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EDITORIAL COMMENT

His Bundle Pacing

The Holy Grail of Pacing?*

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Cardiac pacing has been the cornerstone of therapy for management of bradyarrhythmias since the early 1960s. For decades, right ventricular (RV) apical pacing was the primary strategy to improve survival and quality of life in patients requiring permanent ventricular pacing. The deleterious effects of long-term RV apical pacing on left ventricle (LV) function have been documented by several large prospective studies. In the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial, patients with LV dysfunction randomized to a dual-chamber pacing mode (DDDR) with a baseline pacing rate of 70 beats/min had a significantly higher primary composite endpoint of death or heart failure (HF) hospitalization than patients randomized to a single-chamber ventricular pacing mode (VVI) with backup pacing at 40 beats/min (1). Similar findings were reported in a substudy of the MOST (MOde Selection Trial), where >40% RV apical pacing was strongly associated with increased incidence of HF hospitalization and atrial fibrillation, even though most patients had normal cardiac function (2). Worse outcomes are associated with increased RV apical pacing, especially in patients with HF primarily attributed to intra- and interventricular dyssynchrony created by nonphysiologic activation of the ventricles (3). Furthermore, chronic RV apical pacing has also been shown to result in left atrial remodeling and impair atrial function, predisposing to atrial arrhythmias (4-6).

The quest for an optimal ventricular pacing site to curtail these potential adverse outcomes has been one of the biggest challenges in the field of cardiac electrophysiology over the past 2 decades. Several studies have examined RV nonapical pacing sites (RV outflow tract and RV septal pacing); however, data for the potential benefits of mitigating LV dysfunction have conflicted (7-9). Cardiac resynchronization therapy (CRT) was developed for patients with HF and cardiac dyssynchrony, particularly those with left bundle branch block, and demonstrated significant improvement in HF symptoms, quality of life, and more importantly, reduction in all-cause mortality (10-12). The beneficial effects of CRT are attributed to resynchronization-induced reduction in cardiac dyssynchrony, leading to a sustained increase in LV performance, favorable LV remodeling, and improvement of LVEF (11). CRT has also been shown to be superior to chronic RV pacing in patients with high-grade atrioventricular block and LV ejection fraction (EF) of 50% or less (13). However, CRT therapy may not always be feasible due to technical difficulties, and a significant percentage of patients may not respond in a predictable way to this pacing therapy (14). There are also limited data for the benefit of CRT among patients with right bundle branch block (12).

The advent of His bundle pacing (HBP) as an alternative site of pacing holds tremendous promise as it provides a more physiological, simultaneous activation of both the ventricles, thus circumventing the detrimental effects of the mechanical dyssynchrony seen with RV pacing. Since the original description of HBP in 2000 by Deshmukh et al. (15) in patients with atrial fibrillation and cardiomyopathy, several investigators from around the world have reported the safety, feasibility, and superiority of HBP over RV pacing in routine clinical practice. His bundle pacemakers have been successfully implanted in patients with normal His-Purkinje conduction (15-18) bundle branch block, complete nodal and infranodal atrioventricular block (19,20), and in selected patients

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as an alternative to CRT (21-23). Several small studies have demonstrated that HBP significantly improves LV hemodynamic parameters, LVEF, and New York Heart Association functional class and decreases HF hospitalizations, an effect similar to that with CRT (24,25). HBP pacing also improves left atrial function compared with conventional RV pacing (6).

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In this issue of the *Journal*, Abdelrahman et al. (26) present the largest, single-center series of HBP published to date, comparing the clinical outcomes of HBP to RV pacing (RVP) from Geisinger HBP registry (26). All consecutive patients with standard indications for a pacemaker implantation (35% for sinus node dysfunction and 65% for atrioventricular nodal block) underwent HBP at 1 hospital (332 patients) and a conventional RV lead implantation (433 patients) in a sister hospital. The primary outcome was a composite of death from any cause, first episode of HF hospitalization or the need for upgrade to biventricular pacing.

Permanent HBP was successful in 92% of the patients. The primary composite endpoint was significantly lower in the HBP group than in the RVP group (25% vs. 31.6%, respectively; hazard ratio [HR]: 0.71; $p = 0.02$) over a mean follow-up duration of 725 ± 423 days. The primary outcome was largely driven by a significant decrease in HF hospitalization in the HBP group than with the RVP group (12.4% vs. 17.6%, respectively; HR: 0.63; $p = 0.02$). When the outcomes were stratified based on ventricular pacing burden, patients with higher ventricular pacing burden >20% had significantly lower primary composite endpoint in the HBP group than in the RVP group (25.3% vs. 35.6%, respectively; HR: 0.65; $p = 0.02$). Again, the results were largely driven by a significant decrease in HF hospitalization in the HBP group than in the RVP group (12.4% vs. 20.1%, respectively; HR 0.54; $p = 0.01$). Among patients with ventricular pacing burden ≤20%, the primary outcome was similar in both the HBP and RVP groups (22% vs. 23.7%, respectively; $p = 0.34$). Similar to prior published reports (3) in the RVP group, patients with baseline LVEF <50% had significantly increased risk for reaching the primary endpoint (HR: 1.785; 95% confidence interval [CI]: 1.054 to 3.023; $p = 0.03$) compared to patients with LVEF >50%. This was not observed in the HBP group when stratified according to LVEF.

The authors are to be commended for this important contribution to our understanding of long-term outcomes between the HBP and RVP. To date, there have been no randomized control trials comparing these 2 strategies for permanent ventricular pacing. Nonetheless, performing randomized controlled trials is expensive and not always feasible. The present study was conducted at 2 different institutions, only 60 miles apart and part of the same health system, which explains the similar patient profile. In aggregate, the results are striking and overwhelmingly support HBP, especially in patients who are anticipated to have high degree of ventricular pacing burden (e.g., >20%) for reduction in adverse outcomes of death and HF hospitalization or need for upgrade to biventricular pacing. The superiority of HBP was driven solely by reduction in first HF hospitalization event, and mortality was not influenced by the choice of the device. As the authors appropriately acknowledged, studies with larger cohorts and longer follow-up periods are needed to show mortality benefit of HBP over RVP.

Several investigators have reported detrimental effects of chronic RV pacing. In a large tertiary care referral center, the incidence of pacing-induced cardiomyopathy was 12.3% among patients with complete heart block and normal EF who had RV pacing burden of >20% (27). In a retrospective, observational study derived from a large administrative database examining 7,000 patients with complete heart block and no prior HF, there was a heightened risk of HF diagnosis within 6 months of pacemaker implantation (HR: 1.62%; 95% CI: 1.48 to 1.79; $p < 0.001$), presumed to be secondary to chronic RV pacing (28). Results of the present study show feasibility of HBP, and use of this pacing modality should be the primary strategy in patients with anticipated high burden of ventricular pacing to prevent pacing induced cardiomyopathy. In addition to these important prognostic findings, a few notable observations from the present study warrant comment.

First, HBP is a relatively new pacing modality, and as with any new technique, there will be a steep learning curve for novice implanters. The same group reported a success rate of permanent HBP implantation of 80% during their initial experience in 2011 (29), as opposed to 92% in the present study conducted between 2013 and 2016. Despite operators' years of experience in the present study, the mean procedure (70 ± 34 min vs. 55 ± 25 min; $p < 0.01$) and fluoroscopy duration (10 ± 7 min vs. 7 ± 5 min; $p < 0.01$) were significantly longer in the HBP group than in the RVP group. Continued efforts to improve the delivery sheaths and mapping systems may circumvent some of the obstacles faced with current technology.

Second, the implant characteristics of HBP, as opposed to RVP, are worth mentioning. Generally, the R-wave amplitudes and lead impedances were significantly lower in the HBP group than in the RVP