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Lessons from the trials

BLOCK-HF: CRT gains new ground

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The detrimental effects of chronic right ventricular (RV) pacing were first demonstrated 10 years ago when the DAVID trial clearly demonstrated the hazards of unnecessary RV pacing - including worsening left ventricular (LV) function, increased heart failure hospitalization and increased mortality.¹ This finding was confirmed in other studies,² prompting the development of various device algorithms to ensure that periods of RV pacing are kept at an absolute minimum, with the ultimate aim of preserving LV function. More recently, the 2012 AHA/ACC/HRS and the 2013 ESC/EHRA practice guidelines recommended *de novo* cardiac resynchronization therapy (CRT) in patients who had indications for permanent pacing with underlying severe LV dysfunction.^{3,4}

It is unknown whether receiving a biventricular (BiV) pacing device at the time of the initial implant – rather than a standard pacemaker – would help preserve LV function in patients with milder degrees of LV systolic dysfunction and a conventional indication for anti-bradycardia pacing. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial was designed to answer this question.⁵

The prospective, multicenter, double-blind study randomized 691 patients with LV ejection fraction (LVEF) of $\leq 50\%$, New York Heart Association (NYHA) functional class I-III heart failure symptoms, and atrioventricular (AV) block to undergo either standard RV pacing or BiV pacing. To preserve double-blinding and equalize risk, a full set of CRT leads was implanted in both groups, with the LV lead being active only in patients randomized to the BiV group. Patients with a “guideline indication” for CRT were excluded from the study. The study’s protocol was revised in 2005 (two years after launching the trial) to allow for using implantable cardioverter-defibrillators (ICDs) when indicated. The mean LVEF for the cohort was $40 \pm 8\%$ (43% in the pacemaker group and 33% in the ICD group) and the mean QRS duration was 124 ± 31 ms. The primary end-point was a composite of all-cause mortality, urgent heart failure care requiring intravenous diuretics or increase in LV end-systolic volume index (LVESVI) $> 15\%$ from baseline. Secondary endpoints included all-cause mortality, death or hospitalization for heart failure and death or urgent care for heart failure. The study was funded by Medtronic and the results were recently published in the New England Journal of Medicine.⁶

After a mean follow-up period of 37 months, at least one of the components of the primary endpoint occurred in 186 of 349 patients (53.3%) in the BiV-pacing group versus 220 of 342 patients (64.3%) in the RV-pacing group. Owing to missing LVESVI values, data for 83 patients in the BiV pacing group and 71 in the RV-pacing group were censored before a primary endpoint event occurred and were not included in the final analysis of the primary outcome. There were 97 cross-overs (84 to BiV-pacing and 13 to the RV-pacing), with 44 crossovers occurring before meeting the primary endpoint. After accounting for censoring and using an intention-to-treat analysis, 160 patients (45.8%) in the BiV-pacing group and 190 patients (55.6%) in the RV-pacing group had events that were included in the primary end-point [HR = 0.74 (0.60–0.90), posterior probability of HR = 0.9978 (achieving the predetermined threshold for statistical significance of more than 0.9775 for combined hazard ratio of less than 1)]. This represents a statistically significant 27% relative risk reduction with BiV pacing. Importantly, the favorable effect of BiV-pacing was observed whether an ICD was implanted or not and

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across all NYHA classes, implying a benefit from BiV-pacing regardless of the severity of underlying LV systolic dysfunction and/or heart failure. Based on these findings, the US Food and Drug Agency (FDA) Advisory Panel issued a recommendation in October 2013 to expand the indication for CRT devices to include patients with AV block and LVEF $\leq 50\%$ who require a high percentage of ventricular pacing.

The potential clinical impact of these results raises several important points that warrant consideration. First, a closer look at the patients recruited in the study shows that 82% had NYHA functional class II or III heart failure symptoms, approximately 30% had a LVEF below 35%, 32.5% had left bundle-branch block, and the mean QRS duration was 124 ± 31 ms. It is therefore possible that many patients already had indications for CRT based on *current* practice guidelines. Second, by routinely implanting an LV lead in all patients, prospective comparison between the risks of BiV-pacing and RV-pacing was not possible. This restricted the analysis of risks associated with BiV-pacing (6.3% of patients suffered from an adverse event related to LV lead placement in this study) to retrospective observational data which can be misleading. Third, the benefit seen with BiV pacing was primarily driven by the LVESVI component of the primary endpoint, with little contribution from decreased mortality or urgent heart failure care. However, it is important to point out that primary endpoint was a composite of time to FIRST event of death, heart failure-related urgent care, or a $>15\%$ increase in LVESVI. It is possible that patients developed a decrease in LVESVI first (rendering it the sentinel event), then subsequently developed heart failure requiring treatment or died. Finally, the trial was not designed to test whether routine baseline implantation of a CRT device in *all* patients with underlying LV systolic dysfunction is superior to upgrading an initially implanted standard RV-pacing system to BiV pacing in those with worsening LVEF *only*. The answer to this question has significant financial and logistic implications. In many parts of the world, the implantation of a standard permanent pacemaker is frequently performed by a cardiologist who does not have CRT experience. Conversely, implantation and programming of a CRT is a more technically-demanding procedure, particularly in patients with aberrant venous anatomy and in those with underlying LV structural (scar) and/or functional conduction blocks. Risk associated with CRT implantation is inversely proportional to the institutional and operator experience/volume, highlighting the importance of dedicated programs which are understandably not available in every hospital. The health-care cost implications of routine CRT placement in these patients are not negligible; a CRT system on average costs 4–5 times that of a standard DDD pacemaker. These concerns, while obviously being beyond the scope of a single study, remain largely unaddressed.

WHAT HAVE WE LEARNED?

The results of BLOCK-HF show superior long-term clinical and functional outcomes of BiV pacing in patients with AV block who have indications for pacemaker implantation and mild/moderate LV dysfunction. The clear benefits seen with BiV pacing, long follow up and the previously recognized detrimental effects associated with chronic RV pacing collectively led to the aforementioned recommendation issued by the FDA in October. A surge in the use of CRT-P devices seems almost certain, especially in hospitals where the service is already available. On the other hand, in hospitals where the existing resources cannot support such a strategy because of financial and/or personnel constraints, it seems prudent to develop protocols that ensure close monitoring and early detection of worsening ventricular function and/or heart failure in patients receiving a standard pacemaker (especially those with impaired LVEF at baseline), and eventually referring them to a center capable of upgrading the device to BiV pacing. This approach is recommended by the European Society of Cardiology and European Heart Rhythm Association in their latest practice guidelines⁴ and seems reasonable until further data and risk stratification algorithms are available to help identify patients who are – at the time of initial implant – at high risk for developing new-onset or worsening LV dysfunction with chronic RV pacing.

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