European Heart Journal Supplements (2023) **25** (Supplement G), G27–G32
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad116

ESC European Society of Cardiology

Frontiers in conduction system pacing: treatment of long PR in patients with heart failure

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KEYWORDS
First degree AV block;
PR prolongation;
Heart failure

Patients with heart failure who have a prolonged PR interval are at a greater risk of adverse clinical outcomes than those with a normal PR interval. Potential mechanisms of harm relating to prolonged PR intervals include reduced ventricular filling and also the potential progression to a higher degree heart block. There has, however, been relatively little work specifically focusing on isolated PR prolongation as a therapeutic target. Secondary analyses of trials of biventricular pacing in heart failure have suggested that PR prolongation is both a prognostic marker and a promising treatment target. However, while biventricular pacing offers an improved activation pattern, it is nonetheless less physiological than native conduction in patients with a narrow QRS duration, and thus, may not be the ideal option for achieving therapeutic shortening of atrioventricular delay. Conduction system pacing aims to preserve physiological ventricular activation and may therefore be the ideal method for ventricular pacing in patients with isolated PR prolongation. Acute haemodynamic experiments and the recently reported His-optimized pacing evaluated for heart failure (HOPE HF) Randomised Controlled Trial demonstrates the potential benefits of physiological ventricular pacing on patient symptoms and left ventricular function in patients with heart failure.

Introduction

Atrioventricular (AV) conduction delay, identified by the presence of PR interval prolongation, is a potential electrical treatment target for pacing therapy in patients with heart failure. About 15–51% of patients with heart failure are affected by a long PR interval (>200 ms). PR prolongation is an important prognostic marker and is associated with an increased risk of morbidity and mortality.[1,2]

While not all prognostic markers are good treatment targets, in the case of a long PR interval, there are reasons to be optimistic, as the mechanism of harm has the potential to be easily corrected with pacing therapy.

Excessive prolongation of the delay between atrial and ventricular contractions results in reduced cardiac output, due to impairment of ventricular filling and diastolic mitral valvular regurgitation.[3]

Early studies, which used right ventricular pacing to shorten AV delay, suggested that there was the potential to improve cardiac function.[4,5] However, PR interval as a treatment target was not pursued further at that time. This was due to the recognition of the potential harmful effects of ventricular dyssynchrony, resulting from right ventricular (RV) myocardial pacing, which may offset the potential benefits of AV delay shortening.

The success of biventricular pacing in patients with left bundle branch abnormality (LBBB) and the findings from subanalyses of biventricular pacing (BVP) trials reawakened interest in PR interval as a potential treatment target. Patients with LBBB and a prolonged PR interval were found to gain more benefit from BVP, compared with those with a normal PR interval, suggesting that shortening AV delay has the potential to produce increased beneficial effects. Further support for this concept was obtained from trials recruiting patients without LBBB, where only patients with a prolonged PR interval were found to benefit from BVP and not those without a prolonged PR interval.[6]

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Acute haemodynamic studies have demonstrated improvements in left ventricular (LV) function when AV delay is optimized in patients with isolated PR prolongation and impaired ventricular function. The acute haemodynamic improvements appear to be delivered by both reducing mitral regurgitation and improving ventricular filling.[7–9]

The method for delivering ventricular pacing is likely to be important, if pacing therapy is to be delivered to patients with isolated PR prolongation and normal or near-normal LV activation. The beneficial effects of optimizing AV timing may be offset by the introduction of ventricular dyssynchrony relative to intrinsic conduction with non-physiological pacing methods. Right ventricular pacing is known to be harmful when delivered to people with LV impairment.[10] Even biventricular pacing causes harmful prolongation of ventricular activation relative to intrinsic conduction, when it is delivered to people with a narrow intrinsic QRS duration.[11] The BVP-induced ventricular dyssynchrony is the likely mechanism for the harmful effect of BVP when it was delivered to patients with a narrow QRS duration and LV impairment in the Echo-CRT study.[12]

Conduction system pacing may be the ideal method for delivering pacing in this context. By directly stimulating the conduction system, it aims to allow optimization of AV filling time while preserving normal physiological LV activation and not causing ventricular dyssynchrony.[13]

In this review, we discuss the potential role of PR prolongation as a therapeutic target for pacing therapy in patients with heart failure.

PR prolongation: potential mechanisms of harm

In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronisation Therapy) trial, of patients without LBBB who were randomized to the control arm (implantable cardioverter-defibrillator, ICD therapy), patients with a prolonged PR interval (>230 ms) were observed to have a significantly higher risk of heart failure events compared with those with a PR interval <230 ms (60 vs. 26%).[2] This finding was confirmed in other device trials.[14,15] These findings suggest that PR prolongation is an important prognostic maker in patients with heart failure.

The PR interval records the time between onset of atrial and ventricular activation, which is prolonged in the presence of AV conduction disease. Excessive prolongation of the interval between atrial and ventricular contractions can adversely impact cardiac function via two mechanisms. (i) *Suboptimal ventricular filling:* The passive ventricular filling phase (detected by the *E*-wave on the mitral valve pulse wave Doppler) becomes fused with or prematurely interrupted by atrial contraction (*A*-wave). This leads to a reduction in ventricular filling time. (ii) *Diastolic mitral regurgitation:* Early atrial contraction results in the prolongation of the interval before the onset of ventricular activation. Atrial relaxation, which results in a drop in atrial pressure, occurs before papillary muscle contraction, which means the mitral valve is not closed. The end result of the reduced ventricular filling is a decrease in stroke volume due to a reduction in length-dependent myocardial activation via the Frank–Starling mechanism. Overall, these mechanisms can lead to a reduction in cardiac output, but even the individual component of diastolic mitral regurgitation could be responsible for patient morbidity (*Figure 1*).

PR interval measured using the electrocardiogram (ECG) is a quick and simple method for screening for patients who might have pathological prolongation between atrial and ventricular activation. There are, however, limitations to this method. In patients with LV impairment, prolongation of left-sided AV delay, rather than right-sided AV delay, is likely to have the greatest impact on cardiac output. PR interval does not directly measure left-sided AV delay, but it measures earliest atrial activation and earliest ventricular activation. Left-sided AV delay can be impacted by factors that are not measured by the PR interval, such as atrial activation time, intra-atrial conduction delay, and delay in LV activation due to left conduction system disease.

PR prolongation: a potential therapeutic target in heart failure

Using pacing therapy to shorten AV delay is not a novel concept. It was first investigated utilizing dual-chamber pacing with a right ventricular myocardial pacing lead. But despite initial promising results, when it was tested in a randomized trial, it was not found to lead to clinical benefit.[5] This finding, however, does not disprove the long PR hypothesis, but simply highlights the nuanced fact that the interventricular dyssynchrony mandated by right ventricular pacing is likely to offset the potential benefit from shortening pathologically long PR intervals.[9] The emergence of LBBB as a treatment target and the recognition of the harmful effects of right ventricular pacing, subsequently, for a while, tempered interest in PR interval as a treatment target.

The findings from subanalyses of BVP trials, however, rekindled research into PR interval as a treatment target in patients with heart failure. Patients with LBBB and a prolonged PR interval were found to gain more benefit from BVP, compared with those with a normal PR interval, suggesting that shortening prolonged AV delay has the potential to produce improved outcomes.

The COMPANION trial randomized 1520 heart failure patients to either medical therapy or BVP and 51% had PR prolongation (mean 230 ± 34 ms). Of those with prolonged PR interval randomized to medical therapy, there was a 41% increase in all-cause mortality and hospitalization. Although no significant interaction was found between PR intervals and trial outcomes ($P = 0.17$), the investigators found that CRT effectiveness was greater in patients dichotomized by PR > 200 ms (0.54, $P < 0.001$) compared with those with shorter PR intervals (0.71, $P > 0.02$).[14]

However, not all analyses of biventricular pacing in RCTs have shown increased benefit in patients with a prolonged PR interval. In the CARE-HF trial, patients in both arms (medical therapy only or randomized to CRT); a prolonged PR interval [median 198 ms, interquartile range (IQR) 180–208] predicted increased hospitalization

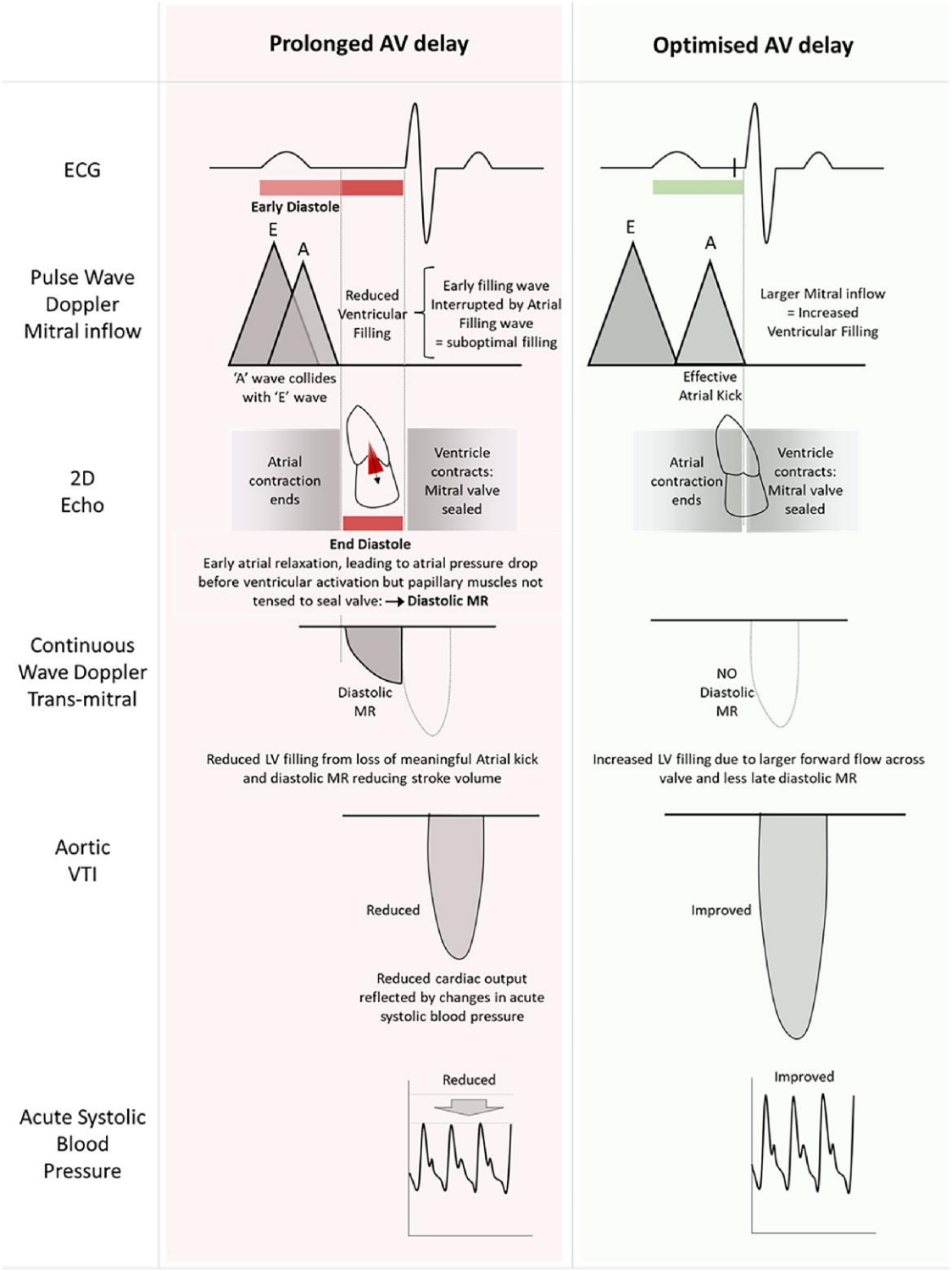

Figure 1 Left-side of figure shows potential mechanisms of harm in patients with prolonged AV delay; including reduced ventricular filling due to interruption of ventricular filling by the early atrial filling wave and also diastolic mitral regurgitation. Right side of figure shows optimal AV timing with normal EA wave timing and reduced opportunity for diastolic mitral regurgitation.

and death. However, despite a marked shortening of PR interval in the CRT group (3-month median PR 160 ms; IQR 140–180 ms), adverse outcomes remained consistent across both arms.[15]

The majority of other subgroup analyses of biventricular pacing RCTs suggest greater risk when a prolonged PR interval is left untreated (control group); however, this is not universally the case (for example, the REVERSE trial).[16] Furthermore, the majority of subgroup analyses have suggested greater benefit when potentially pathological PR prolongation is shortened by biventricular pacing, but this finding is not always the case.[16]

Assuming that the prolonged PR hypothesis is true, the presence of neutral or negative outcomes from targeted treatment might relate to (i) the delivery of biventricular pacing (which could offset AV delay optimization benefit if biventricular pacing is suboptimal), (ii) the approach for selecting the programmed paced AV delay (which could maintain or even worsen AV dyssynchrony), and (iii) the possibility that dichotomizing true AV dyssynchrony on the basis of a measured PR integer may be an oversimplification in identifying patients who have harmful AV dyssynchrony, which is amenable to optimization with pacing techniques.

Interestingly, improving AV timing appears to be an integral part of the mechanism through which BVP delivers benefit to patients with LBBB. Left-sided AV delay may be prolonged even in the presence of a normal PR interval, due to delayed LV activation occurring because of LBBB. Data from both computer modelling studies and acute haemodynamic studies in patients suggest that improving AV timing during conventional cardiac resynchronization therapy (BVP delivered to patients with LBBB) may be responsible for around two-thirds of the benefit of this therapy, while only about one-third is due to ventricular resynchronization.[17,18]

Therefore, the findings from patients with LBBB provide support for the concept that improving AV timing with pacing therapy has the potential to deliver beneficial effects. This group of patients, however, are benefiting from both AV delay shortening and ventricular resynchronization. The next question is whether targeting isolated AV prolongation (in the absence of LBBB) has the potential to lead to clinical benefits.

Support for this concept is provided by data from BVP trials. Patients without LBBB [i.e. right bundle branch abnormality (RBBB), non-specific interventricular conduction disease] generally do not benefit from BVP.[19] This may be because there is limited opportunity for delivery of ventricular resynchronization with BVP in these patients. Ventricular activation time is not reduced, relative to intrinsic conduction, when BVP pacing is delivered to patients with non-specific interventricular conduction delay.[11] However, patients with non-LBBB QRS prolongation who have a prolonged PR interval appear to gain benefit from BVP. The logical conclusion must be that this is through the benefit of AV delay optimization.

In the MADIT-CRT trial, 534 patients had either RBBB or IVCD (interventricular conduction delay) (non-LBBB cohort). In this non-LBBB group, BVP conferred a 67% reduction in risk of HF and death [hazard ratio 0.33, 95% confidence interval (CI) 0.16–0.69, $P = 0.003$] in patients with a PR interval >230 ms; however, strikingly, it trended towards harm for patients with a normal or borderline PR interval (<230 ms).[2]

Using pacing therapy to shorten AV delay in patients with a narrow QRS duration presents an additional challenge, as BVP may prolong ventricular activation time relative to intrinsic conduction. This pacing-induced ventricular dyssynchrony has the potential to offset the beneficial effects of optimizing AV timing.

Salden *et al.* performed an acute haemodynamic study assessing the impact of delivering AV-optimized BVP to patients with a narrow QRS or non-LBBB (mean QRS duration 123 ± 19 ms). They observed significant improvements in LV stroke volume and stroke work (34 ± 40 and 26 ± 31%, respectively) with AV-optimized BVP. Using computer simulations and animal studies, they demonstrated that this improvement was delivered by increasing LV fulling due to both larger mitral inflow (*E*- and *A*-wave areas) and a reduction in diastolic mitral regurgitation.[9]

We have also similarly observed a significant acute haemodynamic benefit, with AV-optimized His bundle pacing in heart failure patients with PR interval prolongation (mean, 254 ± 62 ms) and narrow QRS duration ($n = 13$; mean QRS duration: 119 ± 17 ms) or right bundle branch block ($n = 3$; mean, QRS duration: 156 ± 18 ms). The magnitude of haemodynamic improvement was ~60% of that which is typically seen when biventricular pacing is delivered to patients with LBBB. When this is contextualized, while the benefit is only 60%, this is a patient cohort with heart failure and narrow QRS, who would otherwise not have any pacing modalities available as a therapeutic strategy.[18]

Although the available data so far have shown that biventricular pacing can shorten prolonged AV delay in patients with LBBB, RBBB, IVCD, and narrow QRS, CRT delivery with biventricular pacing can induce new ventricular dyssynchrony if it prolongs ventricular activation. This can potentially offset any benefit derived from targeting AV dyssynchrony and is the premise upon which novel pacing methods have been explored as a heart failure therapy for patients with PR prolongation.

Utilizing conduction system pacing approaches for treatment of PR prolongation in heart failure

Targeting pathological PR prolongation through pacing approaches mandates obligatory artificial stimulation of the ventricles. The choice of ventricular pacing approach has the potential to determine whether the intervention is beneficial or harmful. Patients with preserved intrinsic ventricular activation (narrow QRS) are particularly vulnerable to ventricular pacing–induced desynchrony. In these situations, the beneficial effects of PR shortening might be offset by the non-physiological ventricular activation occurring both through the use of right ventricular pacing and biventricular pacing.

His bundle pacing allows AV delay shortening with either no (during selective capture) or (usually) only minimal (during non-selective capture) prolongation of ventricular activation time. His bundle pacing is the most physiological method for ventricular pacing, which either preserves native physiological activation in patients with a narrow QRS at baseline or may even provide ventricular resynchronization when delivered to patients with RBBB or LBBB.

Over the past 5 years, left bundle branch area pacing (LBBAP) has emerged as the dominant approach for conduction system pacing. It is potentially more attractive than His bundle pacing, as it is associated with lower-capture thresholds, less incidence of late threshold rises, and more readily overcomes distal sites of conduction block. However, LBBAP typically results in non-physiological right ventricular activation, which

could theoretically offset some of the benefits of optimizing AV delay. We compared His bundle pacing with LBBAP in a within-patient study where we compared ventricular activation times and patterns and acute haemodynamic responses to pacing.[20] We found that LV activation time and pattern were the same with both pacing approaches. Left bundle branch area pacing did result in a modest increase in total ventricular activation time, due to slower right ventricular activation, but we did not detect a difference in acute haemodynamic response between the approaches.

It is, therefore, reasonable to assume similar benefit from the more pragmatic LBBAP compared with His bundle pacing when targeting PR prolongation.

His-optimized pacing evaluated for heart failure: a randomized trial of atrioventricular-optimized His bundle pacing for heart failure

Building on the promising acute haemodynamic data of His bundle pacing in patients with PR prolongation, the His-optimized pacing evaluated for heart failure (HOPE-HF) trial was the first randomized, placebo-controlled, blinded cross-over trial of AV-optimized His bundle pacing in patients with heart failure (left ventricular ejection fraction, LVEF ≤40%) and a prolonged PR interval (≥200 ms) without left bundle branch block.[21] The trial aimed to test whether the acute haemodynamic effects of AV-optimized His bundle pacing translated into an improvement in exercise capacity and heart failure-specific quality-of-life measurements. Safety endpoints included impacts on cardiac function and BNP (B-type natriuretic peptide). All patients had a His lead implanted, and optimal AV delay was identified using non-invasive haemodynamic assessment with beat-by-beat blood pressure and an algorithm of multiple repeated measurements to improve precision. Pacing was compared with intrinsic conduction, which meant that the acute haemodynamic impact of pacing could be assessed.

The trial found no overall benefit on its primary endpoint of a significant improvement in peak VO_2. However, the AV-optimized His bundle pacing period was preferred by the majority of patients (76%) and resulted in a significant improvement in heart failure quality-of-life as measured by the Minnesota Living with Heart Failure questionnaire (−3.7, 95% CI −7.1 to −0.3, $P = 0.03$). Importantly, there was no signal of harm during the His bundle pacing period, with no decline in ventricular function or increase in BNP. This contrasts with all other forms of ventricular pacing which have been found to be harmful when delivered to patients with a narrow QRS duration and LV impairment.

Recently presented subgroup analyses did not show an interaction between PR interval and endpoint outcomes. However, interestingly, we found that patients who obtained an improvement in acute haemodynamics (measured at time of randomization) of at least a 1 mmHg with AV-optimized His bundle pacing showed improvement in all endpoints (peak VO_2, quality-of-life (QOL), and LV function). This suggests that there is a group of patients who are likely to benefit from pacing therapy to optimize AV interval, but it appears that using the PR interval measured on the ECG is an imperfect method for identifying patients who are likely to respond.[22]

As discussed above, PR interval has potential limitations as a selection method, for AV-optimized pacing therapy. It does not directly assess left-sided AV delay, whereas prolongation of left-sided AV delay is likely to be the dominant mechanism of harm in patients with LV impairment. Left atrial activation time, intra-atrial delay, and the presence of left-sided conduction abnormalities all impact left-sided AV delay and are not directly measured in the simple measurement of PR interval. Furthermore, there may be additional patient factors beyond left-sided AV delay which determine whether a patient is likely to benefit from optimization of AV delay. For example, atrial disease which leads to reduced left atrial compliance could theoretically impact the response to AV optimization. Increased stiffness may result in smaller volume effects at similar changes in diastolic pressures. As a result, haemodynamic response to AV optimization may be reduced in stiffer hearts; further work is required to investigate this.

How to programme atrioventricular delay in patients with prolonged PR interval

While out-of-the-box settings for AV delay programming have been shown to be no worse than personalized AV delay programming in patients with normal PR interval (<200 ms) programming, optimal AV delay for patients with longer PR intervals (and therefore potentially more complex mechanisms underpinning their AV dyssynchrony) is more challenging. Atrioventricular delay optimization can be done using echocardiographic measures, haemodynamic protocols, heart sounds, or electrical measures.[23-25] Determining the most pragmatic, user-friendly, and efficient approach remains challenging for the widespread adoption of optimal AV delay programming. Given that multiple factors can interact to determine optimal programmed AV delay (such as atrial conduction time, whether there is atrial pacing or intrinsic rhythm, ventricular activation time, and possibly left atrial substrate), we favour a measure such as acute blood pressure measurements, which reflect overall net changes in cardiac output.

Conclusions

Patients with PR prolongation and heart failure are at a greater risk of adverse clinical outcomes, compared with those with a normal PR interval. The mechanism of harm is likely to be due to the prolongation of left-sided AV delay, which adversely impacts ventricular filling. Data from BVP trials suggest that shortening AV conduction time can lead to improved clinical outcomes when delivered to patients with QRS prolongation.

Isolated AV conduction delay (patients without LBBB) represents a potential treatment target. Conduction system pacing may be the optimal method for delivering ventricular pacing to this group of patients. It aims to maintain physiological LV activation, thereby avoiding

pacing-induced desynchrony, which otherwise may well offset the potential beneficial effects of optimizing AV delay.

The results of the HOPE-HF trial were promising, and they showed symptomatic improvement without a signal for harm, when AV-optimized His pacing was delivered to patients with PR prolongation and LV impairment, without LBBB. Refining patient selection remains a challenge, as does the delivery of a reliable and pragmatic method of identifying optimal AV delays for programming.

Funding

This manuscript was published as part of a supplement sponsored by Medtronic. The content was developed independent of the sponsor. Authors did not receive an honorarium.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Nikolaidou T, Ghosh JM, Clark A. Outcomes related to first-degree atrioventricular block and therapeutic implications in patients with heart failure. *JACC Clin Electrophysiol* 2016;**2**:181–192.
2. Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C *et al*. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. *Circ Arrhythm Electrophysiol* 2014;**7**:645–651.
3. Nishimura RA, Hayes DL, Holmes DR, Tajik J. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. *J Am Coll Cardiol* 1995;**25**:281–288.
4. Brecker SJ, Xiao HB, Sparrow J, Gibson DG. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *Lancet* 1992;**340**:1308–1312.
5. Gibson DG, Chamberlain DA, Coltart DJ, Mercer J. Effect of changes in ventricular activation on cardiac haemodynamics in man. Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles. *Br Heart J* 1971;**33**:397–400.
6. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y *et al*. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clin Res Cardiol* 2016;**105**:944–952.
7. Whinnett ZI, Davies JE, Willson K, Manisty CH, Chow AW, Foale RA *et al*. Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. *Heart* 2006;**92**:1628–1634.
8. Sohaib SMA, Wright I, Lim E, Moore P, Lim PB, Koawing M *et al*. Atrioventricular optimized direct His bundle pacing improves acute hemodynamic function in patients with heart failure and PR interval prolongation without left bundle branch block. *JACC Clin Electrophysiol* 2015;**1**:582–591.
9. Salden FCWM, Huntjens PR, Schreurs R, Willemen E, Kuiper M, Wouters P *et al*. Pacing therapy for atrioventricular dromotropathy: a combined computational-experimental-clinical study. *Europace* 2022;**24**:784–795.
10. Wilkoff BL, Kudenchuk PJ, Buxton AE, Sharma A, Cook JR, Bhandari AK *et al*. The DAVID (dual chamber and VVI implantable defibrillator) II trial. *J Am Coll Cardiol* 2009;**53**:872–880.
11. Ploux S, Eschalier R, Whinnett ZI, Lumens J, Derval N, Sacher F *et al*. Electrical dyssynchrony induced by biventricular pacing: implications for patient selection and therapy improvement. *Heart Rhythm* 2015;**12**:782–791.
12. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J *et al*. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
13. Kaza N, Keene D, Whinnett ZI. Generating evidence to support the physiologic promise of conduction system pacing: status and update on conduction system pacing trials. *Card Electrophysiol Clin* 2022;**14**:345–355.
14. Lin J, Buhr KA, Kipp R. Effect of PR interval on outcomes following cardiac resynchronization therapy: a secondary analysis of the COMPANION trial. *J Cardiovasc Electrophysiol* 2017;**28**:185–191.
15. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A *et al*. CARE-HF investigators surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail*. 2009;**11**:699–705.
16. Senfield J, Daubert C, Abraham WT, Ghio S, St John Sutton M, Cerkvenik J *et al*. The impact of the PR interval in patients receiving cardiac resynchronization therapy: results from the REVERSE study. *JACC Clin Electrophysiol* 2017;**3**:818–826.
17. Jones S, Lumens J, Sohaib SMA, Finegold JA, Kanagaratnam P, Tanner M *et al*. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace* 2016;**19**:1178–1186.
18. Arnold A, Shun-Shin M, Ali N, Keene D, Howard JP, Francis DP *et al*. Contributions of atrioventricular delay shortening and ventricular resynchronization to hemodynamic benefits of biventricular pacing. *J Am Coll Cardiol* 2023;**9**:117–119.
19. Keene D, Whinnett ZI. Advances in cardiac resynchronisation therapy: review of indications and delivery options. *Heart* 2022;**108**:889–897.
20. Ali N, Arnold AD, Miyazawa AA, Keene D, Chow JJ, Little I *et al*. Comparison of methods for delivering cardiac resynchronization therapy: an acute electrical and haemodynamic within-patient comparison of left bundle branch area, His bundle, and biventricular pacing. *Europace* 2023;**25**:1060–1067.
21. Whinnett ZI, Shun-Shin MJ, Tanner M, Foley P, Chandrasekaran B, Moore P *et al*. Effects of haemodynamically atrio-ventricular 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. *Eur J Heart Fail* 2023;**25**:274–283.
22. Keene D, Kaza N, Arnold AD, Howard JP, Tanner M, Foley P *et al*. Predictors of the efficacy of AV-optimised His bundle pacing in patients with a prolonged PR interval: a stratified analysis of the HOPE-HF clinical trial. *Europace* 2023;**25**:euad122.
23. Whinnett ZI, Sohaib SMA, Mason M, Duncan E, Tanner M, Lefroy D *et al*. Multicenter randomized controlled crossover trial comparing hemodynamic optimization against echocardiographic optimization of AV and VV delay of cardiac resynchronization therapy: the BRAVO trial. *JACC Cardiovasc Imaging* 2019;**12**:1407–1416.
24. Westphal P, Luo H, Shahmohammadi M, Prinzen FW, Delhaas T, Cornelussen RN. Machine learning-powered, device-embedded heart sound measurement can optimize AV delay in patients with CRT. *Heart Rhythm* 2023;**20**:1316–1324.
25. Gold MR, Niazi I, Giudici M, Leman RB, Sturdivant JL, Kim MH *et al*. A prospective comparison of AV delay programming methods for hemodynamic optimization during cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2007;**18**:490–496.