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INVITED EDITORIAL

His bundle pacing for correcting atrioventricular dyssynchrony in heart failure: HYPE or HOPE?

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This article refers to 'Effects of haemodynamically atrioventricular optimized His bundle pacing on heart failure symptoms and exercise capacity: the His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) randomized, double-blind, cross-over trial' by Z.I. Whinnett *et al.*, published in this issue on pages 274–283.

Heart failure is a clinical syndrome due to structural and/or functional abnormalities of the heart that result in elevated intracardiac pressures and/or inadequate cardiac output. In patients with heart failure with reduced (≤40%) ejection fraction (HFrEF), impaired left ventricular filling due to atrio-ventricular (AV) dyssynchrony resulting from prolonged PR intervals may contribute to pump failure. The mechanisms which have been suggested are transmitral E/A wave fusion leading to shortening of left ventricular filling time, diastolic mitral regurgitation, and in case of very prolonged PR intervals, simultaneous atrial and ventricular contraction.[1] Computer simulations have suggested that AV timing plays a crucial role in cardiac resynchronization therapy (CRT) by impacting ventricular filling.[2]

In the COMPANION trial, a PR ≥ 200 ms was observed in 52% of the subjects and was associated with increased mortality and heart failure hospitalization in patients under medical therapy (HR 1.41, $P = 0.44$). Cardiac resynchronization therapy (CRT) had a greater impact on reducing these endpoints in patients with a prolonged PR (HR 0.54 $P < 0.01$) than in those with a normal PR (HR 0.71, $P = 0.019$).[3] A subgroup analysis of MADIT-CRT showed that patients with non-left bundle branch block QRS morphology and a PR ≥230 ms benefitted from CRT in terms of heart failure and mortality, whereas those with intervals <230 ms did not.[4] Patients with a narrow QRS have been shown in the EchoCRT trial to have increased mortality when treated with CRT,[5] so biventricular pacing in patients with a prolonged PR interval in this population is unlikely to be of benefit. Right ventricular pacing (RVP) is known to have a detrimental effect on left ventricular ejection fraction resulting from dyssynchrony.[6,7] His bundle pacing (HBP) on the other hand provides a more physiological form of pacing and provides an opportunity to correct AV dyssynchrony without inducing ventricular dyssynchrony.

In the current issue of the Journal, Whinnett *et al.*[8] present the results of the HOPE-HF study, which evaluated whether HBP improves the primary endpoint of peak oxygen uptake in patients with HFrEF, PR interval >200 ms and either QRS <140 ms or right bundle branch block. A total of 167 patients were randomized using a cross-over design to 6 months of DDD pacing (with non-invasive haemodynamic optimization of AV intervals) and 6 months of backup RVP, with double-blinding of treatment allocation. There was no significant difference in the primary endpoint, nor in the secondary endpoints of left ventricular ejection fraction, left ventricular diameters, B-type natriuretic peptide or quality of life as measured by EQ-5D5L visual analogue scale. However, there was a slight improvement in quality of life as measured by the Minnesota Living with Heart Failure Questionnaire and 112/167 (67%) of patients preferred the HBP pacing period.

Although the results are disappointing, the authors may be congratulated for their endeavor and for having conducted the largest randomized controlled study published to date. A number of points may be raised regarding the findings.

First, this was not a study randomizing HBP versus no pacing. During the HBP-off phase, patients were programmed to 'backup' RVP at 30 bpm, presumably mostly in the DDD mode as atrial pacing was on average 16 ± 28% and ventricular pacing 13 ± 28%. It has been shown that as little as 20% RVP may result in pacing-induced cardiomyopathy, and that pacing percentage as a continuous variable is significantly associated with outcome (i.e. that there is no minimum percentage of RVP which has been demonstrated to be harmless).[9,10] Therefore, the only positive findings of the study may have resulted from unnecessary RVP, which may have been avoided by turning off pacing (ODO/OVO mode) or minimized by programming to DDI/VVI 30 bpm.

Second, the average PR interval in the study was only 249 ms with a mean optimized AV delay of 195 ms. Therefore, as acknowledged by the authors, the reduction in AV delay was modest, and

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treatment effect may have been greater in a cohort with longer PR intervals. Indeed, patients who would have been most likely to benefit are those with extremely long PR intervals in whom a 'P on T' phenomenon may be observed at rest or during exercise, leading to a 'pseudo-pacemaker syndrome'. In these patients, atrial and ventricular contraction occur simultaneously, thereby reducing ventricular filling, increasing atrial pressure and resulting in a backflow of blood. Very long PR intervals may also result from algorithms designed to minimize ventricular pacing.[11] RVP has been shown to improve symptoms in these patients,[12] with class IIa level of evidence C recommendation for pacing in symptomatic first-degree AV block (PR >300 ms) according to current guidelines.[10] In these patients with HFrEF and a narrow QRS, HBP is indeed likely to be superior to RVP and even to CRT, but there was no sub-analysis in HOPE-HF of efficacy stratified according to baseline PR interval.

Third, the authors did not evaluate transmitral flow by echocardiography. This is important as patients with HFrEF may have a restrictive pattern, with low-velocity A waves in whom atrial filling contributes little to ventricular filling and are thus less likely to benefit from AV coupling. E/A wave fusion resulting from PR prolongation is often labelled as being detrimental, and prolongation of ventricular filling time with E/A wave separation resulting from ventricular pacing is beneficial. However, it is important to remember that it is the E/A wave *velocity-time-integral* and not the E/A wave *duration* (i.e. ventricular filling time) which determines ventricular filling. Also, E/A wave fusion not only depends on the PR interval but also on heart rate and is physiological during tachycardia. Furthermore, diastolic mitral regurgitation could also have been evaluated by echocardiography, although it is usually only minimal in degree and the correction of this factor is likely to play a minor role in improving haemodynamics.[11] In an elegant acute haemodynamic study on 8 pigs and 22 CRT patients, Salden *et al.*[13] showed that at AV interval programming impacted left ventricular filling and cardiac output by increasing forward flow over the mitral valve (area under the E and A waves) and reducing diastolic mitral regurgitation, although how these factors react to physiological conditions and impact clinical outcome over follow-up is unknown.

Fourth, interatrial conduction delay may mitigate the effect of a long PR interval by delaying left atrial conduction and thereby re-establish left AV synchrony.[11] The HOPE-HF study did not present any data on P-wave duration, and this important factor was not evaluated.

Finally, haemodynamic impact of varying AV delays is not always straightforward. In the BRAVO study, performed by the same group as HOPE-HF, as many as 60% of CRT patients had little impact on E-A wave separation by decrementing AV intervals.[14]

On a positive note, HOPE-HF has shown that HBP was successful in 93% of patients with a single procedure and with reasonable thresholds at randomization and 12 months (1.33 ± 1.07 V and 1.47 ± 1.21 V at 1 ms), and did not adversely affect outcome in patients with HFrEF. Lead dislodgment or significant rise in threshold compromising participation in the study was observed in 5.7% of patients, which is in line with previous data reporting a 6% rate of HBP lead revision,[15] which is nevertheless high. Left bundle branch area pacing is gaining adoption and has overtaken HBP according to a recent survey,[16] mainly due to superior electrical parameters. It is possible that conduction system pacing will ultimately replace RVP in many indications, and be used *in lieu* of biventricular pacing in selected cases, for example, in HFrEF patients with a narrow QRS requiring ventricular pacing.

To conclude, HOPE-HF failed to find a benefit of pacing in HFrEF patients with first-degree AV block, but whether conduction system pacing may benefit these patients with more prolonged PR intervals (e.g. >300 ms), deserves further study.

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