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Editorial commentary: His bundle pacing: The road ahead ☆

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His bundle pacing (HBP) has emerged as one of the most exciting developments in cardiac electrophysiology in recent years. This has resulted in an expanding body of evidence but has been driven primarily by enthusiastic physicians. Embraced on social media with a bottom-up, decentralized network of implanters guided by leading proponents, HBP has also broken the mold of conventional top-down dissemination of novel medical practice. In "Updates on His Bundle Pacing: The Road More Traveled Lately" in this issue of the Journal, Ezzeddine and Dandamudi set out the rationale for HBP due to deleterious effects of right ventricular pacing (RVP) and describe the progress made in every aspect of HBP from patient selection and indications through implant technique and equipment to programming and long term lead performance [1].

Ezzeddine and Dandamudi's wide-ranging and comprehensive review allows an illuminating comparison of the early phases of Cardiac Resynchronization Therapy (CRT) via biventricular pacing (BVP) and HBP. The era of biventricular CRT for heart failure with broad QRS began with Leclerq et al.'s seminal hemodynamic observations in 1998 [2]. In the decade that followed, over 6000 patients were randomized to BVP vs conventional treatment with either medical therapy or backup pacing [3–5]. This cemented biventricular CRT as a Class 1A recommendation for improving prognosis and symptoms by the end of this decade [3]. Although Narula demonstrated HBP normalizing left bundle branch block as early as 1977 [6], CRT by means of permanent HBP was first reported in 2005 [7] and Lustgarten et al.'s crossover comparison with BVP in 2015 [8] was the first study using the modern, stylet-less technique. Thus by 2020 we will be at least half way through the first decade of His bundle CRT, using dedicated tools, yet trial registrations on clinicaltrials.gov suggest that less than 150 patients will have been randomized to His bundle CRT vs biventricular CRT by then (NCT03452462, NCT02700425, NCT02805465, NCT03614169).

This randomization gap between HBP and conventional therapy exists across all the major potential indications set out in Ezzeddine and Dandamudi's review. For CRT (HBP vs BVP), bradycardia pacing (HBP vs RVP), AV node ablation (HBP vs BVP or RVP) and prolonged PR interval (HBP vs medical therapy), HBP's established comparator has RCT evidence for its own efficacy that HBP does not yet enjoy. Exploring the reasons for this evidence gap reveals important features of HBP.

In fact, the latter indication, prolonged PR interval, is the only population to have a larger scale HBP randomized controlled trial currently recruiting (HOPE-HF NCT02671903 [9]). It is no coincidence that this is the only population for whom there is no conventional pacing therapy available: his bundle pacing does not need to supplant RVP or BVP. This is helpful for recruitment: patients with refractory heart failure symptoms are very willing to enroll into a crossover design when the alternative is the certainty of continued deterioration. Furthermore, since HBP clearly carries upfront risk and expense compared to continued medical therapy, powering for superiority is uncontroversial.

Trial design for other potential HBP indications is less certain. The normalization of LBBB observed with His bundle CRT suggests that HBP may be superior to BVP for important clinical outcomes. His bundle CRT has been perceived as challenging but Ezzeddine and Dandamudi point out that the reported technical success of His bundle CRT has greatly improved [1]. However the degree, success-rates and thresholds of real-world LBBB correction by less experienced operators is likely to be lower. Furthermore, biventricular pacing has established efficacy, making superiority a tall order for His bundle CRT. These are not reasons to eschew randomization altogether as there is an argument to be made for non-inferiority designs if overall efficacy is similar.

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Despite twenty years of implant tool and technique refinement, conventional biventricular CRT is a time consuming, often technically challenging procedure, requiring nephrotoxic contrast and constrained by coronary sinus anatomy. His bundle CRT is in the infancy of technique and tool development but already carries many advantages over BVP, before even considering its resynchronization effects. His bundle CRT offers quicker, easier, contrast-free implants in many patients, no matter how accessible or suitable the coronary sinus branches are. It should be noted that BVP implant technique and technology developed alongside its RCTs.

RCTs of HBP for bradycardia and AV nodal ablation face an interesting comparator challenge. BLOCK-HF [10], among other trials, showed clinically important benefits of BVP over RVP in patients with a ventricular pacing indication and moderate left ventricular systolic dysfunction. Several trials have shown superiority of BVP over RVP for AV node ablation patients. However, society guidelines [11] offer limited support for BVP in these contexts (IIa or b) and clinical practice does not reflect this, with RVP often the standard of care. Using RVP as conventional therapy would represent real-world practice but this strategy opens up HBP to accusations of knocking down an inferior straw man. Comparing HBP to BVP, however, may require many more participants to adequately power and may not be considered generalizable.

His bundle pacing for any indication faces an additional obstacle to randomization that is inherent to the principle of conduction system pacing. By virtue of its physiological nature, many are persuaded of His bundle pacing's merits by its mechanism of action alone or in combination with highly persuasive observational evidence from pioneering leaders in the field [12,13].

Finally, industry partners are essential to the funding, technical support and logistics of HBP RCTs but it appears that a perceived lack of incentive has so far inhibited industrial involvement in major clinical trials; instead their focus is on HBP education and training. This may change as more companies enter this commercial space, particularly when introducing novel device programming designed for HBP.

Ezzeddine and Dandamudi's review charts a clear course from the past to the present of HBP but its future will depend on how stakeholders, including clinicians, patients, academics and industry, engage with the challenges of RCTs in this field.

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