Cellular and Molecular Aspects of Dyssynchrony and Resynchronization

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KEYWORDS

• Dyssynchrony • Cardiac resynchronization therapy • Animal models • Myocyte • Myofilament

KEY POINTS

- In some instances, cardiac resynchronization therapy (CRT) does not simply reverse the damage done by dyssynchrony, but acts in 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 understand 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.

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 system ensures that fiber shortening 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), lead to a loss of synchrony, and occur in 30% to 50% of patients with dilated cardiomyopathy.[1,2] As a result, regions of the heart stimulated early 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, in which delayed-contracting regions can stretch regions stimulated earlier.[3] The net transfer of blood internally within the heart results in heterogeneity of myocardial work[4] and a reduction in mechanoenergetic performance.[5,6] In the failing heart, in which function is already reduced, dyssynchrony worsens both morbidity and mortality.[7]

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

CRT has traditionally been viewed as a mechanical tuning of the heart. Its simplicity and ease of

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entry into the clinic led to rapid development, testing, and approval; all performed in human subjects. There was little basic science on CRT reported before its clinical adaption. However, there have recently been efforts to reverse engineer CRT, exploring the cellular and molecular mechanisms that are involved. Dyssynchrony and resynchronization therapy induce a wide range of changes beyond the mechanical effects, many of which are unique to both the disease and the treatment.[15–19] In some instances, CRT does not simply reverse the damage done by dyssynchrony, it acts in novel ways to improve function. This article explores the extensive set of cellular and molecular mechanisms chronically and acutely induced by dyssynchrony and CRT.

BEYOND LEFT VENTRICULAR MECHANICS

Although there is little doubt that global cardiac mechanics is a major mechanism behind dysfunction of dyssynchrony and recovery with CRT, key issues indicate that there is more going on. The first is what is referred to as the nonresponder 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 greater than 150 milliseconds (and ejection fraction <35%), and a class IIa recommendation for patients with a QRS complex between 120 and 150 milliseconds.[20,21] However, of the patients who receive CRT, approximately one-third show no clinical or morphometric response to the therapy.[22,23] This nonresponder rate has plagued the field, and despite significant efforts, has remained steady. One of these major efforts was the multicenter PROSPECT (Predictors of Response to CRT) trial, which used tissue-Doppler techniques to quantify regional wall motion to determine dyssynchrony and predict response to CRT. However, despite the rigorous study design, there was little predictive capability[24] and the nonresponder rate persisted. Although 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 nonresponder 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 the group of patients who did not resynchronize at all with CRT is removed, there is no correlation between the magnitude of resynchronized wall motion and long-term remodeling (**Fig. 1**). Other studies found similar results using different indices.[26] This finding suggests that there are other important aspects to both dyssynchrony and resynchronization.

MYOCYTE FUNCTION, CALCIUM HANDLING, AND β-ADRENERGIC SIGNALING

Experimental access to myocardial tissue in humans is limited to end-stage hearts at time of transplantation, limiting studies of CRT. Thus, most of the present understanding comes from animal models. Cardiac dyssynchrony can be induced either by right ventricular pacing or from ablation of the left bundle branch, recreating an LBBB. With dog and pigs, it is possible to use existing human pacemaker systems to introduce right ventricular pacing and CRT, superimposed over models of HF 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 show 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

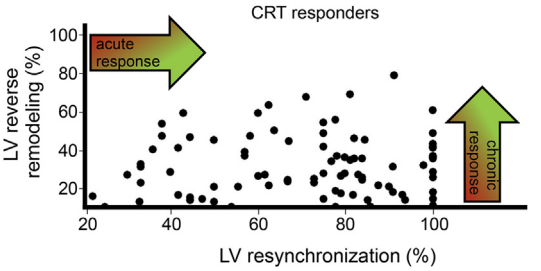

Fig. 1. Immediate LV resynchronization with CRT and change in LV end-systolic volume at 6-month follow-up. An acute response to CRT (>20% LV resynchronization) is necessary for a positive chronic response (>10% LV reverse remodeling), but among these responders there is almost no relationship between acute and chronic response. Therefore, acute hemodynamic response to CRT has little ability to predict long-term benefit. (*From* Bleeker GB, Mollema SA, Holman ER, et al. Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline. Circulation 2007;116:1444; with permission.)