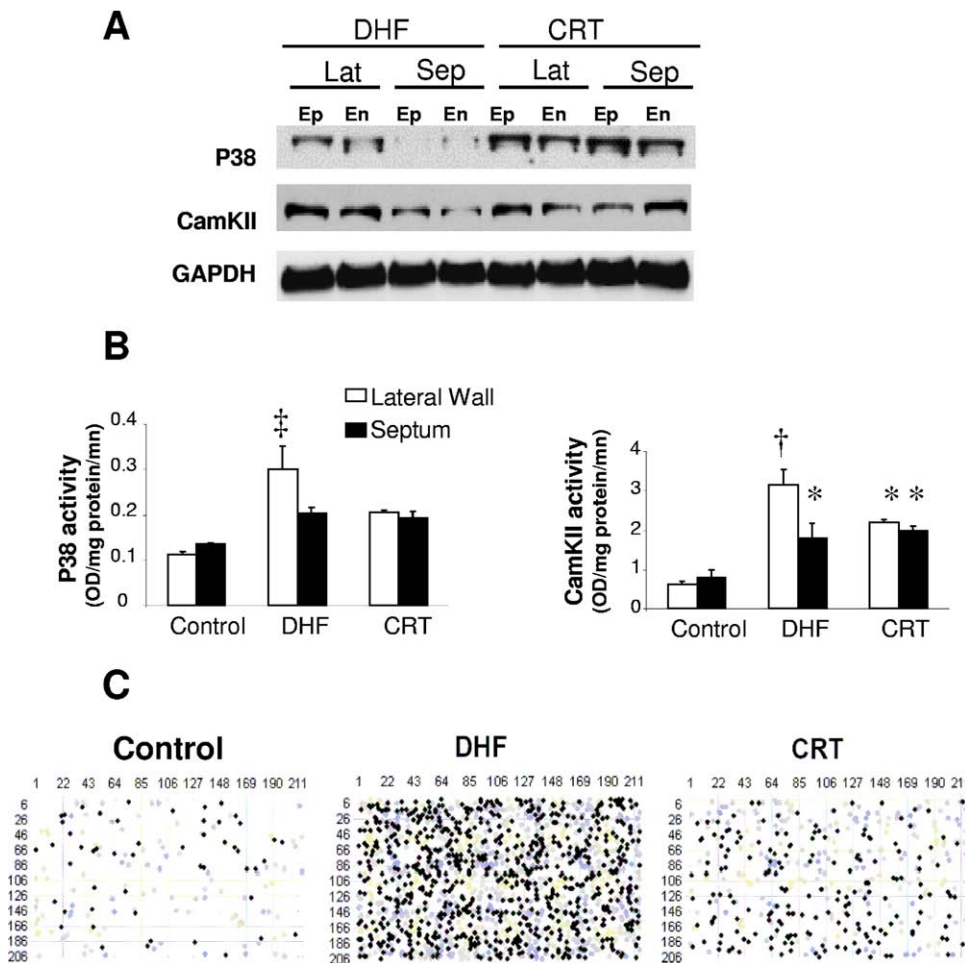


Figure 2 A: Regional differences in stress response kinases [p38 mitogen-activated kinase (P38) and calcium-calmodulin kinase II (CamKII) are shown] in dys-synchronous heart failure (DHF) hearts [higher in lateral (Lat) vs septal (Sep) wall in both endocardial (En) and epicardial (Ep) layers] are rendered homogeneous by cardiac resynchronization therapy (CRT). Example protein expression (western blot) is depicted, with GAPDH expression shown as a loading control. B: Summary data showing kinase activity for each respective enzyme, confirming regional enhancement in the lateral versus septal wall with DHF that is rehomogenized by CRT. C: Heterogeneity of gene expression revealed by sample pseudo-array plots of microarrays (each dot is a different gene; rows and columns reflect full 43.4K array). Genes that are up-regulated (green) versus down-regulated (red) between anterior/septal versus lateral wall from an individual heart are shown. Little heterogeneity is seen normally, profound heterogeneity of gene expression is seen in DHF, and amelioration but not complete restoration of this is seen in CRT hearts. (A,B) modified from Chakir, Daya, Tunin et al²¹; (C) modified from Barth, Alba Halperin et al²².

levels occur in dys-HF and are reversed by CRT has been obtained.^{23,24} Some limited studies have suggested that the ability of CRT to reverse these molecular changes may be related to its capacity to benefit the patient clinically,²⁵ but this work remains preliminary.

Electrophysiologic influences of dys-HF and CRT

The dys-HF heart is characterized by several marked electrophysiologic abnormalities. The Carnes laboratory first reported prolongation of the action potential, reduction in the L-type Ca^{2+} current, and reduced whole-cell Ca^{2+} transients, all of which were reversed by CRT in their chronic canine model.²⁶ Our group recently reported more detailed analyses,²⁷ which revealed reductions in the inward delayed rectifier current (Figure 3A) with dys-HF that were improved by CRT. In contrast, the transient outward current was markedly depressed in dys-HF but was unaltered by CRT, confirming the persistence of an HF phenotype. We also found reduced L-type Ca^{2+} current but only in the late activated (lateral) wall; this corresponded to reduced expression of the beta-2 subunit of the channel. The resulting prolongation of action potential in dys-HF was coupled to more easily induced afterdepolarizations, an effect that was markedly blunted in the CRT model, thus showing the physiologic relevance of these changes (Figure 3B).

Global changes in cell survival signaling

As noted, although some changes in molecular signaling (e.g., stress kinases) were found to vary strikingly between early (anterior-septum) versus late (lateral wall) activated regions, other changes (e.g., I_{K1} , I_{Kr}) were globally altered. The observation that global molecular signaling could also be generated by CRT was first revealed by Chakir et al²¹ with respect to cell survival. Apoptosis was enhanced chamber-wide in dys-CRT and was found to be coupled with a global decline in the phosphorylation and activation of the cell survival signaling kinase Akt. Apoptosis is modulated downstream of Akt by several potential proteins, including BAD, which when bound to Bcl-2 in the mitochondria promotes cell death but when phosphorylated binds to 14-3-3 and is exported out of the mitochondria, where it enhances survival. This signaling cascade appears to play a role globally with dys-HF and is favorably influenced by CRT (Figure 4).

Improved survival signaling raised an interesting question of whether mitochondrial function was favorably altered by CRT. This question was recently examined by our investigative group. In this study, Agnetti et al²⁸ systematically analyzed the mitochondrial sub-proteome and revealed many changes at the expression and posttranslational levels induced by CRT that support improved oxidative phosphorylation, mitochondrial synthesis and

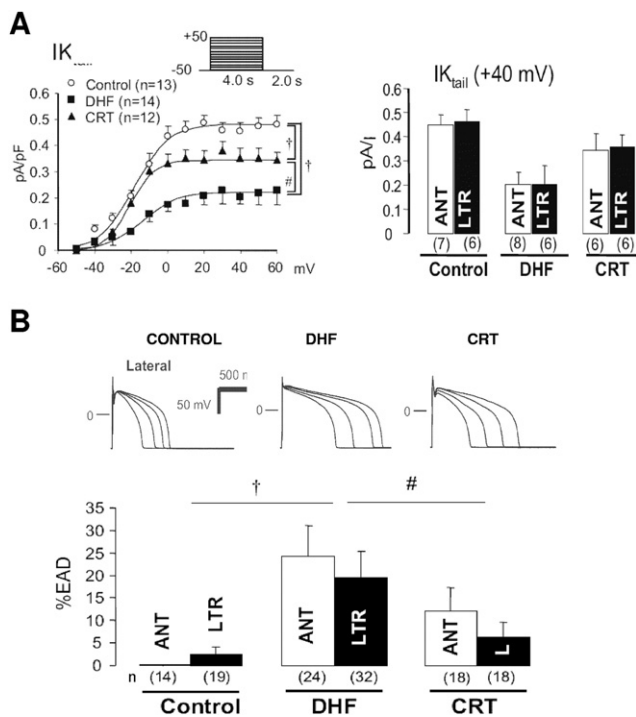


Figure 3 Electrophysiological effects of dyssynchronous heart failure (DHF) and cardiac resynchronization therapy (CRT). **A:** Summary data for the delayed rectifier current (I_K tail current), a potassium current. **Left:** Current-voltage dependence. **Right:** Summary data at +40 mV. The tail current is globally and substantially reduced by DHF and partially and significantly restored by CRT. **B:** DHF displays prolongation of action potential duration (APD), notably in the lateral wall. APD tracings in **upper panels** are generated at varying stimulation frequency (longer APD at slower rates). At each rate, APD prolongs with DHF but is improved by CRT. **Lower bar graphs** show the frequency of early afterdepolarizations (%EAD) in each condition. DHF displayed increased EADs, which were reduced (particularly in the lateral wall) by CRT. (Adapted from Aiba T, Hasketh GG, Barth AS, et al. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation* 2009;119:1220–1230.)

stabilization, and antioxidant effects. Thus, CRT may improve energy balance not only by improving chamber-level efficiency but also by targeted improvement of mitochondrial function. Just how this effect is achieved and its implications for CRT and/or heart failure more generally is under investigation.

Rest and Beta-adrenergic-stimulated myocyte function

CHF typically is a disease of exertion; therefore, understanding the mechanisms by which cardiac reserve capacity is altered paramount. In a recent study, Chakir et al²⁹ isolated myocytes from dys-HF and CRT hearts and compared their rest sarcomere shortening and Ca^{2+} transient behavior to each other and to normal control myocytes. The dys-HF myocytes had highly reduced rest and isoproterenol-stimulated shortening and Ca^{2+} transients compared with normal control myocytes, consistent with our current understanding of heart failure. Yet, both were markedly improved with CRT (Figure 5A). This result is striking, recalling that our CRT model involves 6 weeks of tachypacing, and CRT and dys-HF hearts have substantial and

similar dilation, elevated end-diastolic pressure (EDP). Improved cellular function was accompanied *in vivo* by a decline in myocardial catecholamines, so the balance of neurostimulation and myocyte responsiveness was restored toward normal by CRT. Intriguingly, these cellular changes were *global*, not *regional*. We further tested for mechanisms underlying depressed beta-adrenergic receptor (β -AR) signaling in dys-HF that were ameliorated by CRT. We found that dys-HF reduced both β_1 - and β_2 -receptor gene expression and number (radioligand binding assay); CRT enhanced β_1 - but not β_2 -receptor number. Using forskolin to directly activate adenylate cyclase activity, we found this activity too was depressed in dys-HF and improved by CRT. Among the most striking changes, however, was in inhibitory G-protein (G_i) signaling. As shown in Figure 5B, myocytes from dys-HF hearts showed marked potentiation of the isoproterenol response if the myocytes were first incubated with pertussis toxin, which inhibits G_i . In contrast, CRT myocytes displayed enhanced responses at baseline and showed no effect with pertussis toxin, as if G_i already was inhibited by CRT. $G_{i\alpha}$ was up-regulated in dys-HF, as has been seen in human HF, but remained high in CRT tissue, so it cannot by itself explain the change. However, we found selective up-regulation of proteins called regulators of G-protein signaling (RGS) proteins. RGS proteins negatively regulate G-coupled signaling by acting as GTPase accelerators, removing GTP from the activated α -subunit so that the trimeric G-protein

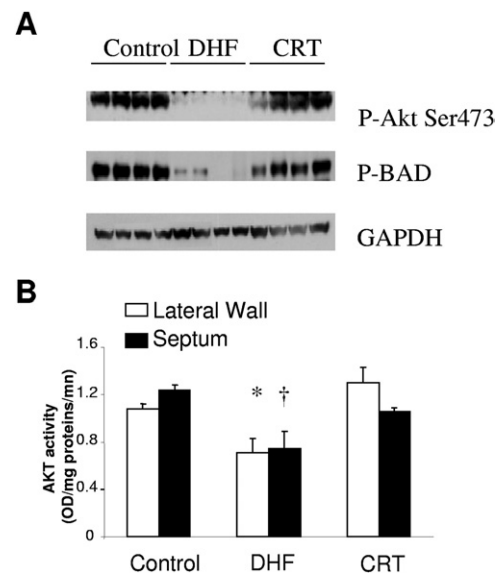


Figure 4 Cardiac resynchronization therapy (CRT) improves cell survival signaling associated with enhanced phosphorylation (activation) of the serine threonine kinase Akt and the mitochondrial apoptosis-regulating protein BAD. **A:** Example phosphor-protein blot showing marked reduction of both Akt and BAD phosphorylation in dyssynchronous heart failure (DHF) that is improved by CRT. The four columns (lanes) for each condition (control, DHF, CRT) reflect anterior and lateral walls and epicardial and endocardial tissue from each region. Thus, these changes are global in nature. GAPDH is shown for protein loading control. **B:** Akt activity assay confirms differential regulation that is similar in septal and lateral walls, with DHF and improved by CRT. (Adapted from Chakir K, Daya SK, Tunin RS, et al. Reversal of global apoptosis and regional stress kinase activation by cardiac resynchronization. *Circulation* 2008;117:1369–1377.)

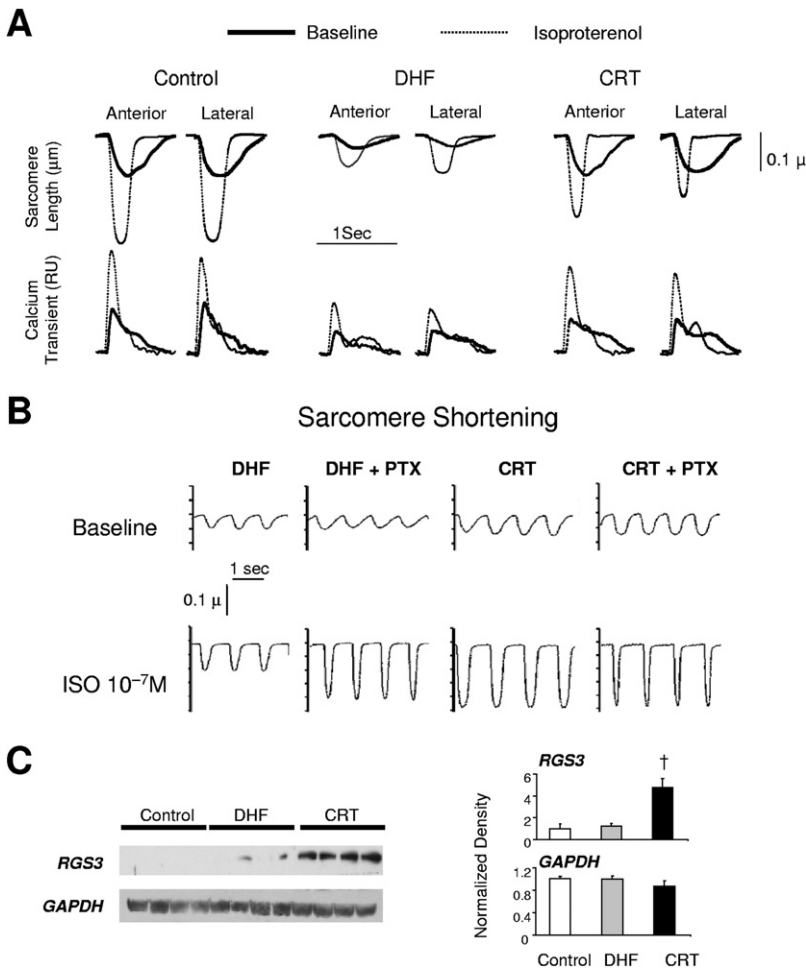


Figure 5 Cardiac resynchronization therapy (CRT) improves rest and beta-adrenergic responsiveness in isolated myocytes from both early and late activated regions. **A:** Example time tracings of sarcomere length (top traces) and whole-cell calcium transients (Fura2-AM; bottom traces) for myocytes isolated from anterior versus lateral walls from control, dyssynchronous heart failure (DHF), and CRT left ventricles. Baseline and results with isoproterenol (ISO) stimulation are shown. Compared to controls, DHF cells displayed marked depression of resting function and calcium transients, and the ISO response in both behaviors was also very blunted. Rest and beta-adrenergic stimulated shortening and calcium transients were both strikingly improved by CRT. **B:** DHF results in enhanced inhibitory G-protein (G_i) coupling in DHF myocytes that is suppressed by CRT. In DHF, pretreatment with the G_i inhibitor pertussis toxin (PTX) enhanced ISO-stimulated contraction, whereas CRT myocytes had enhanced shortening without ISO and showed no further increase with addition of PTX. **C:** Up-regulation of the regulator of G-protein signaling 3 (RGS3) protein, a negative modulator of G_i -coupled signaling, by CRT. **Left:** Example blots. **Right:** Summary densitometry. The four lanes represent four different hearts in each group, with data from the lateral wall. Similar changes were observed in the anterior wall. (Adapted from Chakir K, Daya SK, Aiba T, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. *Circulation* 2009;119:1231–1240.)

complex re-forms and coupled signaling is suppressed. RGS3, a protein known to suppress G_i , was selectively up-regulated in CRT hearts (Figure 5C), and this may be quite important to improved functional reserve with this therapy. Ongoing genetic studies are testing this hypothesis more directly.

Mechanisms for molecular/cellular changes and possible role in nonresponders

The root causes for the many changes observed in both global and regional cellular/molecular signaling with dys-HF and CRT remain uncertain, but we can speculate. As noted, CRT both alters regional stresses and strains and improves global mechanoenergetics. Although many of the observed alterations appear global in nature, I suspect these findings are not simply related to the modest improvement in chamber function generated by our model. Both dys-HF and CRT models induce heart failure from 6 weeks of rapid pacing, so functional differences at the whole-heart level, while present, are not dramatic. Yet, the amelioration of cell survival, potassium currents, and myocyte function and β -AR responsiveness are quite striking. Rather, we hypothesize that these findings reflect a general yet still cardiac targeted effect from CRT resulting from restoration of normal homogeneity of excitation-contraction, perhaps involving local (myocardial) changes in neuron-humoral activation, and mechanical forces. Both early

and late activated regions experience altered timing and magnitude of local stretch and stress. For some cascades (e.g., stress kinases), these difference may be quite important and signaling specific to each area. For other changes (e.g., Akt and I_K), the specifics of regional electromechanical heterogeneities may be less important; they simply may exist throughout the heart and contribute to altered local regulation. Ongoing studies are attempting to better sort out this interesting issue.

Second, it is worth considering how these results may relate to the nonresponder problem. As noted, heart failure and depressed ejection fraction do not necessarily predict the response to specific pharmacologic therapies, and variabilities in the underlying genetics as well as molecular and cellular biology are increasingly thought to be key determining factors.^{30,31} We do not yet know whether underlying cellular and/or molecular signaling responses to dyssynchrony vary among individuals with dys-HF who typically are targeted for resynchronization therapy, but it would be surprising if this were not the case. Differences in etiology, patient's genetics, and myocardial responses to discoordination may well dictate how well a patient will respond to CRT. One could imagine that lack of depressed Akt, I_K signaling or up-regulated G_i coupling in a given dys-HF patient might diminish the impact of CRT if its capacity to ameliorate these changes is indeed central to CRT

effectiveness. The level of molecular heterogeneity as depicted in Figure 2C may itself prove to be a useful marker that dyssynchrony has adversely impacted the ventricle. Others have suggested that nonresponders do not display the same extent of improvement in some gene expression abnormalities as do responders,²⁴ although this notion does not address whether a molecular signature may *predict* a future lack of response independent of apparent mechanical dyssynchrony. It is worth repeating that although studies have claimed that improvement in mechanical dyssynchrony is mandatory for a clinical CRT response, the correlation between response (reverse remodeling based on reduction in end-systolic volume) and extent of resynchronization (tissue Doppler) is poor to nonexistent.^{19,32} Although this finding could reflect our metrics, differences in underlying myocardial pathobiology may play an important role in explaining the variance.

Conclusion

In a relatively short period, we and others have revealed profound basic cellular and molecular changes in the dys-HF heart, many of which appear to be characteristic of this form of failure and are not observed in synchronous HF, as well as how CRT can substantially target these changes and reverse them. Reverse remodeling as we have observed has been reported previously with left ventricular assist devices³³ but is all the more remarkable with CRT given that these hearts remain loaded and contract. It is intriguing to speculate that responders to CRT have a molecular signature that could prove to be an important adjunct to the visible wall-motion changes upon which we have solely focused to date. Future studies testing this possibility are needed.

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