Can Implantable Biventricular Pacing Systems Without Defibrillation Capability Be Justified in Heart Failure Patients?

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Biventricular (BiV) pacemakers and pacemaker-defibrillator (ICD) systems have been shown to improve cardiac function and diminish frequency of heart failure hospitalizations in patients with severe left ventricular (LV) dysfunction and intraventricular conduction disease. The basis for these beneficial effects is multifactorial (1-15). In the case of BiV pacemakers, the primary benefit is presumed to be improved synchronization of ventricular contraction in the diseased heart; for BiV-ICDs an additional antiarrhythmic benefit is provided by the defibrillation feature.

Given the potential of an incremental survival benefit with BiV-ICDs versus BiV pacing alone, there has been a trend toward utilizing BiV-ICD devices in LV dysfunction patients despite substantially greater initial cost. However, if BiV pacing alone provided predictable antiarrhythmic benefit (even if only in an identifiable subset of LV dysfunction patients) as suggested by both the COMPANION (12) and CARE-HF (16) studies, the individual patient treatment costs could be substantially reduced, and for the same overall economic impact more patients could be benefited.

Antiarrhythmic Potential of CRT

BiV cardiac stimulation improves a range of measures of cardiac function in the setting of moderate-to-severe heart failure and a prolonged QRS interval. Ejection fraction is increased (albeit usually modestly), LV end-diastolic dimension decreases, and mitral regurgitation is reduced in many patients (1, 6, 7). Thus, to the extent that more physiologic pacing offered by BiV systems may reduce ventricular volumes and improve cardiac output, it is reasonable to believe that it would also diminish both wall stretch (1, 17) and levels of circulating catecholamines (18); decreasing the latter are 2 factors may be expected to result in decreased tachyarrhythmia risk.

Several reports offer insight into the relative antiarrhythmic merits of BiV stimulation. In the COMPANION study (12), both BiV pacing and BiV ICDs were comparable in terms of mortality outcome at least to the extent of study follow-up period (442 days for pharmacological therapy alone, 495 days for BiV pacing alone, and 479 for the BiV ICD group). COMPANION was a prospective trial in which NYHA class 3 or 4 patients were randomized to optimal pharmacological therapy (OPT),

OPT plus BiV pacing, or OPT plus BiV ICD treatment. Compared to OPT alone, BiV stimulation whether by pacing alone or in conjunction with defibrillation capability reduced the combined end-point risk of 'all-cause mortality or first all-cause hospitalizations' comparably (BiV pacing 34%, BiV ICD 40%, $p<0.002$ and $p<0.001$ respectively vs OPT alone). In terms of mortality outcome specifically, compared to OPT alone, BiV pacing reduced all-cause deaths by 24% ($p=0.059$) while BiV ICDs reduced the risk by 36% alone ($p=0.003$). In brief, the mortality benefit with BiV ICD tended to be greater than with BiV pacing alone, but the BiV pacing effect was nonetheless very impressive, and a potentially very cost-effective choice.

Further evidence highlighting the potential mortality benefit of BiV pacing was provided by CARE-HF, a randomized and controlled trial encompassing 813 heart failure patients (404 BiV pacing vs 409 medically treated). CARE-HF was the first large study to demonstrate a survival benefit attributable to BiV pacing alone (16). CARE-HF reported a 36% reduction of all cause mortality in patients receiving BiV pacing therapy compared to those treated by medical therapy alone. On the other hand, while overall mortality benefit was clear, the number of sudden deaths among all deaths (35 %) in CARE-HF was concerning. In this context, the potential pro-arrhythmic effects of LV epicardial stimulation have raised the disconcerting thought that CRT pacing mortality benefits may be counter-balanced by adverse effects outcomes in large patient populations (19).

Our own observations, although confined to a small non-randomized population, also suggest that CRT pacing may provide an important antiarrhythmic benefit in some patients, particularly those with the most severe heart failure (20). We examined ventricular arrhythmia burden and ICD treatment frequency in patients in whom worsening heart failure dictated the need for replacing a pre-existing conventional ICD system with a BiV ICD. The availability in each of these individuals of a full-featured ICD, both before and after introduction of BiV stimulation, along with absence of substantial alterations of drug therapy, permitted detailed assessment of the impact of BiV pacing on arrhythmia susceptibility in these individuals. The study population comprised a consecutive series of 18 patients who underwent successful upgrade from conventional ICD therapy to a BiV ICD based solely on conventionally accepted heart failure indications. Patients in this study had been followed for 47±21 months prior to BiV upgrade, and for an additional 14±2 months after upgrade. Presenting arrhythmias were ventricular tachycardia (VT) in 55%, ventricular fibrillation (VF) in 28% and non-sustained VT (NSVT) in 17%. The frequency of appropriate antitachycardia pacing (ATP) applications and ICD shocks was significantly reduced after upgrade to BiV stimulation. During conventional ICD treatment, ATP

was applied in 10/18 (56%) patients compared to 1/18 (3%) following BiV ICD placement. Similarly the number of patients receiving ICD shocks diminished following initiation of BiV stimulation. In essence, our experience suggests that in the setting of diminished left ventricular systolic function and worsening heart failure, BiV pacing does diminish tachyarrhythmia susceptibility as assessed by diminished need for either ICD shocks or ATP.

Recently, Voigt et al (21) provided similar observations to our own. In essence they reported ventricular arrhythmia burden observations in 19 patients (average age 67 ±10 years, average ejection fraction 0.24±0.07) in whom ICD therapy was 'upgraded' from a conventional dual-chamber system to a BIV system. Thereafter (adjusting for observation durations), the number of patients receiving ICD therapy for arrhythmia was reduced, as was the number of detected sustained tachyarrhythmias.

In conclusion, current evidence primarily derived from the COMPANION trial (19) suggests that BiV ICDs do offer greater mortality benefit than does BiV pacing alone. However, several lines of evidence indicate that BiV pacing provides a measurable mortality benefit in its own right. Consequently, while the BiV ICD choice is clearly defendable in most patients, its cost may limit the number of patients capable of accessing such treatment. Furthermore, as suggested by COMPANION, the apparent additional mortality benefit offered by BiV ICDs compared to BiV pacing alone may be relatively small. BiV pacing may be more cost-effective from an overall economic impact perspective by permitting treatment of much larger numbers of individuals.

Certain subsets of patients may be particularly best targeted by BiV pacing rather than BiV ICDS. In particular, individuals with very severe LV dysfunction and apparently worsening heart failure may be more prone to die from disease complications other than ventricular tachyarrhythmias. This may be the group at highest risk of electro-mechanical dissociation and bradyarrhythmias – conditions not readily reversed by defibrillation. Such patients may be better served by BiV pacing alone, particularly since it may not be ethical to withhold the potential quality-of-life benefit that may result from a more physiologic stimulation sequence. This latter approach would be especially reasonable in those individuals with existing conventional pacemakers already in place. Placement of a single additional lead may provide months, even if not years, of more comfortable life for these patients.

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CME QUESTIONS

1. **Biventricular stimulation is believed to reduce susceptibility to ventricular arrhythmias in heart failure patients by all of the following mechanisms, EXCEPT WHICH ONE OF THE FOLLOWING:**

   A. Reducing end-diastolic left ventricular volume
   B. Shortening QT interval by reversing transmural repolarization
   C. Improving neurohumoral status
   D. Diminishing Mitral regurgitation
   E. Reducing end-systolic volume

ANS> B

2. **The CARE-HF study showed which one of the following:**

   A. Biventricular pacemakers may reduce mortality in heart failure patients compared to medical therapy alone
   B. Patients with low ejection fractions treated with ICDs exhibit improved survival than do patients treated with optimal medical therapy alone
   C. Biventricular ICD therapy offers a mortality benefit compared to biventricular pacing alone
   D. All of the above are correct

ANS> A

3. **Both biventricular pacemakers and biventricular ICDs offer the same potential cardiac resynchronization hemodynamic benefit**

   A. True
   B. False

ANS> A