EDITORIAL COMMENTARY

The road to improving cardiac resynchronization therapy outcomes: Paved with gold or an alchemist's dead end?

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> "We cannot solve problems with the same thinking we used to create them."
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> — Albert Einstein[1]

Cardiac resynchronization therapy (CRT) has demonstrated clinical benefit (ie, improvements in quality of life, New York Heart Association functional class, left ventricular [LV] functional and structural parameters, heart failure hospitalizations, mortality, etc.) in appropriately selected patients.[2–4] Although numerous methods designed to predict the response to CRT have been advanced, nonresponder rates have been reported to be as high as 30% to 40%.[5] Therefore, the ability to identify patients who are most likely benefit from this therapy remains an important clinical challenge. Preimplantation considerations include QRS duration and morphology, cardiomyopathy type, LV scar, and interventricular or intraventricular dyssynchrony. Peri-implantation challenges are characterized by anatomical venous access limitations, LV lead placement problems (ie, high capture thresholds, diaphragmatic stimulation, and lead stability), uncertainty about the roles of epicardial vs endocardial LV pacing, and ambiguity about the optimal right ventricular pacing site. Finally, postimplantation factors involve the possible inability to maintain persistent LV capture and concerns about the role of atrial fibrillation or ventricular ectopy in limiting the percentage of biventricular pacing. The predictive accuracy of these and other factors to differentiate responders from nonresponders has been assessed in a number of studies.[6–8] Unfortunately, even with the advent of automated intelligence and machine-based learning, a consistent high degree of predictive accuracy has not been achieved to sufficiently permit the delineation of nonresponders from responders and super-responders.[9,10] Consequently, the latest European Society of Cardiology guideline recommendations for CRT remain centered on QRS duration and morphology with the class of recommendation (COR) and level of evidence (LOE) decreasing from COR I and LOE A for patients with a left bundle branch block and QRS duration >150 ms to COR IIb and LOE B for patients with a non–left bundle branch block configuration and QRS duration between 130 and 149 ms.[11]

In this issue of *Heart Rhythm O*^{2}, Bilchick and colleagues present a first-in-human, small, prospective, nonrandomized, acute feasibility study designed to compare the QRS narrowing achieved with noninvasive ultrasound-based temporary LV pacing to the QRS narrowing obtained with standard, transvenous LV lead-based CRT.[12] This novel technique is presented as a possible preprocedural screening tool, intended to estimate the degree of electrical resynchronization that might be possible if standard CRT is undertaken. In this study, noninvasive LV pacing was performed by delivering ultrasonic energy to an echocardiographic contrast agent (Lumason microspheres; Bracco Diagnostics, Monroe Township, NJ) to generate P-wave synchronous pacing resulting from fusion between the intrinsic beat at a variety of LV pacing sites across a range of atrioventricular delays. A CardioInsight mapping vest (Medtronic, Minneapolis, MN) was used to generate 3-dimensional activation maps and to identify the location of the ultrasonically derived epicardial LV pacing site. Electrocardiography tracings and activation maps were obtained at baseline, during ultrasonic pacing, and after CRT implantation. While the information obtained from the CardioInsight activation maps was shared with the implanting physician, lead placement was left to the operator's discretion and was not guided by the CardioInsight maps.

The authors achieved effective ultrasonic pacing, typically in an intermittent manner, in all 10 patients undergoing evaluation. Notably, there was a negative correlation between body mass index and the number of ultrasound-based paced beats. A significant decrease in the QRS duration and standard deviation of activation time (SDAT) was observed in both the ultrasound and lead-based CRT pacing groups when compared with the intrinsic, baseline values. Furthermore, there was no difference in QRS duration or SDAT when CRT pacing was accomplished by ultrasonic or lead-based methods. No safety issues related to use of

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the contrast material were observed with no patients experiencing significant arrhythmias or hemodynamic problems. Although the troponin I assays increased in both the ultrasound and control groups, there were no differences between the 2 groups.

There are several methodological issues that were not addressed in this investigation, which is understandable given its status as a "first-in-human" pilot study without longitudinal follow-up. The authors did achieve a similar reduction in the QRS duration and SDAT, and limited information suggests acceptable activation map correlation between ultrasonic and lead-based pacing. However, they did not provide complete 12-lead electrocardiographic data to demonstrate whether the ultrasound-based and lead-based LV pacing sites, associated with optimal QRS & SDAT improvement, correlated electrocardiographically and anatomically. Additionally, 3 of the 10 patients had complete heart block with permanent right ventricular pacing. Information on how these patients compared with the nonpaced patients with intrinsic ventricular activation is lacking.

To determine if this potentially novel technology can improve the selection process for CRT patients, further studies will need to focus on several important considerations not addressed in this small pilot study. Because this study assessed resynchronization based on fusion between the intrinsic complex and the LV-paced complex, employment of technology to evaluate biventricular pacing in addition to LV pacing only would be advantageous. Potential differences among patients with ischemic vs nonischemic cardiomyopathies must also be appraised. While the use of Lumason to augment the quality of echocardiographic images is well described and has a robust safety profile, future studies will need to ensure that the utilization of this technology to facilitate pacing does not result in proarrhythmic or other negative safety outcomes.[13] A high body mass index placed limitations on the applicability of this technology. Future endeavors will need to define other clinical issues that may create difficulties in employing this technology.

This approach is presented as a possible preprocedural screening technique to identify CRT responders and to pinpoint advantageous LV pacing sites. The potential to identify CRT responders is based on the assumption that the level of electrical resynchronization can be defined by the degree of QRS narrowing achieved. Therefore, future research initiatives will need to evaluate this postulate and probably should include additional comparisons to traditional methods, sometimes employed to achieve CRT optimization, such as those centered on pacing at sites with the longest electrical or mechanical delay (eg, QLV).[7,8] The opportunity for this technique to categorize LV pacing sites as advantageous centers on the assumptions that "optimal" ultrasonic pacing sites, defined by pacing-facilitated maximal QRS narrowing, will correlate electrocardiographically and anatomically with the selected LV epicardial lead-based pacing site and that pacing at those locations can be consistently achieved

Importantly, even if this noninvasive technology can be shown to consistently facilitate LV pacing site choices that result in a reduction in the QRS duration and advantageous activation patterns, prospective longitudinal clinical studies must be undertaken to determine if this technique is operationally feasible and if it is capable of accurately discriminating clinical responders from nonresponders prior to CRT implantation. In conclusion, while much additional research will be essential to determine the future role of this technology, the authors are to be commended for addressing an important scientific question and for their innovative spirit in presenting us with unique information in this small pilot study about a new technology designed to better predict CRT response prior to device implantation.

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