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EDITORIAL COMMENT

Leadless Left Ventricular Pacing

Another Step Toward Improved CRT Response*

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CARDIAC RESYNCHRONIZATION THERAPY: WHERE DO WE COME FROM?

In 1986, it was observed in a canine pacing experiment that left ventricular (LV) pressure decreased linearly as the QRS duration increased (1). A decade later, in patients undergoing elective coronary artery revascularization surgery, epicardial biventricular pacing improved hemodynamic variables compared with right ventricular pacing (2). The MUSTIC (Multisite Stimulation in Cardiomyopathy) trial, published in 2001, was the first of many large randomized clinical trials showing the clinical benefits of cardiac resynchronization therapy (CRT) in patients with symptomatic heart failure with reduced left ventricular ejection fraction and increased QRS width (3). By coordinating LV and right ventricular contraction, as well as atrioventricular (AV) timing, CRT improves LV function, reverses adverse cellular remodeling, and reduces heart failure-related hospitalizations and mortality (4,5). However, a suboptimal response based on echocardiographic criteria of remodeling still occurs in one-third of patients (6). In addition, the response to CRT depends on multiple factors such as patient selection, device programming, comorbid conditions, and therapy for the underlying heart failure (4). Several lead-related issues, including unsuitable coronary venous anatomy, LV scar tissue, and phrenic nerve capture, could also contribute to a suboptimal response to CRT, which might be overcome by leadless pacing (6).

LEADLESS LV PACING: THE FUTURE?

In this issue of the *Journal*, Reddy et al. (7) present a prospective study with data of a wireless left endocardial pacing system (WiSE-CRT system; EBR Systems, Sunnyvale, California) in conjunction with a co-implanted standard right ventricular pacing system in 35 patients. The system consists of a LV endocardial electrode, a subcutaneous battery, and a subcutaneous pulse transmitter. The implantation takes place over 2 consecutive days with surgical subcutaneous implantation of the pulse generator system (2 incisions, 1 for the battery, 1 for the transmitter requiring an acoustic parasternal window of 3 cm^2) followed by catheter placement of the LV endocardial pacing electrode. Biventricular pacing is achieved by sensing right ventricular pacing, followed by the immediate transmission of acoustic energy to the LV electrode, thereby achieving nearly simultaneous (5-ms time difference) pacing of both ventricles.

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Procedural success was very high, with 97% of successful implants within an acceptable period of time (7). After 6 months, 94% of patients continued to receive biventricular pacing. In addition, two-thirds of patients had an increase in quality of life and/or a reduction in New York Heart Association functional score, and one-half of patients exhibited a positive echocardiographic response at 6 months. Importantly, these benefits were achieved in patients who were classified as nonresponders to conventional CRT or in whom conventional CRT could not be deployed due to anatomic considerations. Therefore, the prospect of endocardial LV pacing with more flexibility in terms of LV pacing site selection away from scar tissue and phrenic nerve stimulation looks promising.

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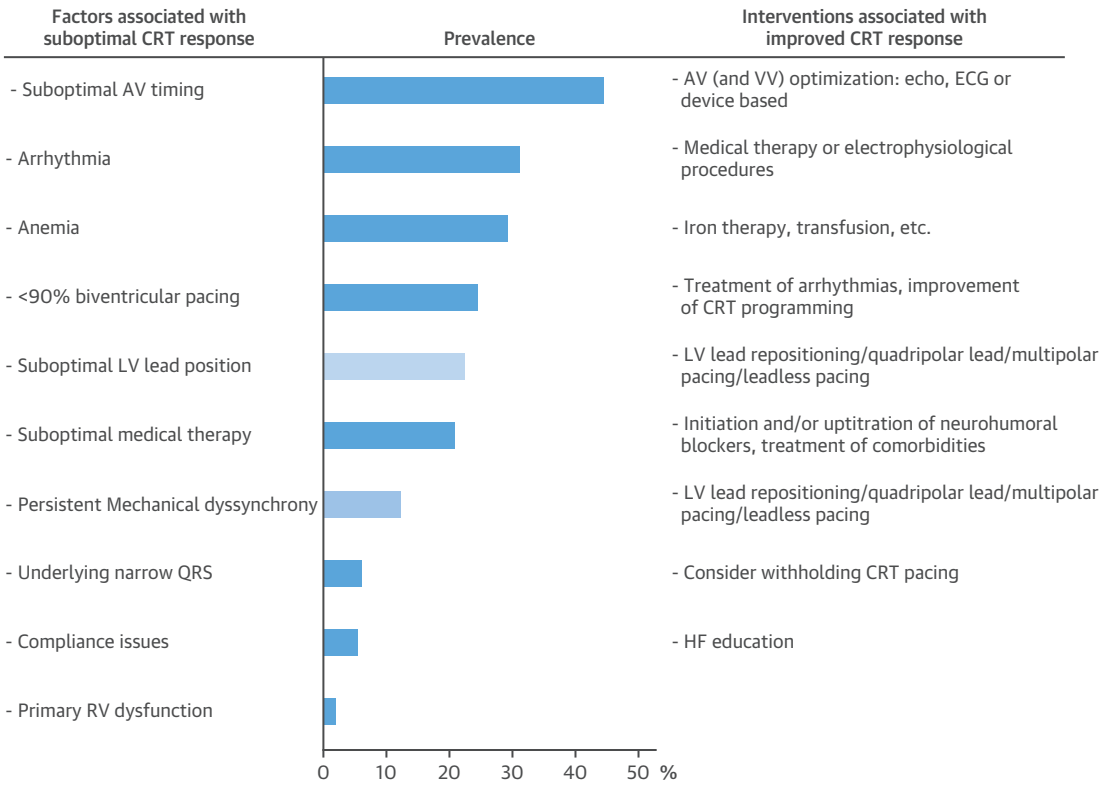
FIGURE 1 **Factors Associated With Suboptimal CRT Response and Possible Interventions**



Leadless left ventricular pacing might improve cardiac resynchronization therapy (CRT) response in patients with a suboptimal lead position, inability to place the left ventricular lead, or persistent mechanical dyssynchrony **(light blue bars)**. However, the majority of factors associated with suboptimal response to CRT should be addressed by other interventions. Adapted from Mullens et al. (16).

Moreover, it has been shown that endocardial pacing results in a more physiological myocardial activation pattern and thereby improved acute hemodynamic function and a narrower QRS complex compared with epicardial pacing (8). Finally, endocardial pacing might be less proarrhythmogenic than epicardial pacing because of the reduced dispersion of ventricular repolarization (9).

Nevertheless, specific technological concerns regarding the ultrasound-based leadless LV pacing system, as well as the high incidence of serious adverse events, remain to be solved (7). First, almost 1 of 10 patients was not suitable due to the absence of a good parasternal acoustic window for the transducer to stimulate the LV electrode. In addition, 3 of 35 patients encountered defective transmitter circuitry within the initial months. Moreover, it is unclear how exercise (as the relation between electrode and transducer may alter during forced breathing), pulmonary pathology, or external radiation, etc., might interfere with the acoustic window and the systems' sensing and pacing performance. Also, energy transfer of ultrasound-mediated pacing systems is inefficient and could result in a short battery life with the need for frequent battery replacements and higher infection risk compared with conventional systems (10). Second, the initial study of the WiSE-CRT system in 2013 was stopped for safety reasons: 3 patients (18%) developed pericardial effusions associated with LV electrode delivery (11). Although this problem was not observed in the present study after redesign of the delivery system, serious adverse events still occurred in 1 of 4 patients. The minority of events were related to the procedure (femoral artery pseudoaneurysm or fistula and catheter-induced ventricular fibrillation), but 6 patients experienced a serious complication (1 embolization of the LV electrode, 3 pocket infections, 1 stroke, and 1 death after catheter-induced ventricular fibrillation).

Because placement and presence of pacing components in the endocardium of the left side of the heart will always carry a certain risk and the potential

for thromboembolic complications, important improvements need to be made in the design and applicability of the system. In addition, it remains unclear if a sufficient percentage of biventricular pacing can be reached and efficient AV as well as interventricular optimization could be performed with this system. Finally, other leadless pacing systems, such as single-component leadless systems eliminating the need for pockets and leads (e.g., the Nanostim leadless cardiac pacemaker [St. Jude Medical, St. Paul, Minnesota] and the Micra Transcatheter Pacing System [Medtronic, Minneapolis, Minnesota]) and the combination of a subcutaneous intracardiac defibrillator and a leadless pacemaker allowing antibradycardia and tachycardia pacing, are currently being investigated (12–14). In addition, the subset of patients in whom a conventional endovascular CRT implantation is not possible due to inadequate coronary sinus anatomy or CRT suboptimal response because of suboptimal LV lead position/phrenic nerve stimulation is rapidly declining as a result of technological advances in both delivery systems and LV lead technology (e.g., quadripolar leads).

OVERCOMING CRT NONRESPONSE: HOW TO GET THE BEST OUT OF THE MACHINE?

Importantly, most often ventricular dyssynchrony is only one of many factors contributing to heart failure, and even an optimal resynchronization technology will not "cure" heart failure. Indeed, the average increase in left ventricular ejection fraction in the large CRT trials (MIRACLE-ICD [Multicenter InSync ICD Randomized Clinical Evaluation], CARE-HF [Cardiac Resynchronization-Heart Failure], REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Trial], and MADIT-CRT [Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy]) ranged from 2% to 11% (15). It has been shown that a variety of heart failure-related factors contribute to a great extent to a suboptimal response to CRT (**Figure 1**) (16). Although most attention has focused on pre-implantation characteristics to optimize CRT response, a variety of post-implant issues should be addressed to achieve the maximum benefit from CRT. Importantly, most of these issues can, in a short period of time, be relatively easily diagnosed and treated with conventional equipment. For instance, despite the convincing literature regarding the benefits in morbidity and mortality of higher dosages of neurohumoral blockers, the "simple" up-titration of these therapies after CRT implantation is still often overlooked but is valuable for increasing the response to CRT (17–19). Indeed, up-titration of neurohumoral blockers after CRT implantation is possible in the majority of patients and associated with improved clinical outcome, similar to patients treated with the guideline-recommended target dose at the time of CRT implantation (20). Second, AV optimization, resulting in improved LV filling, can also lead to improved CRT response in a subset of non-responders in whom initially out-of-the-box timing intervals were programmed (16). In addition, the medical or electrophysiological treatment of arrhythmias preventing efficient biventricular pacing will substantially affect response to CRT. Therefore, it has been shown and advocated that a protocol-driven, multidisciplinary approach, including electrophysiological and cardiac imaging expert input, coupled with a heart failure disease management strategy, can provide insights into the reasons for a suboptimal response beyond the standard of care (16,21).

In conclusion, although many reasons for suboptimal response to CRT exist, leadless pacing may overcome problems related to LV lead placement, LV scarring, or coronary sinus anatomy and will most certainly expand the ability to improve the success of CRT. The WiSE CRT-system may be the first step toward a complete leadless CRT. However, once technical issues have been solved with these systems, randomized clinical trials will be necessary to definitively determine whether leadless systems will be superior to conventional pacemakers.

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