Abstract: Patients with heart failure and decreased function frequently develop discoordinate contraction because of electric activation delay. Often termed dyssynchrony, this further decreases systolic function and chamber efficiency and worsens morbidity and mortality. In the mid-1990s, a pacemaker-based treatment termed cardiac resynchronization therapy (CRT) was developed to restore mechanical synchrony by electrically activating both right and left sides of the heart. It is a major therapeutic advance for the new millennium. Acute chamber effects of CRT include increased cardiac output and mechanical efficiency and reduced mitral regurgitation, whereas reduction in chamber volumes ensues more chronically. Patient candidates for CRT have a prolonged QRS duration and discoordinate wall motion, although other factors may also be important because ≈30% of such selected subjects do not respond to the treatment. In contrast to existing pharmacological inotropes, CRT both acutely and chronically increases cardiac systolic function and work, yet it also reduces long-term mortality. Recent studies reveal unique molecular and cellular changes from CRT that may also contribute to this success. Heart failure with dyssynchrony displays decreased myocyte and myofilament function, calcium handling, β-adrenergic responsiveness, mitochondrial ATP synthase activity, cell survival signaling, and other changes. CRT reverses many of these abnormalities often by triggering entirely new pathways. In this review, we discuss chamber, circulatory, and basic myocardial effects of dyssynchrony and CRT in the failing heart, and we highlight new research aiming to better target and implement CRT, as well as leverage its molecular effects.

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Key Words: cardiac resynchronization therapy ■ cell physiological phenomena
■ heart failure ■ molecular biology ■ myocyte ■ ventricular function
Contraction of the normal left ventricle (LV) is geographically coordinated so that fiber shortening in a given muscle wall layer occurs synchronously and by a similar amount throughout the chamber. This is achieved by the Purkinje conduction system that rapidly delivers endocardial excitation to the myocardium. This contraction pattern can be disrupted by disease in a conducting branch (eg, a left bundle-branch block [LBBB]) or iatrogenically when a ventricle is electrically stimulated at a single site. In both instances, contraction of the LV becomes inefficient because 1 side moves inward before the other and is then stretched as the latter continues contracting. This shifts a portion of blood volume back and forth in the chamber rather than ejecting it, resulting in the net decline of systolic performance.1,2

In the normal heart, the impact of dyssynchrony is quite modest; for years following its early description, clinical interest was minimal. However, in the 1990s, investigators began testing whether dyssynchrony might play a more prominent role in the failing heart and examined pacemaker-like devices that stimulated several places in the heart at once to offset conduction delay. Landmark studies by Cazeau et al,3 Auricchio et al,4 and Kass et al,5 revealed the efficacy of multisite pacing in humans and led to cardiac resynchronization therapy (CRT), the first use of artificial electric stimulation for the primary purpose of altering ventricular function. CRT typically involves electric pre-excitation of 2 opposing sites of the heart: the right ventricular septum or apex and the left ventricular free wall (Figure 1). The latter is positioned by retrograde insertion of a pacing electrode through the coronary sinus into a lateral cardiac vein. The 2 ventricular sites can be stimulated simultaneously or with a slight phase shift (eg, LV slightly earlier). To assure biventricular stimulation, atrial electric activation is sensed or artificially paced, and a programmed shorter atrial-ventricular (AV) delay time used to achieve ventricular pre-excitation. The AV delay is set long enough so not to impair diastolic filling but short enough to achieve biventricular capture. Optimization of the AV delay has a modest impact in most patients and is often set to a physiological default.7 Positioning the LV epicardial lead in the lateral wall where activation is most delayed and having myocardium that can conduct this stimulation to the rest of the heart are more important factors for success.

CRT represents a major advance in heart failure (HF) therapy. It is the only clinical treatment that can both acutely and chronically improve cardiac systolic function while also increasing cardiac work and improving long-term survival. Pharmaceutical efforts to improve systole have been useful in the short-term, but so far they are detrimental in the long-term. Understanding of CRT first developed from clinical studies dominated by integrative physiology. CRT was viewed largely as a mechanical therapy much like tuning a car engine to produce peak pump performance and fuel economy. This perspective kept the focus on methods to visualize dyssynchrony, first using the ECG and subsequently using tissue-Doppler wall motion imaging. Although there is no doubt that mechanical effects of CRT play a major role in its clinical efficacy, growing evidence supports an extensive and often unique set of molecular and cellular changes that it chronically induces, and these likely play important roles as well. As with other HF treatments, CRT ends up impacting a broad range of structural and signaling changes that define the failing heart and, in several instances, does so in manner thus far unique to the treatment. In this context, the previously dyssynchronous failing heart that is resynchronized by CRT does not behave as a heart that was never dyssynchronous to begin with. These differences are suggesting new ways to leverage the biology of CRT to the broader HF population.

In this review, we examine the chamber pathophysiology of dyssynchrony and CRT in the failing heart and discuss new insights into its more basic cellular and molecular biology. We also highlight current areas of research in the field.

Physiology of Ventricular Dyssynchrony and Resynchronization Therapy

Nearly half of all patients with dilated cardiomyopathy have conduction delays, such as a LBBB.8,9 The resulting contractile dyssynchrony generates marked regional heterogeneity of myocardial work10 (Figure 2A), with the early-stimulated region having reduced load and territories of late activation having a higher load.12 This is accompanied by matching changes in regional blood flow.13 Displacement of blood from early to late and back to early activation sites results in a net decline in ejected stroke volume (Figure 2A).14 These volume shifts occur when differences in muscle activation are greatest between early and late contracting zones (Figure 2B), during isovolumic contraction and at late systole into early relaxation (arrows). This is why the rate of pressure increase (dP/dtmax) and late systolic contraction (shortening after aortic valve closure) are common and sensitive metrics of dyssynchrony. The global effect viewed by pressure–volume relations2 reveals a rightward shift of the end-systolic pressure–volume relationship (Figure 2C). Both stroke volume (loop width) and stroke work (loop area) decline. In a failing heart, in which underlying function is already compromised, dyssynchrony further worsens morbidity and mortality.15

Simultaneous biventricular pre-excitation, the common stimulation mode for CRT, restores coordinate contraction, immediately improving net systolic performance within 1 beat7 (Figure 2D) and augmenting chamber ejection and work (Figure 2E). Importantly, this is achieved without an increase in myocardial oxygen consumption, indicating improved chamber mechanical efficiency16,17 (Figure 2F). Other studies have shown that CRT improves coronary blood flow and flow velocity by enhancing the diastolic wave reflection that causes a backward-traveling suction-like wave.18 Successfully

### Nonstandard Abbreviations and Acronyms

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<tr>
<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<td>FMR</td>
<td>functional mitral regurgitation</td>
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<td>HF</td>
<td>heart failure</td>
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<td>LBBB</td>
<td>left bundle-branch block</td>
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<td>LV</td>
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766 Circulation Research August 30, 2013
implemented CRT reduces morbidity and mortality from HF,19,20 and this effect is greatest in patients with basal dyssynchrony.21,22 Applying CRT to patients without dyssynchrony can be detrimental.23

As noted, optimizing CRT timing parameters, AV delay, and right ventricle–LV excitation delay have a modest impact in most patients,5,7,24 whereas the site of electric stimulation has a greater effect. Early stimulation of the right ventricle (as in a LBBB) yields more dyssynchrony and thus LV dysfunction than if the LV is stimulated early (eg, right bundle-branch block).24–26 This has implications in pediatric patients requiring life-time pacing because of conduction block, and recent studies show function is better-preserved if pacing is instituted at the LV apex or midlateral wall.27 In patients with a LBBB, LV midlateral wall pacing alone yields hemodynamic improvements similar to biventricular CRT.28 Although clinical use of LV-only pacing has not been subjected to definitive clinical trials, meta-analysis of multiple smaller studies found similar benefits to biventricular CRT.29

CRT also improves functional mitral regurgitation19,29 (FMR), which confers a worsened prognosis in patients with dilated cardiomyopathy. There are several causes of FMR, including chamber/annular dilation that prevents proper coaptation of the valve leaflets, dysynchrony of papillary muscle contraction, and atrioventricular conduction delay that can amplify presystolic regurgitation.30 CRT reduces FMR by targeting each of these components because it uses a shortened AV delay to induce ventricular pre-excitation, reduces dyssynchronous contraction, and chronically results in smaller chamber volumes.31,32 Of patients with reduced FMR from CRT, >90% have reduced chamber volumes, revealing a virtual full overlap between FMR responders and CRT responders.33

### Identifying CRT Responders

Given its invasive nature and up-front expense, major efforts have been made to identify the patients most likely to benefit from CRT. However, to date, ≈30% of recipients do not show beneficial clinical (or cardiac morphometric) responses and ongoing efforts to develop more robust predictors continue.34,35

**Figure 1.** X-ray of patient receiving cardiac resynchronization therapy. Adapted with permission from Owen et al.6 Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
electromechanical coupling is fairly uniform, then delay in electric activation generates delay in regional mechanics. However, heterogeneity of wall stress, contractility, fibrosis, or other abnormalities can also impact electromechanical association. Discoordinate contraction itself exacerbates electromechanical delay in the late activated (high-stress) regions. Furthermore, wall motion can appear dyssynchronous even when electric activation is normal because of regional heterogeneity of myocardial function. For example, right–left heart dyssynchrony occurs with pulmonary hypertension without QRS widening thought because of higher right ventricle wall stress, and CRT can reverse this. Disparities in wall contraction timing after myocardial infarction may appear as dyssynchronous, although this is far less likely to be ameliorated by CRT.

Current guidelines identify CRT as a class I recommendation for patients with a QRS complex >150 ms (and ejection fraction <35%) and a class IIa recommendation for patients with a QRS complex between 120 and <150 ms. Meta-analyses of 15 large CRT clinical trials found QRS duration predicts two-thirds of responders, and other studies found no correlation between QRS duration and various parameters of functional or cardiac remodeling outcome. Alternative measures of dyssynchrony have focused on regional wall motion. Early excitement over tissue-Doppler methods was dampened by the multicenter Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial that revealed marked variability in dyssynchrony index assessment even between expert cores and poor overall predictive value. Newer methods involve speckle tracking and 3-dimensional echocardiography. MRI-based techniques, and single-photon emission computerized tomography nuclear imaging. Some integrate information on both the magnitude and the spatial distribution of dyssynchrony. Still, definitive trials remain needed if any of these approaches are to become widely accepted and used.

A drawback to primarily focusing on myocardial motion to index dyssynchrony is that it ignores the corresponding electric activation that is central to the impact of CRT. For example, mechanical dispersion in the absence of electric delays occurs in patients with a narrow QRS complex. A role for CRT in this setting was suggested early; however, more recent multicenter studies did not show benefit with 1 terminated prematurely because of futility and safety concerns. Methods combining electric and mechanical assessments have been reported but remain to be rigorously tested in clinical trials. Finally, other types of biomarkers, such as blood-born or heart tissue assays, may ultimately be found to define a responsive heart.

**Does CRT Involve More Than LV Mechanics?**

Although a guiding theory of CRT has been that its efficacy relates principally to improved cardiac mechanics, persistent difficulties in predicting responsive patients suggest something is being missed. Basal dyssynchrony and acute resynchronization of wall motion after CRT implantation have both been reported to predict responder patients. However, the relation between chronic response magnitude and such wall motion measures is weak. For example, Bleeker et al found CRT must acutely reverse LV dyssynchrony to lead to chronic reduction in end-systolic volume (reverse remodeling index). However, the extent of resynchronization among these patients, all with class I indications for CRT, varied markedly (Figure 3). Beyond identifying a minimal threshold of response required to observe any benefit, the data showed no correlation between the magnitude of resynchronized wall motion and chronic end-systolic volume decline (Figure 3, inset). Similar issues apply to recent work using radial strain delay analysis in which a threshold effect linking chronic response to basal dyssynchrony exists, but beyond this, the association is weak. Other approaches such as two-dimensional echocardiographic speckle tracking to optimize lead placement or cardiac output to optimize AV and ventricular–ventricular delays have been tested, and although both have been suggested to lower the nonresponder rate, it still remains near 30%.

Several factors likely contribute to a persistent 30% nonresponder rate among patients clinically indicated to receive CRT. Some have poor venous anatomy and difficulty in advancing leads in the appropriate territory limiting effectiveness. In others, the underlying disease may be too advanced, or the underlying myocardium may be too heterogeneous because of scar tissue that impedes electric activation from the pacing lead. Another cause is that the assessment of dyssynchrony was misleading in that wall motion discoordination was not really caused by electric conduction delay but rather by regional myocardial properties, and thus is difficult to offset by pre-excitation.

Finally, we should entertain the hypothesis that equating CRT efficacy solely to its impact on regional mechanics and hemodynamics is itself limiting. Like all HF therapies, secondary changes in molecular and cellular function are also induced and, over time, these become intertwined with the mechanical effects altering the pathobiology. It would be difficult to dissociate these mechanisms, yet molecular/cellular changes induced by dyssynchrony and offset by CRT pose a...
novel perspective for the field. First, such changes may pave a path to alternative biomarkers for responders. Second, molecular responses induced by CRT might themselves be leveraged as HF therapy in patients that are not dyssynchronous. Again, the unique feature of CRT is that systole is acutely and chronically improved, yet mortality is also enhanced. This is not simply a matter of improving cardiac output, but how it is accomplished at the organ, cellular, and subcellular levels. In the next section, we review studies revealing such mechanisms.

**Cellular and Molecular Aspects of Dyssynchrony and Resynchronization**

Advances in the basic science of dyssynchrony and resynchronization began taking shape after the therapy was clinically approved for human use in the early 2000s. Spragg et al. reported the first data showing dyssynchrony-induced regional enhancement of stress kinase expression and depression of calcium-handling proteins in the failing canine heart. This animal model was then modified to include 6-week tachypacing with dyssynchrony (left bundle ablation) or 3-week dyssynchrony followed by 3-week biventricular tachypacing (CRT). The latter displayed a slightly improved ejection fraction over dyssynchronous HF; however, both models manifested dilated hearts with decreased global systolic function and elevated diastolic pressures. Other variants of this model have used longer pacing periods ranging from 4 to 24 months, although these pose some practical (and expense) limitations.

**Effects of Dyssynchrony and CRT on Myocyte Function and Ca\(^{2+}\) Handling**

Myocyte calcium handling is rendered abnormal by HF with or without dyssynchrony, but recent studies indicate that restoring synchrony has benefits even in the absence of much improvement in global chamber function. Sarcomere shortening in the dyssynchronous failing heart declines and contraction and relaxation kinetics are slowed, and both are coupled to reductions in whole-cell calcium transient amplitude and delayed dynamics (Figure 4A). These changes were observed similarly in both early- and late-activated territories in HF with dyssynchrony and in cells from epicardium vs endocardium. By contrast, the L-type calcium current was preserved in early-activated myocardium but reduced in the lateral wall in CRT-responsive patients. In the canine model, Aiba et al. found phospholamban and Serca2A protein expression declined, and Na\(^+-\)Ca\(^{2+}\) exchanger levels increased throughout the myocardium in HF with dyssynchrony (Figure 4C).

![Figure 4. Dyssynchrony reduced baseline cellular function, which is restored by cardiac resynchronization therapy (CRT). A. Myocyte sarcomere shortening and corresponding whole-cell calcium transients in myocytes taken from control (Con), dyssynchronous heart failure (HF\(_{dys}\)), synchronous heart failure (HF\(_{sync}\)), and CRT. Adapted with permission from Chakir et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. B. Peak current–voltage relationships for I\(_{Ca,L}\). C. Western blots for calcium-handling proteins. Arrows show the direction of change in HF\(_{dys}\) and CRT groups as compared with control. B and C. Adapted with permission from Aiba et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. D. Three-dimensional reconstructions from confocal microscopic images showing t-tubule structure (blue) and ryanodine receptors (red). Adapted with permission from Sachse et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. ANT1 indicates anterior; LTR, lateral; NCX, sodium-calcium exchanger; PLN, phospholamban; and RyR2, ryanodine receptor 2.](http://circres.ahajournals.org/Downloaded from)
However, CRT did not reverse these changes and regional modifications were often at odds with Ca\textsuperscript{2+} transient changes in the same territory. Alternative mechanisms such as post-translational modifications (phosphorylation, oxidation, or nitrosylation) or structural changes are still being investigated. Another mechanism is a change in the structural organization of transverse t-tubules and the sarcoplasmic reticulum (SR) reported by Sachse et al.\textsuperscript{82} Dyssynchrony disrupted the regular longitudinal spacing of the t-tubular system and its registration with ryanodine receptors (Figure 4D) in the lateral, but not anterior, wall, and this was partially reversed with CRT. Structural disruption of the tubular SR has been reported in failing hearts and is thought to contribute to abnormal calcium handling.\textsuperscript{85} Finally, the responsiveness of the myofilaments to calcium also seems to be impacted by dyssynchrony and CRT. Preliminary data reveal significantly lower Ca\textsuperscript{2+} sensitivity and decreased maximal activated force in dyssynchronous or dyssynchronous HF, as observed in human HF,\textsuperscript{92,93} accompanied by increased efferent sympathetic tone that is often elevated in patients with HF.\textsuperscript{90} Acutely, CRT blunts sensitivity to sympathetic stimulation.\textsuperscript{88,89} Work to identify the mechanism(s) is ongoing, but new quantitative mass spectrometry methods may pave the way for assessing post-translational changes in myofilament proteins that control Ca\textsuperscript{2+} sensitivity.\textsuperscript{87}

**CRT and β-Adrenergic Signaling**

CRT-responsive patients display an enhanced cardiac responsiveness to sympathetic stimulation.\textsuperscript{83,89} Acutely, CRT blunts efferent sympathetic tone that is often elevated in patients with HF,\textsuperscript{90} and chronically CRT results in upregulation of β1-adrenergic receptor gene expression in responsive patients.\textsuperscript{91} More detailed analysis of β-adrenergic signaling has been performed in the canine model. Myocytes from always dyssynchronous or synchronous HF display a blunted response to isoproterenol, affecting both sarcomere shortening and calcium transients (Figure 5A). Both responses are restored to near-normal with CRT.\textsuperscript{80} accompanied by increased β1-receptor expression and membrane density, and adenylate cyclase activity.\textsuperscript{14}

Experimental studies also revealed a unique effect from CRT on β2-adrenergic signaling via coupling to inhibitory G-protein. G\textsubscript{β3}-signaling was increased in always synchronous or dyssynchronous HF, as observed in human HF,\textsuperscript{92,93} with blunted cAMP activation and downstream activation of protein kinase A at the sarcoplasmic reticulum (Figure 5D).

Incubation of cells with pertussis toxin, which blocks G\textsubscript{αi}, increased these responses on exposure to zinterol, a β2-agonist (Figure 5B). In contrast, cells from CRT hearts had a greater basal zinterol response that was unaltered by pertussis toxin. G\textsubscript{αi} protein expression was elevated in each of these models similarly, but CRT enhanced coexpression of 2 negative regulators of G-protein signaling, RGS2 and RGS3, that can suppress G\textsubscript{αi} signaling\textsuperscript{80} (Figure 5C). Upregulation of either RGS protein in myocytes from dyssynchronous or synchronous HF resulted in behavior similar to that of myocytes from CRT hearts\textsuperscript{80} and were also no longer responsive to pertussis toxin. RGS2 and RGS3 gene expression were also increased in human LV biopsy specimens from CRT responders, providing translational support for this mechanism.\textsuperscript{80}

**CRT Modulation of Ion-Channel Expression and Function**

Ventricular arrhythmia is a common complication and cause of death from HF. Many channelopathies are involved that often lead to prolongation of the action potential duration and slowed conduction velocity. Pharmacological targeting of these changes has been generally counterproductive, and defibrillation by implantable devices serves as the primary therapy. In patients with HF receiving CRT, ventricular arrhythmia declines.\textsuperscript{94-98} Although some raised concerns that epicardial stimulation used by standard CRT may be proarrhythmic,\textsuperscript{99} in practice, CRT seems to be antiarrhythmic,\textsuperscript{98} reducing the incidence of a first ventricular tachycardia event.\textsuperscript{101} This is another unique feature of CRT in that it directly enhances systolic function while also countering malignant arrhythmia.

Mechanisms for dyssynchrony and CRT-related electrophysiological changes have been explored in some detail in canine models. Dyssynchrony without LV dysfunction can itself induce regional abnormalities of conduction and repolarization.\textsuperscript{79} Whereas conduction is normally fastest in the endocardium, in nonfailing hearts with LBBB, the epicardium became fastest in the late-activated lateral wall. This was accompanied by a dislocalization of connexin 43 from the intercalated disk to the longitudinal plasma membrane. The latter was not observed, however, in a long-term study of dyssynchrony only in piglets.\textsuperscript{102}

Figure 5. β-Adrenergic pathways are reduced in dyssynchronous heart failure (HF\textsubscript{dyss}) but restored via regulators of G-protein signaling 2/3 (RGS2/3) signaling in cardiac resynchronization therapy (CRT). A, In response to isoproterenol, HF\textsubscript{dyss} exhibited a much smaller augmentation in sarcomere shortening and calcium transient amplitude, which was reversed by CRT. B, Pertussis toxin (PTX) preferentially inhibits G\textsubscript{αi} signaling, and it restored the isoproterenol response in HF\textsubscript{dyss} but had no effect on CRT, suggesting that CRT enhances β-adrenergic response via this pathway. C, RGS2/3 can inhibit G\textsubscript{αi} and were significantly upregulated in CRT. D, Example tracings of sarcoplasmic reticulum (SR)-AKAR3 FRET in zinterol (Zin)-treated cells. Protein kinase A (PKA) activation in the SR was only observed in the CRT model. Con indicates control; and SS, sarcomere shortening. Adapted with permission from Chakir et al.\textsuperscript{80} Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
HF involves many channel abnormalities\textsuperscript{103–105} that may contribute to conduction block.\textsuperscript{106} and when both are combined, one observes substantial prolongation of action potential duration associated with declines in multiple ion currents and worsened conduction.\textsuperscript{107} Action potential duration is prolonged more in the late-contracting zone in dyssynchronous hearts,\textsuperscript{91} and CRT partially reverses this.\textsuperscript{83,84} Specific repolarizing potassium currents (the inward rectifier K\textsuperscript{+} current $I_{K1}$, transient outward K\textsuperscript{+} current $I_{Kt}$, and delayed rectifier K\textsuperscript{+} current $I_{Kf}$) decline in dyssynchronous HF,\textsuperscript{81} concordant with a decline in protein expression for the corresponding channel proteins (Kir 2.1, Kv4.3 and KChIP2, and KvLQT1, respectively). CRT partially reversed changes in $I_{K1}$, $I_{Kt}$ (but not $I_{Kf}$), and their related proteins. CRT also reversed increased late sodium current ($I_{Na-L}$) observed in dyssynchronous HF. The $I_{Na-L}$ inhibitor, ranolazine, shortened the action potential duration and reduced the incidence of early afterdepolarizations in dyssynchronous HF but had no impact on either behavior in myocytes from CRT dogs. The combined effect of CRT on these repolarizing currents reduces arrhythmia. It is again important to remember that these electrophysiological changes from CRT are being observed in an animal model in which chamber dilation and dysfunction persist, and therefore more likely reflect the impact of discordant contraction that is resynchronized.

**Modulation of Cell Survival Signaling**

Myocyte apoptosis contributes to cardiac dysfunction. It is observed in dyssynchronous HF in both experimental models and humans. In humans, markers of apoptosis were elevated in LV biopsy samples from dyssynchronous HF and subsequently reversed after initiating CRT.\textsuperscript{108} Another study found that the proapoptotic protein annexin A5\textsuperscript{109,110} declined in patients responding to CRT.\textsuperscript{111} Antiapoptotic effects of resynchronization have been observed in canine\textsuperscript{77} and pig models.\textsuperscript{112}

Several stress kinases that can trigger apoptosis\textsuperscript{113} are also more active in dyssynchronous HF, including septal extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase (MAPK) expression and increased lateral wall activity of p38 MAPK, calcium/calcmodulin-dependent protein kinase II (CaMKII) and tumor necrosis factor-\textgreek{a}.\textsuperscript{77} However, these changes are regional, appearing in the late-activated high-stress wall, whereas apoptosis is more globally impacted, indicating other modulators are involved. One kinase that is globally inactivated is Akt that is, in turn, linked to reduced Bcl-2-associated death promoter phosphorylation and consequent proapoptotic signaling. CRT reverses both the regional stress kinase and the global Akt activation changes.

**Biomarkers of CRT in Circulating Blood**

Although one might not anticipate that discoordination in electromechanical timing of the heart would lead to detectable circulating plasma markers, several clinical studies have explored this possibility and reported limited but positive findings. Examples include matrix modulators such as protein tenasin-C, metalloproteinase-2 and metalloproteinase-9 (decline after CRT),\textsuperscript{114} tissue inhibitor of matrix metalloproteinase-1 (increases after CRT),\textsuperscript{115} and the G-coupled receptor ligand apelin\textsuperscript{116,117} (increases with CRT). Whether these are specific to dyssynchrony or reflect overall enhanced LV function by CRT is uncertain.

**CRT and Mitochondria Energetics**

HF is often considered a disease involving energy starvation.\textsuperscript{118,119} The dyssynchronous heart is inefficient at the chamber level, and regional disparities in metabolism reflected by glucose uptake have been documented.\textsuperscript{120,121} These, along with global chamber efficiency, are improved by CRT\textsuperscript{17,122} (Figure 2F). However, recent evidence shows CRT also favorably impacts underlying mitochondrial function. Mitochondrial basal oxygen consumption is increased in canine dyssynchronous HF\textsuperscript{23} but accompanied by a decline in ATPase activity.\textsuperscript{124} CRT increased the mitochondrial respiratory control ratio, an index of ATP synthetic capacity (Figure 6A), to levels similar to those in healthy controls. CRT altered expression of H30 different proteins within the mitochondrial proteome, many involving the respiratory chain.\textsuperscript{123}

Improved oxidative phosphorylation after CRT has been further mechanistically linked to oxidative post-translational modifications in the \textgreek{a}-subunit of ATP synthase.\textsuperscript{124} On exposure to reducing conditions, ATPase activity in dyssynchronous HF reached levels in control or CRT myocardium, supporting an altered oxidative environment in dyssynchronous HF (Figure 6B). Two disulphide bonds between ATP synthase-\textgreek{a} subunits were increased in dyssynchronous HF (Cys 294-Cys294 and Cys294-Cys103) and reduced by CRT. Cys294 was also S-glutathionylated, and CRT suppressed this while favoring S-nitrosylation at the same residue. S-Nitrosylation

![Figure 6. Effect of dyssynchrony and cardiac resynchronization on mitochondrial function and oxidation. A. Respiratory control ratio (mitochondrial O\textsubscript{2} consumption in present of substrate with ADP vs without ADP) is decreased in dyssynchronous heart failure (HFdys) and augmented to control levels by cardiac resynchronization therapy (CRT). *P<0.001 vs CRT, P<0.05 vs control (Con); #P<0.05 vs CRT. B. ATP synthase activity (measured in gel assay) at baseline and with exposure to reducing agent dithiothreitol (DTT). Activity was reduced in HFdys vs CRT but augmented to control levels by DTT. This indicates that oxidation plays an important role in decreased mitochondrial function in HFdys. Adapted with permission from Agnelli et al\textsuperscript{123} and Wang et al.\textsuperscript{124} Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.]
of ATP synthase-α occurs in ischemic preconditioning and may be cardioprotective.125 Thus, the S-nitrosylation/S-glutathiolation balance seems to be a regulatory mechanism for ATP synthase that is targeted by CRT.

Figure 7 summarizes the various molecular and cellular changes that have been identified in both HF with dyssynchrony and the response to CRT.

Clinical Challenges and Future Directions

Lead Placement and Optimal Implementation of CRT

Although the LV lead used in CRT is generally placed in the lateral and posterolateral wall, this can vary among patients and ongoing efforts continue to improve optimizing this placement. Several studies indicate the LV free-wall territory in which effective CRT can be obtained is sizable (≈40% of the free wall),126,127 but coronary venous anatomy may preclude even this lead placement.128 New leads with multiple selectable electrodes may improve this limitation and reduce the nonresponder rate.129 Others are exploring LV endocardial pacing either via transseptal puncture130 or via a wireless system with microstimulators placed within the LV endocardium that is actuated by ultrasound to stimulate the muscle.131,132 These remain works in progress.

CRT and Atrial Fibrillation

Atrial fibrillation is common in patients with moderate to severe HF, and it makes implementation of CRT more difficult because timing for pre-excitation of the LV cannot be accurately predicted.133 In the Resynchronization for Ambulatory Heart Failure Trial (RAFT), patients with permanent atrial fibrillation were randomized to a defibrillator or defibrillator plus CRT, and CRT showed minimal benefits and a trend toward reduced HF hospitalizations.134 Although CRT superimposed with atrioventricular node ablation guarantees biventricular stimulation, one compromises physiological heart rate regulation. This remains a population in which the efficacy of CRT is compromised.

Is Transient Dyssynchrony Beneficial

Although sustained dyssynchrony has been well-established to worsen HF outcomes, several studies have explored the impact of brief exposure to dyssynchrony, for which the effect is quite different. Vanagt et al135,136 subjected rabbit hearts to short ventricular pacing (dyssynchrony) before or after coronary occlusion and observed major reductions in infarct size. Postconditioning efficacy of transient dyssynchrony has also been reported in pigs.137 Two factors involved with ischemic postconditioning, hypoxia inducible factor-1α and heat shock 70kDa protein,138 are induced by dyssynchrony,139 with activation observed in the region opposite to where pacing was instituted (eg, late-contracting wall), suggesting a role for increased wall stress.

Another example where short-term exposure dyssynchrony appears beneficial is in the failing heart. In dogs subjected to 6 weeks of atrial tachypacing (synchronous HF), 2 weeks of right ventricle tachypacing (dyssynchrony) was substituted during weeks 3 and 4. Myocytes from the latter hearts displayed substantial improvement in rest and β2-stimulated myocyte function140 and a decline in Gαi-coupling.

The molecular consequences from transient dyssynchrony remain to be determined, but these recent studies raise intriguing possibilities. For example, might transient dyssynchrony in an otherwise synchronous failing heart improve myocardial function and cytoprotection? Should patients with CRT undergo occasional pacing vacations (restoring dyssynchrony from the underlying conduction block), perhaps reigniting the biological response to resynchronization? Can transient dyssynchrony be used to offset ischemic damage in the human heart? These and many other related questions will need to be explored in future research.

Conclusions

CRT remains a major advance in HF therapy since the adaption of β-blockade and implantable defibrillators. Although understood and accepted for its capacity to improve chamber-level mechanics and thus circulatory hemodynamics, chronic CRT...
has revealed myocardial changes that were not previously envisioned. Whether this is all attributable to improved global function may be impossible to unravel, although the capacity to reverse abnormalities often to healthy control levels, as well as some of the more unique changes observed, suggests more is at play. More definitive analysis of the importance of specific molecular changes because of dyssynchrony and CRT will require the use of genetically engineered models, and this work is ongoing. Nonetheless, for a treatment that first sounded to many to be too simple to achieve much benefit, CRT has proven the opposite on both counts.

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**Disclosures**

None.

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