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Review Article

Multipoint left ventricular pacing as an addition to cardiac resynchronization therapy: a bridge to the holy grail?

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Abstract: Cardiac resynchronization therapy (CRT) constitutes a cornerstone to the treatment of advanced dyssynchronous heart failure (DyssHF); moreover it represents one of the few instances that a revolutionary approach was pursued, yielding previously unfathomable benefits to patients out of realistic therapeutic options. However, as is rather extensively established, nonresponse, or even negative response, to CRT continue to plague its course, precluding favourable effects in up to 40% of recipients, for a multitude of reasons. Given the scope of the issue of nonresponse, attempts to negate it by means of altering CRT delivery mode, and, more specifically, by introducing multipoint left ventricular pacing (MPP) have been focused on. Possible reasons for divergent trial results will be presented, as well as potential criteria for predicting whether MPP activation may reap additional benefits as compared to conventional biventricular pacing (BVP). Finally, an alternative framework for approaching CRT in general will be put forward, including advancements which in the (near) future may once more revolutionise heart failure treatment.

Keywords: Heart failure, resychronization therapy, multi-point pacing

Introduction

Cardiac resynchronization therapy (CRT) aims to improve cardiac performance by reversing the deleterious effects of dyssynchrony that lead to belated activation of left ventricular myocardial segments. Currently, the presence and degree of dyssynchrony are determined by QRS morphology and duration (≥120 or ≥130 msec per guidelines [1, 2]). Beyond the well-known and intuitive mechanical effects of simultaneous blood expulsion and benefits to energy efficiency of preventing early contraction against yielding sections, as well as late contraction of the latter from an unfavourable (in terms of Frank-Starling principle) overstretched initial condition, several additional pathways have been elucidated [3]. In short, applying CRT to dyssynchronous heart failure (DyssHF) improves cellular bioenergetics by altering expression levels of key cellular metabolism-related proteins, thus promoting aerobic glycolysis in mitochondria, and by allowing for restoration of myosin isomorphs expression pattern. The crucial link between contractility and metabolomics appears to reside in the function of costameres, subsarcolemmal multiprotein complexes that allow for crosstalk between cellular deformation/stretching and energy metabolism. CRT appears to reverse the deleterious effects of supraphysiological deformation/stretching observed in DyssHF, which would normally lead to energy reallocation towards cell sustenance and survival, forsaking function.

Consequently, it is not difficult to imagine, given the above effects of CRT, that a "the more the better" approach would be appealing and plausible in overcoming the issue of nonresponse to CRT which plagues up to 40% of recipients [4, 5]. Thus, generation of more activation fronts in the left ventricle, leading to more synchronized activation, as assessed mainly by means of

QRS duration shortening [6], and, less often, by mechanical dispersion reduction [7], would theoretically suffice to procure better short- and long-term results and outcomes than conventional biventricular pacing (BVP) as a means of CRT delivery. Of the attempts at generating multiple left ventricular activation/contraction wavefronts, multisite and multipoint pacing were the most likely contenders for broad clinical use. However, due to the former's requirement for an additional coronary venous branch catheterization, leading to unacceptable complication rates in the 20% range [8-13], along with the unavailability of differential programming of the 2 left-sided leads (only a Y-connector was offered by the industry), multipoint pacing (MPP) has emerged as the more likely potential solution to CRT underperformance.

How does MPP differ from (conventional) BVP in terms of CRT delivery? Most importantly a modern quadripolar coronary sinus (CS) lead allows for both BVP and MPP delivery- and alternating between them, provided an appropriate generator is implanted. The defining feature is the generation of an additional left-sided pulse leading to formation of an additional activation wavefront [14]. Most commercially available MPP-capable devices offer the ability to program either "local" left ventricular dipoles (between poles both located on the CS lead) or "extended" ones (one pole on the CS and the other provided by the right ventricular coil-RVC) or a combination thereof. In theory, mixed dipole configurations lead to divergent activation planes, increasing myocardial mass capture/activation. Intraventricular (LV1-LV2 pulse) and interventricular (LV2-RV pulse) delays are programmable (range 0-80 msec). It has been postulated that, should a local LV dipole be used, setting a higher-than-required output for the pulse may lead to anodal stimulation, which, contrary to its occurrence in conventional LV-RVring BVP configurations, is actually beneficial, inasmuch as it generates an *additional* activation wavefront in the LV. In fact, this may be occurring in almost half of BVP patients in whom a CS-only dipole is used for left ventricular pacing [15]. Finally, combination with preferential, anticipatory, left ventricular pacing [16], possible with both MPP and BVP modes, yields a *fourth or even fifth* LV activation wavefront, through the interventricular septum fibres [17]. Obviously the above is not possible in cases of complete, "true", left bundle branch block or with high-degree atrioventricular block when the RV *must* be paced. In this scenario, each local dipole accounts for two wavefronts (should anodal stimulation be conscientiously pursued), each extended one for a single wavefront, and septum fibres for the final one. Moreover, preventing iatrogenic right ventricular dyssynchrony has been shown to significantly improve patient performance status and outcomes [18-20]. Indeed, noninvasive ECG-imaging techniques [21] have verified that in some (but not all) CRT recipients MPP does lead to faster LV activation (see below for interpretations).

On a more practical side, configuration possibilities with MPP devices (dipole combinations, atrioventricular, intraventricular, and interventricular delays, pairing with preferential LV pacing) are starting to exceed the average HF and electrophysiology specialists' capacity to select the unambiguously best one for a given DyssHF patient. Furthermore, the additional pulse, along with the tendency to overshoot the required threshold (see above) will shorten generator longevity. Indeed [22], MPP activation will shorten battery life by 5.6% if thresholds are ≤1.5 V and by up to 16.9% for thresholds ≤4.0 V. A dubious solution to this issue would be programming LV pulses with the one with the higher threshold to be delivered first, allowing for better use of automatic capture management algorithms-however at the expense of optimal sequencing of LV activation.

Clinical evidence of MPP vs. BVP performance

Broadly, CRT-receivers candidates for MPP can be classified into 2 categories: i) those with more or less clear-cut intraventricular abnormalities, such as complete (true) left bundle branch (per Strauss criteria [23]) and ii) those with myocardium exhibiting complex conduction abnormalities. These groups display divergent behaviour regarding additional MPP-associated benefits, over those of traditional BVP. More specifically, in the former case, a single pulse distally to the line of block may suffice to adequately resynchronise the ventricule, whereas in the latter multiple wavefronts may be necessary to achieve the same effect-thus

dilated cardiomyopathy patients may fare sufficiently well with BVP [24, 25], and ischaemic ones with MPP [26].

Concerning acute effects, despite encouraging initial findings for MPP effects on dP/dt_{max}, pressure-volume loop area, and left ventricular outflow tract integral [27-29], when compared with optimised BVP, optimised MPP showed a non-significant increase in pressure rise rate [30], with no discernible subgroup trends. On the other hand, initial studies used a rather rigid programming pattern, without any restriction for dipole selection and combination, while setting intraventricular delay to 0 (simultaneous LV1 and LV2 pulses). In contrast, when there was an explicit search for maximal myocardial mass capture, translated into evaluating those dipoles with the maximal anatomic pole separation, and a small intraventricular pulse delay was introduced (10 msec), it led to less synchrony but potentially more physiological activation sequence [7]. As a matter of fact, significant improvements were noted in acute response rates (now defined as cardiac index increase ≥10%-85.2% vs. 62.9%, P<0.001 favouring MPP) and mechanical left ventricular dyssynchrony, as assessed by maximal radial strain temporal dispersion (P=0.05 favouring MPP). Of note, correlation between acute effects and outcomes, at least regarding BVP, has not been firmly established [17, 31].

Regarding long-term outcomes of MPP compared to BVP, Pappone et al [32] were the first to report sustained superior response with MPP at 12 months, consisting of significantly greater reductions to end-systolic volume and increases to ejection fraction (-25% vs. -18% and +15% vs. +5%, respectively). However, response rates (end-systolic volume reduction ≥15%) were not statistically significantly different among pacing modality groups, although this could be attributable to small sample size (n=44 patients), given their absolute values (76% vs. 57%). Interestingly, although no clear trends were noted between LBBB presence and aetiology-based groups, those with ischemic cardiomyopathy exhibited a trend towards greater functional class improvement. MPP optimisation method was quite laborious, using invasively determined dP/dt maximisation as guide, without any restrictions regarding dipole selection and intraventricular delay timing-which in hindsight, and given other studies' findings, may account for the similar MPP performance regardless of LBBB presence and cardiomyopathy aetiology.

The pioneer trial of MPP pacing has been the randomised MultiPoint Pacing Trial [14], where it was shown that MPP is, in general, not inferior to BVP in terms of non-responder rates at 3 and 9 months and it was confirmed that MPP outcomes are heavily dependent on programming. More specifically, should anatomic separation be pursued defined as distance between *cathodes of LV1 and LV2≥30 mm*, thus leading to pulses/wavefronts with markedly different orientation, (even if LV pulses are practically synchronous, Δt=5 msec) significant improvements are observed regarding responder status at 9 months (92% vs. 65%, P<0.001) compared to *MPP using any other programming configuration*. This held true despite the higher percentage of ischemic patients in the anatomic separation MPP group (65% vs. 43%, P=0.005). There was no direct comparison of $MPP_{anatomic\ separation}$ and BVP-although an element of bias could have existed, given that only patients with increases in mitral E/A integral with MPP were subsequently randomized. As put forward by the Authors the element of anatomic separation may be crucial to achieving MPP superiority over BVP since, due to concealed anodal stimulation, BVP may actually be similar to non-anatomic separation MPP in terms of wavefronts generated. Unfortunately, the recent MORE-CRT MPP trial [33] (544 randomised patients) found only a trend of conversion rate improvement with $MPP_{anatomic\ separation}$ compared with BVP (45.6% vs. 33.8%, P=0.10). Similar performance of the two modes was noted regarding mortality and end-systolic volume reduction. No subgroup effects were noted in the analysis. Smaller studies have nevertheless reported increased super-responder rates (end-systolic volume reduction ≥30%), compared to dP/dt_{max} optimised BVP when the principle of cathode anatomic separation is pursued [34] (71% vs. 22%, P<0.005).

A signal for improved $MPP_{anatomic\ separation}$ performance was reported in a post-hoc analysis [35] of the MultiPoint Pacing Trial regarding those with dilated left ventricles (left ventricular end-diastolic volume index >1.1 ml/cm). However, the difference in the composite clinical score

(a combination of NYHA class, Patient Global Assessment, heart failure event, and cardiovascular death) was mainly driven by improvements in patient quality of life, although positive trends were noted in the other parameters as well. This may be related to more pronounced failure of BVP to rapidly capture a sufficient percentage of the dilated left ventricle, in which QRS is already widened due to increased dimension and mass [36].

More recently, another single-arm trial [37] attempted to compare outflow tract velocity-time integral-optimised MPP and BVP and reported significant additional MPP effects regarding outflow tract velocity-time integral, 6-min walking distance, NYHA functional class, stroke volume, left ventricular ejection fraction, and right ventricular 2-dimensional strain-though no effects were noted regarding responder rates (based on end-systolic volume reduction ≥15%). All patients initially received velocity-time integral-optimised BVP for 6 months, subsequently converting to similarly optimised MPP and being followed up for additional 6 months. However, a point of criticism could be the absence of a control BVP group at 12 months, to account for potential accumulation of late effects-as seen in the MORE-CRT MPP study [33]. The encouraging results came at the cost of laborious optimization, combining both optimising vector selection, as well as LV2-RV delay. Other programming principles were a mixture of previous ones (similar to [7] regarding anatomic separation definition-though not obligatory, and similar to [14] regarding LV1-LV2 delay). Additional attempt for a combination of local and extended dipoles took place (thus, a similar effect to cathode separation could have been randomly achieved). Unexpectedly, a loss of available MPP dipoles in the 20% range was reported, in stark contrast to previous studies [14].

A simple, noninvasive blood pressure measurement can be a useful tool in assessing the effects of MPP configuration, optimising it, and comparing them to those of optimised BVP [26]. In a population with mostly non-ischaemic heart failure (75%) and LBBB presence (favouring BVP as mentioned above), optimised MPP was associated with superior haemodynamic effects and increased response rates (although only 5 BVP patients were included in the analysis). Notably, in 58% of cases the optimal MPP configuration included delays >20 msec, as opposed to previous findings. Unfortunately, small patient number precluded any analysis regarding superiority of anatomical MPP programming vs. electrical MPP programming (LV1 *earliest* activated site during atrial pacing and LV2 the *latest* one) and vs. spatial MPP programming (combination of a local and extended dipole as LV1 and LV2 pulses). However, another study [38] reported that pressure-volume loop-optimised and empirically (with maximal cathode anatomical separation and minimal delay between pulses) programmed MPP yielded similar 6-month results in terms of ejection fraction improvement, responder rate, and functional status, without any effect of cardiomyopathy type on findings.

In any case, atrioventricular delay optimization should not be overlooked, inasmuch as it may be crucial in allowing for the septal excitation wavefront to contribute to cardiac resynchronization by an additional 10% QRS duration shortening, compared to optimal interventricular delay settings [18] (BVP-only study, however findings applicable, in principle, to MPP as well). Several studies have indeed shown superiority of this approach as compared with obligatory RV pacing [19, 39-41]. Combining meticulous optimal atrioventricular delay assessment by means of invasive pressure-volume loop area maximisation and similarly optimized MPP and BVP pacing configurations, van Everdingen et al [24] reported that, in 43 true LBBB patients, there was no difference regarding stroke work improvement (however, once more, LBBB presence as inclusion criterion may have favoured BVP). Moreover, a wide interindividual variation regarding pacing protocol necessary to optimise stroke work was noted, with no clear advantage of simultaneous LV1 and LV2 delivery. Male sex and more severely depressed left ventricular function were the only predictors of favourable MPP effects vs. optimised BVP in multivariate analysis, with ischemic cardiomyopathy only achieving significance in the univariate level. Another study [43] found that pursuing "multi-*fusion* pacing", i.e. MPP (in this case with simultaneous LV1, LV2 and RV pulses) modified to allow for intrinsic septal activation (fused QRS), leads to significantly larger QRS duration reduction, as opposed to biventricular fusion pacing

(25.6% vs. 22%, P<0.05, nearly double the effect without fusion, 13.3% vs. 11.9%, P=NS).

Whether the combination of MPP and preferential LV pacing (allowing for intrinsic RV activation) may prove advantageous has not been tested so far, yet a relevant trial protocol has been published [44]. Theoretically, it would combine the best of all approaches: Multipoint LV activation (1-2 wavefronts from each LV1/LV2 pulses-see above, plus 1 wavefront from septum if atrioventricular delay is optimized) along with normal, fast RV activation.

A recent (although prior to MORE-CRT MPP publication) meta-analysis [45] of MPP vs. BVP clinical outcomes [32, 46-55] (of note including one study [49] comparing quadripolar and bipolar CS leads, *not* pacing modes) reported that MPP was associated with reduced heart failure-related hospitalisations (odds ratio 0.41, 95% confidence interval 0.33-0.5), greater increases in ejection fraction (6.37%, 95% confidence interval 3.6%-9.14%), and more than tripled the response rate (odds ratio 3.64, 95% confidence interval 1.68-7.87). (The study in question was not included in the above metrics). Due to inclusion of the questionable study no conclusions can be drawn regarding total mortality, yet *cardiovascular* mortality appeared significantly reduced with MPP (odds ratio 0.21, 95% confidence interval 0.11-0.40).

A schematic comparison between MPP and classical BVP is shown in **Table 1**. To summarize, it appears that, despite all its issues MPP remains a valuable tool in the treatment of DyssHF, possibly with significant untapped into potential. In short, clear-cut conduction abnormalities are sufficiently treated with BVP, whereas more dilated ventricles, with more pronounced reduction of contractility, especially when ischemic in origin, may require MPP to ensure sufficient response rates. It should be highlighted that no definitive guidance can be offered and divergent findings of studies should be interpreted in the light of wildly differing enrolee characteristics, optimisation-guiding parameter(s), and MPP programming protocols. Although a more arduous optimisation [37] process has led to benefits over BVP in a mixed ischaemic and non-ischaemic population, no group has so far attempted to meticulously study *all* potential temporal and spatial pulse and dipole configurations, not least due to logistics (an expert electrophysiologist, a technician, and a heart failure/imaging specialist are required), highlighting the extremely important role that accurate modelling of cardiac contraction and the effects of interventions will play in the future.

Synchrony versus sequence

The problem on non-response, or at least of absence of incremental benefit with MPP compared to BVP, is present [33, 37], despite reports of the contrary [14]. Usual approaches to non-response [56] are also applicable with MPP, meaning that pacing percent issues should be resolved, compliance to therapy addressed, and atrioventricular synchrony optimized, to name a few. Right ventricular pacing (and dyssynchrony) avoidance can be tackled by exploiting the potential for selective LV pacing offered by contemporary devices. However, it is the Authors' belief that evidence from literature presented herein point to a need for a more fundamental modification of CRT notion, if we are to improve response rates and make the most out of the future combinatorial approaches (see below).

An often neglected issue is that, in the most clinical meaning, CRT should be thought of as a work in progress, rather than a single-shot intervention that yields the maximal possible benefit at once. As myocardial segments are resynchronised, cellular energetics and contractility recover and normal conduction anisotropy is restored (favouring fast coaxial rather than slow perpendicular activation wave propagation in cardiomyocytes, and thus orderly and timely activation [57-59]). At the same time, and partially due to the above, afterload and ventriculoarterial coupling may change as well so repeated optimal dipole/delay configuration changes may needed to elicit further favourable remodelling and improved outcomes [60]. This perspective may explain the finding that a single optimisation attempt fails to deliver even when invasive parameters are used [38].

Our very perception of dyssynchrony and CRT may need to be modified. Dyssynchrony, or rather a-synchrony (lack of synchrony as opposed to *bad* synchrony) exists in every heart, and its magnitude is equal to the QRS duration. The heart achieves its remarkable efficiency by a strictly choreographed sequence of segment

Table 1. Comparison of the advantages and disadvantages of MPP and BVP

Feature	BVP	MPP
Clearly defined target population	Several landmark trials have established the DyssHF population that *may* benefit from CRT in its classical BVP mode-however there is no certainty that these patients *will* benefit.	Although still unresolved, it appears that DyssHF patients with extensive, non-specific intraventricular conduction abnormalities benefit more from multiple LV pulses which shorten LV activation time. Of note, CRT devices from all major manufacturers are MPP-capable (not with the same options), allowing for easy transition if deemed necessary.
Complexity of implantation	Identical.	
Presence of suitable dipoles	Almost always achievable (quadripolar leads).	Usually achievable. Due to constraints regarding dipole combination, although multiple BVP-suitable dipoles may be present, their serial use may be unfeasible. Also, rates of MPP loss of up to 20% have been reported.
Ease of programming	A basic setting has emerged that is often followed in practice-LV/RV pulses either simultaneous (nominal setting) of with up to 30 msec LV precedence. However, regarding reaping maximal benefit, programming becomes exponentially more laborious/complex (see text for details).	There is no consensus regarding a basic setting that could be subsequently be improved upon. This notwithstanding, most relevant trials have suggested opting for dipoles allowing for maximizing left ventricular myocardial mass capture, thus exploiting the innate advantage over BVP, and using minimal delay between LV pulses. Moreover, achieving *optimal* settings is quite cumbersome and resource-intensive (see text).
Acute effects	In most studies with direct BVP-MPP comparison, the latter outperformed the former regarding acute hemodynamic effects, at least when basic settings (see above) were used.	
Long-term effects	Firmly established survival benefits, at least compared to pharmacotherapy.	Encouraging findings regarding reduced cardiovascular mortality and performance status compared to BVP, even in their respective *optimized* modes (non-randomized studies and meta-analyses).
Pairing with additional modalities (LV-only pacing, QRS fusion, magnetic resonance guidance)	Identical. However, MPP offers more versatility and can better adapt to the suggestions of advanced LV output optimization approaches.	

In general, MPP could be considered an enhanced version of conventional BVP, offering more options, especially when non-response remains an issue. Admittedly, the core issue of whether MPP should be pursued in patients with satisfactory response to BVP cannot be resolved, inasmuch as there are randomized long-term trials of the two modalities.

activation, many of which exhibit differing contraction properties (e.g. different phosphorylation patterns in papillary muscle myosin allow for more protracted contraction to ensure prevention of valvular regurgitation throughout systole [61]). The concepts of torsion and changes to chamber geometry to ensure smooth redirection of blood from the inflow to outflow tract, without vortices' formation [62] are firmly established. Indeed, the concept of MPP is, in its core, rooted in the ability to more precisely and selectively, compared to BVP, sculpt the activation pattern of LV. However, the unending pursuit of the narrowest QRS may constitute a chimera precluding meaningful research to alternatives. Intriguingly, studies have reported that response to MPP is determined by the time to activation of 90% of cardiomyocytes, not by final QRS duration [63], as opposed to previously reported [30]. More recently [64], absence of correlation between QRS duration and acute haemodynamic response with MPP has been reported. This has been interpreted as stemming from sacrificing *sequence for synchrony* (i.e. forsaking the most belatedly activated cardiomyocytes which-since they most probably lie between fibrotic layers-would not offer any meaningful contribution to cardiac performance whatsoever). Furthermore, it has been noted that MPP acute effects are mediated by rotation of the QRS vector, indication a more left-dominated activation sequence [64] - possibly related to presence of more confluent activation wavefronts.

Thus, perhaps it is time to rebrand CRT as Cardiac Re*sequencing* Therapy, in order to highlight that efforts should be directed not towards bringing all segments' activation together, but towards elucidating the optimal activation sequence for a given failing heart. Obviously for the most part and in most cases with pronounced dyssynchrony QRS narrowing will be coterminous with improved cardiac remodelling and performance. However, given the level of experience and degree of resynchronization achieved with current means, as well as the, rarely seen, deleterious effects of CRT in some patients, it may be useful to clarify that proper (to the individual patient's myocardium) sequence of activation is potentially a sine qua non for further improving response and outcomes.

Future directions

Of all probable future solutions and improvements to CRT, two stand out as having the power to radically redefine the field.

i. Untangling the issue of modeling

One of the major hurdles in simulating the effects of alternative activation sequences (dipole and delay selection effects on a given myocardium with specific fibre orientation, scar localization and conduction velocity, all needing to be included in a comprehensive model [65]) lies in the obscenely demanding, in terms of calculation power, requirements (often exceeding 80 minutes for a single beat of a patient with the use of 127 processing cores [60]). Current computer designs simply cannot cope with the number of parameters and downstream domino of effects elicited by different BVP, let alone MPP programming patterns.

On the other hand, quantum computers [66] are poised by design to be incomparably superior to classical ones regarding optimization problems. Briefly, contrary to current processors' need for evaluating each programming pattern in a serial manner, quantum computers take advantage of the phenomenon of quantum entanglement between single "twin" electrons' spins and evaluate all possible solutions *simultaneously*. Moreover, the potential for machine learning (i.e. predicting the best programming for the optimal resequencing result for a given patient based on previous cases) is advanced considerably with quantum computers. It is thus conceivable that, in the near future, findings from a high field intensity cardiac magnetic resonance scan [67], determining values for fibre orientation, scar location and conduction velocity per voxel will be inserted to such a computer and a determination of the optimal device programming will be available in real time. In addition, in a more fundamental level, selection of the most appropriate target vein prior to device implantation may be assisted.

ii. Illuminating the path to resynchronisation/ resequencing

Another problematic aspect of CRT lies in its finite ability to generate activation wavefronts, especially in comparison to the intrinsic con-

duction system with the final branches of Purkinje fibres. A technology with the potential to reshape our approach to pacing and even defibrillation is optical pacing-i.e. pacing the heart with light [68]. Broadly, optogenetics is the science of inserting light-sensitive ion channels to cardiomyocytes through use of viral vectors and then illuminating cardiomyocytes with light of the proper wavelength to induce depolarization. Given that areas of illumination of 1 cm^2 suffice for ventricular pacing [69], it is conceivable that a significant number of wavefronts can be generated with sequential illumination through optical fibres of select myocardial areas-in fact, these areas, and their sequence of illumination, could in theory be modified if optimization requires so. Moreover, insertion of transmural implantable multi light-emitting diode optical probes [70] has been shown, in mice, to allow for transmural pacing, overcoming poor penetration of light in the myocardial wall of larger animals. Finally, the conduction system itself can be specifically targeted and improve even more our ability to elicit the desired activation sequence of the heart, in an even more physiological manner [69].

Conclusions

Multipoint left ventricular pacing has offered significant improvements in the field of CRT regarding patient outcomes and response to therapy. However, it is plagued by difficulties in determining the right programming for the individual patient, and although general guidance has been inferred by existing studies, the goal of personalised CRT remains elusive. Despite this, the conceptual framework of CRT itself is poised for significant developments over the next years, ranging from improved evaluation tools (quantum computers) and delivery methods (optical pacing), to redefining its very essence (resequencing as opposed to resynchronising).

Disclosure of conflict of interest

None.

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