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EDITORIAL COMMENT

The Riddle of Determining Cardiac Resynchronization Therapy Response

A Physiologic Approach to Dyssynchrony Therapy*

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Recently published studies have emphasized the technical difficulty of assessing mechanical left ventricular (LV) synchrony in patients undergoing cardiac resynchronization therapy (CRT). The failure of a large, multicenter study to identify benefit from CRT in dyssynchronous, narrow complex heart failure (1), as well as the failure of synchrony markers to predict success of CRT (2), has cast a cloud over the utility of assessment of mechanical synchrony.

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The study reported by Ypenburg et al. (3) in this issue of the *Journal* should go some way towards balancing the recent negative reports of mechanical assessment of synchrony. These investigators related the results of speckle tracking radial strain and LV lead position on chest X-ray in 244 CRT candidates, and followed them sequentially with: 1) an echocardiogram at 6 months; and 2) long-term clinical follow-up. Concordance between the site of maximal delay and lead position was obtained in 63% of patients, who demonstrated significant reverse remodeling, in contrast to patients with discordance between the site of maximal delay and lead position, who showed no significant changes in LV volume.

Moreover, the combination of death and heart failure hospitalization over the ensuing 32 months was less in the patients with concordant lead position, with a hazard ratio of 0.22. Importantly, although the groups with concordant and discordant lead position differed in other ways (e.g., ischemic etiology and QRS duration), multivariate analysis confirmed the relationship of maximal delay to lead position to be independently related to outcome.

This is an important observation that adds further insight into the mechanism of effective CRT. There are conflicting beliefs regarding the importance of mechanical synchrony to CRT response. One is based on the outcomes evidence obtained from the CARE-HF (Cardiac Resynchronization Heart Failure) and COMPANION (Comparison of Medical Therapy, Resynchronization, and Defibrillation Therapies in Heart Failure) studies (4,5), which show that device therapy is effective across populations defined on the basis of electrical dyssynchrony. As mechanical synchrony had only a minor role in the selection of patients for the CARE-HF study, proponents of this viewpoint emphasize the efficacy of device therapy across this group, and support the principle of implanting devices irrespective of the evidence (or lack thereof) of mechanical dyssynchrony.

Another school of thought has a more physiologic approach to CRT therapy. The proponents of this viewpoint contend that the mechanism of effect of CRT is mechanical resynchronization of the ventricle, allowing more efficient, uniform contraction, and they anticipate that it is this effect that is responsible for the improvement of LV function, functional class, and survival. Studies have demonstrated that the degree of dyssynchrony changes with CRT correlates with the improvement of LV volume (although not across the whole spectrum of synchrony improvement) (6). Indeed, a correlation has been demonstrated between the degree of improvement of dyssynchrony, cardiac remodeling, and functional outcome (7).

Figure 1 emphasizes the relationship of electrical and mechanical synchrony and their implications for CRT response. In the middle are a group of patients with both mechanical dyssynchrony and electrical dyssynchrony due to conduction disease—these patients usually present with a wide QRS (>150 ms) and a normal-sized but dyssynchronous LV with reduced ejection fraction. Patients in this group are typically dramatic responders, as long as CRT is properly deployed (i.e., in the posterolateral wall). A related group has both mechanical dyssynchrony and electrical dyssynchrony due to myocardial disease or ischemia. These patients have a wide QRS (>150 ms) and a large and dyssynchronous LV with reduced ejection fraction, who can be expected to respond to CRT if the myocardium is viable and the pacing site corresponds to the site of maximum delay. Next, there is a group of patients with significant mechanical dyssynchrony but without profound electrical dyssynchrony (narrow QRS). Such patients (often described as having "narrow QRS") would probably respond if mechanical dyssynchrony could be reliably identified and leads were placed in the optimal position. The last group—and perhaps the most important patient population in which CRT could be avoided *if evidence was gathered with an appropriate marker of*

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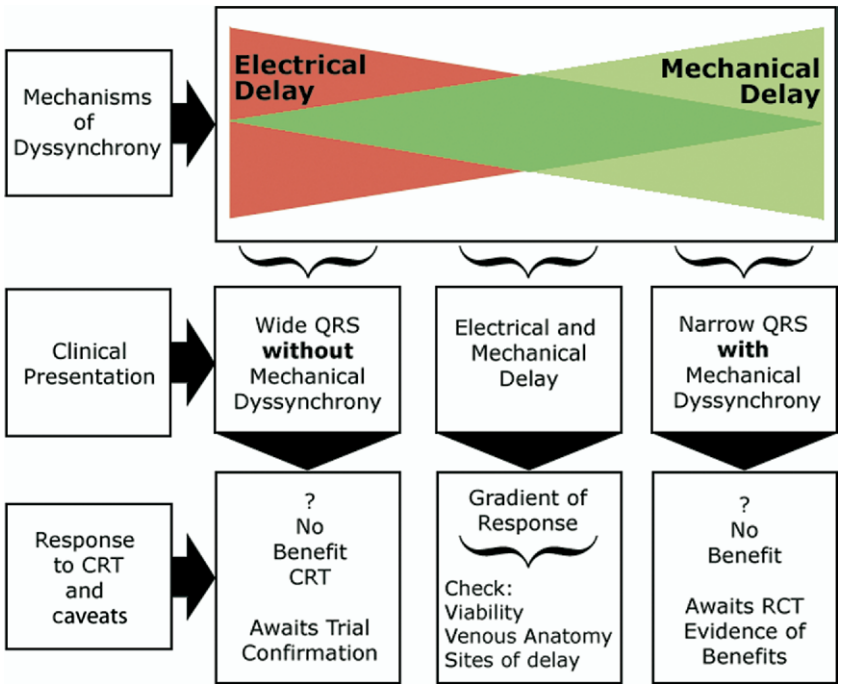

Figure 1 **A Spectrum of Electrical and Mechanical Dyssynchrony Exists for Most Patients and Often Both Are Interrelated**

Interrelationship of electrical and mechanical dyssynchrony is indicated by the overlap. Patients with either electrical or mechanical dyssynchrony alone require further validation to determine if they derive benefit from cardiac resynchronization therapy (CRT). RCT = randomized controlled trial.

mechanical synchrony—is the group with electrical dyssynchrony but without mechanical dyssynchrony.

Most patients with a wide QRS have a subjective clinical response, as mechanical dyssynchrony is often associated with electrical dyssynchrony; this explains why LV mechanical dyssynchrony predicts outcome with CRT (6,7). This concept also explains why the large outcomes trials have shown a relationship between QRS duration and CRT benefit (4,5). This CRT benefit is explained by "being in the right place (lateral wall) at the right time" (reducing the right ventricular/LV interventricular conduction delay). Unfortunately, the identification of mechanical dyssynchrony (mechanism) and proper lead location (place) are required to achieve the optimum achievable in any given patient. Some patients, however, just do not have the proper anatomy to achieve the ideal place (venous anatomy), and some have just too much scar tissue and not enough recruitable myocardium.

The investigations that have correlated the site of maximal dyssynchrony and the pacing site have offered a fresh angle in this argument. This investigation follows several previous reports (Table 1), which have emphasized the benefits of lead localization in the site of latest activation (8–13). These studies have shown that the closer that pacing is performed to the site of maximal dyssynchrony, the greater benefit to the patient, at least in terms of cardiac function. This landmark study moves this observation to the next level, by demonstrating that correlation between pacing site and site of maximal dyssynchrony translates into better clinical outcomes proven with hard end points (mortality and heart failure hospitalizations). It should also be emphasized that these *incremental clinical benefits* were achieved after evidence-based medical therapies were optimized.

The findings of this report support the importance of restoring synchrony as the mechanism of effect of CRT. They support the hypothesis that the failings of recent trials relate to other matters than a lack of importance of mechanical synchrony. LV leads are implanted in an anterior or anterolateral vein in >30% of cases (14), despite evidence that long-term hemodynamic and neurohormonal benefit depends on lead position (15). Of course, there are also shortcomings of current techniques used for the assessment of mechanical synchrony, and, indeed, these limitations justify the failure to include mechanical synchrony in most, but not all, guidelines. Nonetheless, the findings of the study of Ypenburg et al. (3) should encourage us in the ongoing search for an optimal marker of synchrony that can be used in patient selection to help solve the riddle of CRT response. Indeed, the stakes in this are high—assuming that only 10% of implants are inappropriate (a conservative estimate), the potential savings in the U.S. alone would be over $2 billion. The increase in prevalence of heart failure and the expense of this modality certainly justify the need for a sequence of careful investigations that will evaluate myocardial viability, the site of maximal dyssynchrony, and the venous anatomy, to ensure that patients who have a device

Table 1 Previous Studies of the Hemodynamic and Exercise Effects of Pacing Within the Site of Maximal Delay ("Most Delayed") and Other Sites

	Ansalone et al. (13)	Murphy et al. (11)	Becker et al. (10)	Becker et al. (12)	Becker et al. (9)
n	31	54	58	47	47
Follow-up time (months)	<1	6	12	10	3
Imaging technique					
Paced segment	TDI	TSI	3DE	2DS	2DS
LVESV					
Most delayed	−28 ml	−23%	−32 ml	42 ml	9%
Intermediate		−15%			
Least delayed	−9 ml	+9%	−21 ml	27 ml	5%
p value	0.04	<0.0001	<0.01	<0.001	<0.001
EF					
Most delayed	9%	23%	10%	12%	
Intermediate		16%			
Least delayed	2%	−9%	6%	7%	
p value	0.04		<0.01	<0.001	
NYHA functional class					
Most delayed	−0.5	−29%			1.3
Intermediate		−21%			
Least delayed	−0.3	−12%			1.0
p value	0.45	<0.001			0.2
Exertion	Workload (W)	None	Peak VO_2 (ml/kg/m)	Peak VO_2 (ml/kg/m)	Peak VO_2 (ml/kg/m)
Most delayed	9.0		2.4	2.8	2.0
Intermediate					
Least delayed	−0.7		1.5	1.9	1.1
p value	0.03		<0.01	0.035	0.01

EF = ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; TDI = tissue Doppler imaging; TSI = tissue synchronization imaging; VO_2 = volume of oxygen; 2DS = 2-dimensional strain (circumferential); 3DE = 3-dimensional echocardiography.

implanted are likely to enjoy a clinical and physiologic response. The continued avoidance of mechanical dyssynchrony in favor of QRS duration alone to identify candidates for CRT therapy will propagate the pool of CRT recipients that are "nonresponders."

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