Cardiac resynchronization therapy (CRT) has been implemented as a novel “hemodynamic therapy” for advanced heart failure patients. Resynchronizing the mechanical coordination between left and right ventricles with reduction of the inefficient dyssynchronous contractions improves the mechanical efficiency of the chamber contraction-relaxation cycle, leading to a better hemodynamic profile. Various mechanical efficiency of the chamber contraction-relaxation the inefficient dyssynchronous contractions improves the coordination between left and right ventricles with reduction of heart failure patients. Resynchronizing the mechanical coordination between left and right ventricles with reduction of the inefficient dyssynchronous contractions improves the mechanical efficiency of the chamber contraction-relaxation cycle, leading to a better hemodynamic profile. Various randomized trials demonstrated an improvement in symptoms and exercise tolerance in patients with congestive heart failure and cardiac dyssynchrony on top of optimal medical therapy, which translates into better prognosis and improved survival. Favorable alterations of clinical outcome were consistent across multiple studies, and CRT has evolved into a Class I indication for such patients with broad QRS complex and severely depressed left ventricular function.

The dyssynchronous contractions in heart failure patients with left bundle-branch block morphology represent a specific disease entity, named dyssynchronous heart failure. Besides typical ventricular dilatation and asymmetric hypertrophy, the disease is characterized by regional differences in loading and contractile work, as well as in myocardial blood flow and oxygen consumption. In dyssynchronous hearts, the workload is typically lowest in the septum and highest in the left ventricular lateral wall and is accompanied by regional differences in wall stress. This ultimately results in regional differences in wall thickness and chamber remodeling. In contrast to other forms of cardiomyopathy where wall thickness is reduced in all regions, cardiomyopathy related to dyssynchronous electrical activation is characterized by regional differences in relative wall thickening with hypertrophy and molecular alterations most pronounced in the late-activated lateral wall.

In addition to differences in chamber mechanics and remodeling, dyssynchronous heart failure is associated with a distinct pattern of the molecular portrait. Although the basic features of molecular changes and activation of the fetal gene program are common, experimental dyssynchrony is associated with regional differences in gene expression. The temporal disparity in regional stretch and loading results in a disparity in a number of regulated transcripts between the early- (anterior) and late-activated (lateral) regions. In this regard, differences in gene expression of proteins involved in calcium handling, metabolic pathways, extracellular matrix remodeling, and myocardial stress responses have been reported. On the other hand, a transcriptome-based approach indicated that experimental CRT with pacing of the lateral wall is able to correct alterations in gene expression in the anterior wall, thereby reducing the regional heterogeneity of gene expression. This raises the hypothesis that the restoration of the relative balance in gene expression levels between the anterior and lateral wall may contribute to the reverse chamber remodeling observed in CRT.

In this issue of Circulation, 2 studies provide new insights into the molecular characteristics of dyssynchronous heart failure, including the impact of resynchronization therapy. In a canine model of pacing-induced dyssynchronous heart failure, Aiba et al describe the electrophysiological consequences of cardiac dyssynchrony by investigating its effects on regional differences in function and expression of ion currents, as well as on action potential profiles between early and late-activated regions of the left ventricle. They demonstrate that regional differences in load cause electrical remodeling with prolongation of the action potential in the earliest activated regions. On the other hand, shortening of the action potential together with frequent early afterdepolarizations were typically observed in the late-activated lateral wall. The electrical remodeling was paralleled by differences in ionic currents and Ca²⁺ transients between myocardies isolated from the anterior and lateral left ventricle myocardium. Interestingly, CRT partially restored dyssynchronous heart failure–induced ion channel remodeling, abnormal Ca²⁺ homeostasis and attenuated the regional heterogeneity of the action potential duration. Potassium channel remodeling occurred in both the anterior and lateral wall. However, in contrast to the inward rectifier K⁺ current (I_K) and the delayed rectifier K⁺ current (I_K), the transient outward K⁺ current (I_TO) and its associated genes remained unaffected after CRT. This dichotomy in response may suggest differential molecular regulation of K⁺ currents, with I_TO being regulated by tachycardia or heart failure and not solely by dyssynchronous activation. Ca²⁺ current remodeling was most prominent in the lateral wall, thereby mitigating dyssynchrony-induced regional heterogeneities in I_K density and gating. Taken together, the work of Aiba is important...
because it highlights changes in the electrical phenotype of the failing dysynchronous heart that are likely to predispose to arrhythmia susceptibility observed in animal models and patients with heart failure. Although speculative, partial normalization of the electrical phenotype as demonstrated in this experimental CRT model may provide an explanation for the reduced risk for arrhythmias and better overall prognosis after CRT. In addition, the dichotomy in K⁺ currents in parallel with other ionic current changes and its electrophysiological implications deserve further studies to pinpoint arrhythmogenic targets in other forms of congestive heart failure.

The study by Chakir et al, also in this issue of Circulation, brings to our attention the importance of force-frequency and adrenergic responsiveness in congestive heart failure. The blunted force frequency responsiveness underlies the reduced contractile force in response to exercise in heart failure. Recently, human studies have shown that the blunted force-frequency amplification as well as its adrenergic control are partially restored by CRT, thereby improving cardiac contractility and symptoms. It has been suggested that the restoration of the force frequency relationship may be related to increased expression of β1-adrenergic receptors. Chakir et al further extend our understanding of the underlying molecular mechanisms. They confirm upregulation of the β1-adrenergic receptors as the basic mechanism related to improvement in adenylyl cyclase activity and provide novel insights by reporting suppression of the inhibitory Gi-coupled signaling with upregulation of regulators of G-protein signaling proteins. These molecular changes have not been described in previous medical or interventional therapeutic strategies for congestive heart failure and appear to be a unique feature of resynchronization intervention. Whereas other heart failure therapies target a specific neurohumoral factor or unload the left ventricle to improve β-adrenergic responsiveness, CRT is able to achieve the same effect without excessive catecholamine stimulation. The restoration of normal balance between catecholamine stimulation and myocyte adrenergic responsiveness without increase in catecholamine content is remarkable in comparison to other therapeutic interventions. This study is consistent with the data of Aiba and colleagues on reduction of Ca²⁺ currents and earlier findings on CRT effects on energy expenditure.

From the molecular physiology perspective, these studies imply that substantial changes in energy metabolism and energetics play a key role in the transition from compensated to decompensated heart failure. Hence, similar to the electrical remodeling highlighted by Aiba et al, Chakir et al have put forward a parallel mechanism potentially accounting for the beneficial effects of CRT.

What take-home messages and implications can clinicians and scientists get from the presented work? It is obvious that by detailed analysis of the “global or regional” mechanics and electrophysiological aspects and by zeroing in on the molecular portrait, both studies provide important insights into the fundamentals of dyssynchronous heart failure. Bioinformatics, proteomics, and genomics hold the potential to further unravel comprehensive molecular networks underlying the benefits of CRT. Likewise, such an approach can be useful for identifying sets of critical molecular targets associated with the reversibility of dyssynchronous heart failure. Despite overall improvement in symptoms and survival, 30% of patients do not benefit from CRT. Currently, the most widely used predictor of reverse remodeling is the presence of marked mechanical dyssynchrony, which failed to be superior to assessment of the QRS duration. Therefore, it is of note that the present experimental data do corroborate recent human studies demonstrating the reversibility of the altered molecular profile by CRT. These changes were observed only in responders whereas CRT did not exert any significant changes in structural or Ca²⁺ handling proteins in nonresponders. Responders and nonresponders were characterized by differences in baseline gene expression profiles despite similar baseline hemodynamic derangement, suggesting that “molecular profiling” with use of the proteomic or genomic platform can facilitate further optimization of the patient stratification. The features of dyssynchronous heart failure and its reversibility, however, also offer a unique opportunity to decipher more general biomarkers and therapeutic targets and may help to further advance population-based as well as individualized treatment of patients presenting with congestive heart failure.

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None.

References


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