Defining dyssynchrony: The ongoing search for cardiac resynchronization therapy "response"

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March 22, 2023

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There are no relevant disclosures.

There are no sources of financial support.

The first trial to demonstrate the benefits of cardiac resynchronization therapy (CRT) was published in 2001. The single-blind crossover study demonstrated significant improvement in quality of life, NYHA class, and 6 minute walk test for patients with a left ventricular ejection fraction less than 35%, NYHA class III, an enlarged left ventricle, and a QRS duration greater than 150 ms.[1] CRT represented an exciting advancement in cardiac implantable electronic device (CIED) therapy. While implantable cardioverter defibrillators (ICDs) had been in use for decades and represented a reliable, life-saving measure to treat fatal ventricular arrhythmias, for the first time, there was a device therapy that could improve quality of life for heart failure patients. The CARE-HF trial went on to demonstrate reduction in hospitalization and mortality in a similar population, and subsequent studies, such as MADIT-CRT suggested that the benefits extended to patients with NYHA class I or II.[2,3]

While there was quick adoption of CRT and over the years and many patients have benefitted, it quickly became clear that there were unresolved issues and questions.[4] First, there were patients who could not receive a coronary sinus pacing lead. This was predominantly due to variation in the coronary sinus anatomy and phrenic nerve stimulation. Developments such as quadripolar left ventricular pacing leads and improved sheath design have certainly reduced the number of failed implants, however, they will never be completely

eliminated. Second, despite successful implants in "good" locations, some patients simply did not have clinical improvement. Further work identified subgroups that were more likely to respond, particularly those with a wide left bundle branch block (LBBB); however, even now, only about 70% of patients who meet generally accepted criteria for CRT experience improvement after a successful implant. Finally, while symptom improvement was the standard measure for most studies, there were patients who were "super responders" who actually developed improvement in their left ventricular ejection fraction after CRT, and it is difficult to predict which patients might receive this advantage.[5]

As the data increasingly have shown that patients with LBBB are more likely to benefit from CRT compared to right bundle branch block or non-specific intraventricular conduction delays, most society guidelines require a true LBBB to meet a class I indication for CRT.[6,7] The difficulty with using LBBB as a metric for CRT candidacy is that defining it has been controversial. Multiple criteria have been proposed. In their 2021 guidelines statement for pacing and CRT, the European Society of Cardiology (ESC) altered their definition of LBBB.[8] Specifically, they added the requirement of notching or slurring in 2 adjacent leads to define a true LBBB, thus making the definition of LBBB more restrictive. In addition, the 2021 guidelines also moved patients with narrower LBBB (120-149 ms) to a Class IIa recommendation. This obviously has important implications as to guidelines recommendations and benefits of CRT.

In this edition of the Journal of Cardiovascular Electrophysiology, Rijik, et al present a retrospective analysis of 1202 consecutive patients from a registry who received a CRT device between 2000 and 2015. They applied the 2013 European Society of Cardiology (ESC) definition of left bundle branch block (LBBB) to the population and then the 2021 ESC definition of LBBB and assessed how patients would have qualified for CRT based upon those criteria. In addition, the authors reviewed the actual patient response to CRT in comparison to the guidelines recommendation for CRT implantation by 2013 and 2021 guidelines. Applying the more stringent 2021 criteria dramatically reduced the number of patients with a true LBBB from 80.9% of the population to 31.6%. This moved many patients out of a class I indication for CRT. In addition, they found that the 2013 criteria better discriminated the patients who actually did respond to CRT therapy. When evaluating a combined end point of transplantation, left ventricular assist device implantation, and mortality, the patients with a LBBB by the 2013 criteria and a QRS duration $>$ 150 ms had significant benefit and those without did not. The same was true for echocardiographic response. When applying the 2021 criteria, differences were not seen between the two groups, implying that many patients who no longer had LBBB by 2021 guidelines still benefitted from CRT.

The authors should be congratulated for adding important understanding to how we think about CRT and patient selection. These data show that employing a more strict definition of LBBB does not discriminate those who are most likely to benefit from CRT and might discourage implantation in patients who may benefit. The ESC is not the only society that has supported a more restrictive definition of LBBB.[9] It is difficult to know how these definitions and guidelines directly influence practice, but we don't want to risk denying patients an important therapy that could improve their quality and quantity of life. It is also difficult not to reflect that this paper shows both how far we have come with device therapy for our heart failure patients and how much further we have to go. We have been implanting CRT devices for over 20 years. Many patients have benefitted from this novel therapy, and yet there is so much that we don't know.

We must consider what the role for CRT will be in the future. Novel methods of leadless left ventricular pacing are being developed.[10] There are observational and retrospective data suggesting that left bundle branch area pacing may be as good or better than CRT in improving clinical outcomes and heart function.[11,12] Further, with experience, it is potentially faster to implant a left bundle area lead compared to a coronary sinus lead, and there has been wide early adoption of the technique compared to His bundle pacing. A multi-center, randomized controlled trial evaluating conduction system pacing compared to CRT should start enrolling soon and we should have more information in the coming years.[13] It is possible to envision a future where coronary sinus pacing leads are no longer the norm in this patient population. It is also unlikely that the need for successful coronary sinus lead placement will be completely eliminated. Regardless of what the future holds, the insights from CRT studies, the effects on hemodynamics, electrical function, and outcomes

will inform new directions.

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