Comparison of left ventricular and biventricular pacing: Rationale and clinical implications

Polychronis Dilaveris, Christos-Konstantinos Antoniou, Panagiota Manolakou, Ioannis Skiadas, Konstantinos Konstantinou, Nikolaos Magkas, Panagiotis Xydis, Christina Chrysohoou, Konstantinos Gatzoulis, Dimitrios Tousoulis

First University Department of Cardiology, Hippokration Hospital; Athens-*Greece*

Abstract

Cardiac resynchronization therapy constitutes a cornerstone in advanced heart failure treatment, when there is evidence of dyssynchrony, especially by electrocardiography. However, it is plagued both by persistently high (~30%) rates of nonresponse and by deterioration of right ventricular function, owing to iatrogenic dyssynchrony in the context of persistent apical pacing to ensure delivery of biventricular pacing. Left ventricular pacing has long been considered an alternative to standard biventricular pacing and can be achieved as easily as inserting a single pacing electrode in the coronary sinus. Although monoventricular left ventricular pacing has been proven to yield comparable results with the standard biventricular modality, it is the advent of preferential left ventricular pacing, combining both the powerful resynchronization potential of multipolar coronary sinus and right-sided electrodes acting in concert and the ability to preserve intrinsic, physiological right ventricular activation. In this review, we aim to present the underlying principles and modes for delivering left ventricular pacing, as well as to highlight advantages of preferential over monoventricular configuration. Finally, current clinical evidence, following implementation of automated algorithms, regarding performance of left ventricular as compared with biventricular pacing will be discussed. It is expected that the field of preferential left ventricular pacing will grow significantly over the following years, and its combination with other advanced pacing modalities may promote clinical status and prognosis of patients with advanced dyssynchronous heart failure. *(Anatol J Cardiol 2019; 22: 132-9)*

Keywords: dyssynchronous heart failure, cardiac resynchronization therapy, biventricular pacing, preferential left ventricular pacing, right ventricular function

Introduction

Although cardiac resynchronization therapy (CRT) is a major breakthrough in and a cornerstone of advanced heart failure (HF) treatment (1, 2), nonresponse constitutes a major therapeutic issue (3, 4) with a multitude of interpretations offered (3). Despite the unquestionable validity of several of them [suboptimal left ventricular (LV) electrode site, failure to optimize, suboptimal delivery as in the case of atrial fibrillation (AF), suboptimal biventricular pacing (BVP) percentage, alterations due to underlying disease rather than left bundle branch block (LBBB) itself as in advanced dilated cardiomyopathy with diffuse fibrosis (5)], a more radical reasoning may be pursued, linking nonresponse to iatrogenic right ventricular (RV) dyssynchrony and atrial dysfunction. Thus, a different mode of CRT, namely preferential LV (pLV) pacing –"preferential" referring to the conscientious and active avoidance of RV pulse delivery–might offer an appealing alternative to standard BVP, especially in cases of nonresponse, with coexisting significant RV and atrial BVP ramifications (6).

Although LV pacing may represent an appealing approach in cases warranting ventricular pacing due to atrioventricular block without concomitant QRS widening (to avoid LV function deterioration), also competing with BVP as an option (7), this review will focus on the underlying mechanisms and its utility when both ventricular dysfunction and LV intraventricular conduction aberrations exist.

Underlying principles

A high percentage (30%–60%) of patients with advanced HF exhibit evidence of ventricular dyssynchrony, defined either electrocardiographically or mechanically, respectively (8-10). This could be a result of Purkinje fibers (PF) in humans not cours-

Address for correspondence: Polychronis Dilaveris MD, First University Department of Cardiology, Hippokration Hospital; 22, Miltiadou street, 155 61, Athens-*Greece*
Phone: 0030-210-6531377 E-mail: hrodil1@yahoo.com

Accepted Date: 12.07.2019 **Available Online Date:** 11.08.2019

DOI:10.14744/AnatolJCardiol.2019.35006

ing transmurally as in other species (11), which leads to activation sequence being vulnerable to formation of non-conducting/abnormally conducting tissue at the subendocardial region (otherwise excitation could bypass the block through adjacent PF, reducing its dyssynchrony-inducing effect). Under normal conditions (5, 12) LV activation follows a septal-to-lateral wall and apicobasal course, ensuring, through the high conduction velocity of PF, not only synchronous activation of the chamber but mechanical efficiency as well, given the ensuing squeeze-like behavior. In contrast, left intraventricular conduction abnormalities of varying degrees yield a sequence with delayed activation of basal lateral/posteroinferior segments (13), without clear apicobasal directionality (14), which leads to electrical and consequently mechanical dyssynchrony [ejection fraction (EF) reduced by as much as 40% (15)]. These effects are accentuated in the case of "true" or "complete" LBBB, where breakthrough conduction occurs only by currents stemming from the RV crossing the mid-apical septum and not by LV currents propagating through the septum/anterior wall interface (14). Moreover, ventricular dilatation and hypertrophy aggravate these effects. At the same time, atrial function is impaired, inasmuch as LV segments may continue to contract during diastole, impeding mitral valve opening (16).

As anticipated, resynchronization effects are markedly greater in cases of true LBBB (17), also reflected in relevant guidelines recommendation levels for CRT use in various forms of intraventricular conduction aberrations (6). Finally, restoration of synchronous activation has significant effects on cardiomyocyte energetics (18), stemming from alleviation of supraphysiological cardiomyocyte stretch/stress levels, allowing for restoration of proper cellular metabolism/function.

However, current implementation of CRT, with delivery of an LV pulse through a coronary sinus (CS)-residing multipolar electrode appears to solely focus on LV, rather than cardiac, function. More specifically, restoration of LV synchrony often comes at the cost of its RV counterpart (second pulse delivered at RV apex). Studies have reported significant prognostic effects of intrinsic RV (dys)function in patients with HF (19), allowing the conjecture that its BVP-induced counterpart will exhibit similar features. Indeed, some degree of RV activation precedence over its LV counterpart has been shown to acutely improve hemodynamic responses in cases of LBBB (20-22) – in any case, initial septal activation on surface ECG is normally directed to the right. It should be clarified that this means to no extent that LV intraventricular dyssynchrony should be acceptable. Rather, it signifies that the RV, as a chamber, should be activated through the intrinsic conduction system (23) and slightly earlier that the LV, whose internal dyssynchrony should be rectified as much as possible. Presence of interventricular septum (common structure) renders this feat difficult to achieve given that it should be allowed to depolarize intrinsically, while late-activated LV segments (LBBB pattern) should be resynchronized with their septal counterparts, without transposing activation of the LV as a whole before the RV. Indeed, in a proof-of-concept study, Varma et al. (24) demonstrated that in isolated left-sided HF with reduced ejection fraction, pLV pacing with a CRT device allowed for significantly shortened duration of RV activation, indistinguishable from that of endogenous conduction, without introducing areas of delayed conductivity, contrary to BVP or RV pacing. This in turn could abrogate perturbed RV hemodynamics reported with RV pacing (25) and potentially impact disease progression.

Atrial stress is also increased by curtailing ventricular filling due to frequent need for short atrioventricular delays to ensure satisfactory levels of BVP (26, 27) – an alteration with hemodynamic effects by itself (28). Although dyssynchrony itself may cause atrial dysfunction (see above), it is not alleviated by CRT since the latter induces it as well, albeit through a different mechanism. In any case, this may lead to supraventricular tachyarrhythmias, most importantly AF–occurring to ~25% of CRT recipients (29, 30) – with detrimental effects on response (31).

Ventriculoarterial coupling (VAC) is an old yet newly resurfaced concept attempting to assess the function of the cardiovascular system as a whole (32). In essence, it estimates the extent to which cardiac external work is transferred to the vasculature and, given that in hydraulics work is the product of volume and pressure, the extent to which cardiac work translates to tissue perfusion and potentially organ function. Although most studies have focused on left-sided VAC (33, 34), RV-pulmonary artery coupling (right-sided VAC, RVAC) has been found to offer prognostic information in cases of HF with preserved EF (35). Notably, normal RVAC values are associated with optimal energy efficiency rather than maximal work transfer (36), reflecting the energy-sparing behavior of the RV in the low resistance–high flow pulmonary circulation. Regarding pLV pacing, it could be argued that prevention of RV dyssynchrony may lead to normalization of RVAC values compared to standard BVP although we lack relevant studies to verify or refute this claim.

Modes of LV pacing

Pacing the LV is not per se difficult. Options include epicardial pacing through either surgically implanted electrodes or through a CS catheter, or even endocardial implantation of either conventional pacing leads (through the interatrial or interventricular septum) (37), or of a leadless, ultrasound-activated device endocardially (Fig. 1) (38). In theory, all but the CS approach offer wide range of options regarding selection of appropriate pacing sites, either at the cost of being laborious or not having displayed superiority to standard BVP. The essence of the modern approach to LV pacing as an alternative modality to BVP lies in its preferential nature–that is, focusing not only on achieving maximal LV resynchronization but also on preserving RV synchronicity by avoiding iatrogenic dyssynchrony induced through the RV pulse. Although in principle pLV pacing could be coupled with the LV lead being surgically implanted or functioning through an ultrasonic pulse, currently, the pursued approach involves classical CRT (BVP)-capable devices, with dedicated new algorithms.

Anatol J Cardiol 2019; 22: 132-9
DOI:10.14744/AnatolJCardiol.2019.35006

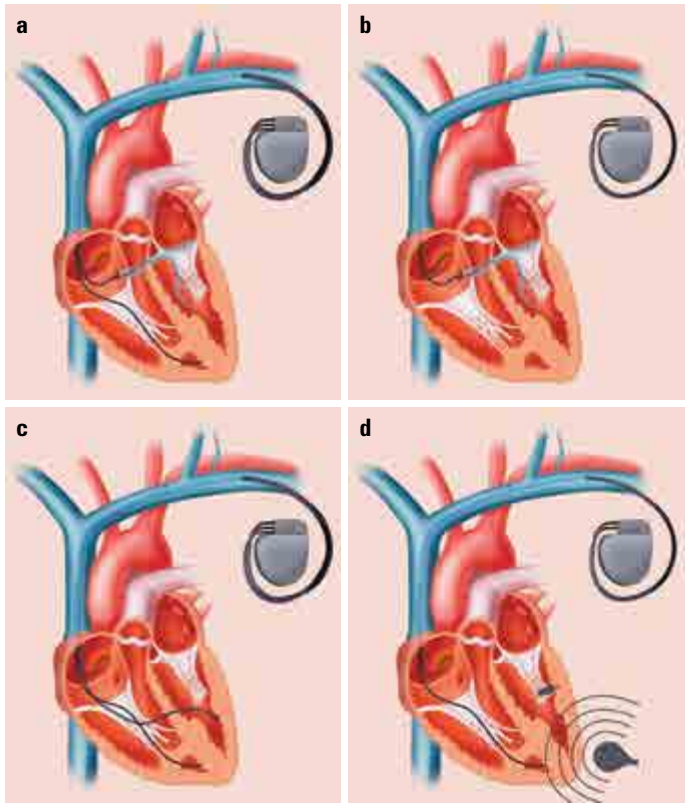

Figure 1. Modes of left ventricular (LV) pacing. (a) Epicardial LV pacing with an electrode (with two or four poles) lodged in the coronary sinus, one to right ventricular apex and one in the right atrium. This configuration may be used to deliver both standard BVP and pLV pacing–see text for differences. (b) Monoventricular epicardial LV pacing (mLV pacing). Note absence of RV electrode. The totality of the heart is activated with a rightward direction (not leading to QRS duration shortening). (c) Endocardial LV pacing–interventricular septum approach–an alternative approach using standard devices, allowing for more versatility in LV site selection. (d) Endocardial LV pacing–the WiSE study approach–although allowing for the greatest versatility regarding site, it does not use CRT devices, rather a dual-chamber pacemaker communicates with an ultrasound generator that in turn activates the electrode in the left ventricle

How does then pLV pacing, delivered through a CRT device, differ from plain LV pacing, delivered through a simple dual-chamber device (monoventricular LV-mLV-pacing)? The answer lies in the versatility offered by multipolar electrodes and the existence of a wide RV pole (RV-coil) that can partake in dipole formation. More specifically, multipolar electrodes assist in more accurately sculpting the LV activation sequence, allowing for better optimization of LV output, and the RV pole creates vectors linking lateral/anterior/apical segments with the interventricular septum that also span a wide area of myocardium (triangular shape containing excitatory vectors–more myocardial mass simultaneously activated), while minimizing the possibility of anodal stimulation (and thus RV pacing), compared to RV tip pole (reduced electric charge density). Furthermore, newer algorithms (such as AdaptivCRT®) allow for anticipatory/preferential LV pacing, that is, the relevant pulse is delivered at a programmable interval prior to intrinsic RV activation, which is monitored every minute and adjusted for accordingly (obviously relatively preserved atrioventricular conduction and–absence of high degree atrioventricular block–and rhythmicity are essential). Once more, it is emphasized that even in RV-coil inclusive dipoles depolarization is induced at the LV, with the vector directed toward the RV (no RV pacing per se occurs). Moreover, given limitations of current algorithms (see below), CRT-capable devices can always revert to BVP mode, maintaining the multitude of options for vector selection.

In contrast, mLV pacing would necessitate short atrioventricular delays to avoid RV>LV conduction, potentially compromising the basic tenet of avoiding RV dyssynchrony (LV > RV conduction) – admittedly a rare occurrence due to the slow propagation of the epicardial LV pulse as compared with the PF-based intrinsic impulse propagation in the RV (20). Thus, the requirement for short atrioventricular delays to ensure BVP delivery is negated and their negative effects abrogated in CRT device-based pLV pacing with RV intrinsic fusing with paced LV_{site1}>LV_{site2} conduction. Additionally, mLV pacing is associated with QRS widening compared to baseline, given its epicardial nature and the extremely leftward skewed depolarization initiation (39). Mitral regurgitation may be an issue as well, given asynchronous papillary muscle activation (40). Monoventricular LV pacing could also promote arrhythmogenesis, especially through triggered activity, given that myocardial segments may be subjected to initial stretching prior to actively contracting. In contrast, BVP has been shown to possess intrinsic arrhythmia-suppressing properties, through prevention of abnormal, supraphysiological myocardial segment deformation (41) – mechanistically effects on both mitral regurgitation and arrhythmia can be extrapolated to pLV pacing, given that intraventricular LV synchronicity is achieved to a greater extent.

Finally, regarding standard BVP, it is noteworthy that even in the uncommon cases when, due to CS lead position and/or the nature of LV intraventricular conduction alterations, optimal mechanical effects require an RV>LV configuration (thus pLV pacing is irrelevant); and although RV apex has already been activated intrinsically, pacing through an RV-coil-inclusive dipole remains a valid option for LV pacing inasmuch as the cathode lies in the CS electrode and thus depolarization is localized but also has directionality toward the RV (incidentally, this configuration essentially renders anodal stimulation irrelevant, given that the RV is already depolarized).

Clinical evidence

Most initial studies comparing LV and BVP have been performed on patients with dilated cardiomyopathy (DCM), to ensure a rather homogeneous effect of diffuse fibrosis on conduction, as opposed to the more severe yet more localized, impact of dense scars of ischemic cardiomyopathy (ICM). It should be highlighted that older studies employed mLV and not pLV pacing.

Monoventricular LV pacing

Initially focused on establishing mLV pacing noninferiority to BVP, as early as 1997, several studies started suggesting that LV pacing, especially when delivered at the lateral/posterior wall area (42) procured hemodynamic responses at least on par with BVP (20, 21, 42) – notably dp/dt of the LV increased by almost 25%. These effects were not correlated with QRS shortening–an intuitive finding, based on the epicardial nature of pacing. Regarding clinical and echocardiographic endpoints (6-min walking distance, anaerobic threshold, NYHA functional class, mitral regurgitation severity, and LV EF), they were also found not to differ between mLV and BVP, with the exception of LV end diastolic diameter that was found significantly lower in the BVP cohort, perhaps due to more options regarding intraventricular resynchronization offered by the two electrodes configuration (43). This interpretation is compatible with the report by Auricchio et al. (44) that mLV pacing benefits CRT candidates with baseline QRS duration >150 ms (true LBBB), without clinical improvement (peak oxygen consumption, 6-min walking distance, quality of life) detected in those with LBBB and QRS duration 120-150 ms. Indeed, the former had, by definition, markedly belated activation of the LV lateral segments, thus CS-based mLV pacing was suitable, targeting precisely that area, while the latter may have exhibited more subtle dyssynchrony that would require selection of different pacing vectors, offered only by BVP. In fact, importance of LV free wall activation timing in ventricular synchrony is demonstrated also in cases with mechanically, but not electrocardiographically, proven dyssynchrony (i.e., patients had QRS duration <120 ms), where effects of both BVP and mLV pacing were associated with their impact on expediting LV free wall activation (45).

The first landmark study for the comparison of mLV and BVP was the BELIEVE pilot study (74 patients, QRS>130 ms with an LBBB pattern, 1:1 randomization) (46), where response to pacing at 12 months, defined as at least 5% LV EF improvement and/or ≥10% increase in 6-min walking distance, was similar between mLV and BVP groups (75% vs. 70%, respectively, p=0.788). Although underpowered to establish noninferiority (estimated post hoc to require ~1100 patients per pacing modality), the study did establish safety, feasibility, and favorable profile (regarding LV EF and 6-min walking distance) of mLV pacing. Upon evolution in BVP-capable device technology, namely potential for independent programming of ventricular leads and more options for atrioventricular and interventricular delays (47-49), and following echocardiographically guided optimization [despite difficulties of such a feat (50-52)], no difference between BVP and mLV was noted regarding exercise capacity and quality of life, although NYHA class was significantly better in BVP recipients (53). Although the same argument as before could be made based on the crossover design of the study, a different point of view could be that performance of mLV pacing, a rather unsophisticated pacing mode, was on par with quite advanced modalities of BVP delivery.

Noninferiority in clinical and echocardiographic parameters was demonstrated in the B-LEFT HF trial (54), having enrolled 176 patients (LV EF <35%, NYHA class III-IV, randomizing 90 to BVP and 76 to mLV) and with a follow-up of 6 months. The Evaluation of Resynchronization Therapy for HF (GREATER-EARTH) (55) trial further confirmed beneficial effects of mLV pacing, equal to those of BVP, and, although falling short of establishing superiority (an interesting shift in mentality), further elaborated on them, by reporting that 20.5% of non-responders to BVP achieved responder status upon mLV pacing initiation, and conversely, 31.4% of non-responders to mLV pacing responded to BVP. Unfortunately, no further data on these subgroups are provided, and it could be hypothesized that mLV pacing unique responders had compromised RV function on BVP (again this was a crossover design trial), whereas BVP unique responders had either different features of dyssynchrony (necessitating different LV pulse configuration–notably the RV pulse may contribute to LV depolarization, especially in cases of abnormal endogenous conduction), or improved more on other parameters, such as mitral regurgitation. Of note, BVP did retain an advantage regarding LV diastolic function, mitral regurgitation, and systolic pulmonary artery pressure (expectable findings given greater versatility for fine-tuning resynchronization) (56).

The above trials (46, 54, 55), along with later metaanalyzes (57, 58), which demonstrate parity in terms of mortality [OR 1.25, 95% confidence interval (CI) 0.48–3.24 for mLV pacing vs BVP], peak exercise capacity (standardized difference in means for peak O_2 consumption 0.306, p=0.052), and hospitalizations (OR 0.86, 95% CI 0.49–1.50 for mLV pacing vs BVP) were instrumental in firmly establishing the role of mLV pacing as an alternative to BVP, especially in cases of nonresponse, allowing for its inclusion in relevant guidelines (6).

In contrast, findings in patients with HF with AF, after His bundle ablation, were not favorable for mLV pacing, compared with BVP, even at baseline QRS duration of >140 ms (59). More specifically, mLV pacing yielded inferior results in terms of exercise performance (including cardiopulmonary exercise test), while being associated with increased ventricular arrhythmogenesis (in the form of premature ventricular complexes). This discrepancy could be attributed to crossover study design, given that effect of one pacing modality could persist beyond its cessation.

Preferential LV pacing

Although studies' findings reproducibly pointed to mLV pacing noninferiority to BVP, leading to suggestions of using plain DDD/VDD pacemakers for its delivery, especially in cases with significant comorbidities or economic constraints (60), pathophysiological rationale and early evidence (24) suggested the existence of an untapped potential for combining RV function preservation and LV resynchronization, and created the impetus for the development of relevant algorithms. Focus of these algorithms is on assessing intrinsic atrioventricular conduction and, when within certain limits, allow for PF-mediated RV activation while pre-

Anatol J Cardiol 2019; 22: 132-9
DOI:10.14744/AnatolJCardiol.2019.35006

emptively/preferentially pacing the LV (pLV pacing). This allows for normal RV activation and LV resynchronization–it is stressed once more that intrinsic RV activation may partake in LV segment depolarization, contributing to the desired dyssynchrony minimization, thus overall LV activation constitutes a fusion.

More practically, and based on the currently available algorithm (61), when intrinsic atrioventricular conduction time does not exceed 220 ms in cases of sensed atrial activity and 270 ms in cases of atrial pacing a sole LV pulse is delivered (whose dipole's configuration is modifiable given a quadripolar CS electrode) at 70% of the measured atrioventricular conduction interval (to ensure CRT delivery to the LV). Measurements of endogenous atrioventricular conduction are performed once per minute, following prolongation of programmed atrioventricular delay interval. Currently, no fine adjustment of the intrinsic RV activation–LV pulse time delay is feasible and the algorithm cannot operate in cases of irregular heart rhythm (anticipatory pacing), compromised atrioventricular conduction, or at heart rates exceeding 100 bpm. In any of the above cases, programming reverts to BVP with the potential for optimizing interventricular delay by assessing QRS conduction interval, defined as the time from the RV sensing to the end of the QRS complex in the device electrogram. Additionally, automatic optimization of atrioventricular delay is performed as well. Obviously, due to current constraints of pLV pacing algorithms, it is unfeasible to compare pure pLV pacing and standard BVP. Thus, all pLV recipients will also at periods receive BVP, potentially confounding correlations, although in practice that percentage may be extremely low (down to 0.5% of CRT delivered).

Preferential LV pacing was quickly brought to the forefront of CRT armamentarium following results of the Adaptive CRT trial (62), where noninferiority to echocardiographically optimized BVP was demonstrated after a follow-up of 6 months (522 patients, between subjects design). Notably, the clinical composite score, introduced in 2001 (63), with a rather strict definition of improvement was used to define response to treatment, which did not differ between groups (73.6% vs. 72.5%, p=0.0007 for noninferiority), while no inappropriate programming occurred as a result of algorithm implementation. A potential limitation lies in the different mode for CRT optimization (atrioventricular and interventricular delay programming) between groups, performed either echocardiographically (BVP arm) or based on electrical parameters (pLV pacing group). However, a strong correlation between values chosen by the device and those suggested by echocardiography was noted in the pLV pacing arm, both at baseline, and at 6 months (0.93 and 0.90, respectively). A notable limitation lies in the fact that 50.9% of CRT delivered to the pLV pacing group was in the form of BVP, potentially confounding outcomes (either blurring pLV pacing effects or ensuring noninferiority).

This issue was clarified in a subsequent analysis and extended follow-up of the Adaptive CRT trial participants (64), where pLV pacing ≥50% of CRT was independently associated with reduced risk for death or heart failure-related hospitalization (HR 0.49, p=0.012). Patients attaining such levels of pLV pacing were more frequently female, had nonischemic cardiomyopathy and more often displayed LBBB ECG patterns (interestingly the same predictors for response to CRT in general–conceivably because they focus the problem on the LV, and are more amenable to resynchronization and less probable to induce atrioventricular conduction abnormalities precluding pLV pacing). Obviously, these patients also predominantly had normal intrinsic atrioventricular conduction intervals at randomization. Equally importantly, when patients from both treatment arms with normal atrioventricular conduction were compared (thus indirectly selecting those in the pLV arm with the higher selective LV pacing percent and minimizing BVP effects) death and heart failure-related hospitalization rates were significantly lower at 1 year in the pLV pacing group (HR 0.52, p=0.044), with a trend for increased response at the same time (77% vs. 66% p=0.076). These findings were subsequently confirmed in a metaanalysis comparing pLV recipients from the Adaptive CRT trial with a historical cohort comprised of echocardiographically optimized patients with standard BVP from previous studies, reporting a greater rate of clinical composite score improvement, as well as increased likelihood for improvement, favoring the former (Δ percentage 11.9%, 95% CI 2.7–19.2%, odds ratio 1.65, 95% CI 1.1–2.5) (65).

Effects of pLV pacing have been shown to extend beyond RV dyssynchrony improvement and at least parity with BVP in clinical outcomes. More specifically, AF incidence, defined as >48 h on AF based on device-stored electrograms was found significantly reduced both in the pLV pacing arm of the Adaptive CRT trial, after an extended follow-up of 20.2 months (hazard ratio 0.54, p=0.03) (66), and after remote follow-up of >37,000 patients for 15.5 months (hazard ratio 0.53, p<0.001) (67). Furthermore, the reduction benefited mostly patients with baseline prolonged atrioventricular conduction (66) – so in the standard BVP mode, atrial contraction would have been abruptly terminated by the initiation of ventricular activation through delivery of pacing pulses to ensure CRT, and correlated with the percentage of pLV pacing (hazard ratio 0.05, p<0.001 when pLV levels >92% were compared with levels 0%–5%). Although underlying mechanisms for AF incidence reduction remain obscure, potential implications regarding clinical course of patients with HF are evident, given both importance of atrial function for prognosis (68) and the effects of ablating AF in this population (69)–an intervention that could be complemented by the implementation of a pacing algorithm further reducing arrhythmia occurrence.

To summarize, current limited clinical evidence suggests that pLV pacing, notwithstanding programming limitations, when actually delivered to patients, leads to improved clinical outcomes (death and HF-related hospitalizations) over BVP. A significant number of BVP non-responders do echocardiographically and physically respond to pLV pacing. Furthermore, its effect extends to supraventricular arrhythmia burden reduction, in the form of reduced AF occurrence, in a percentage-related manner. Unexpectedly, there is a paucity of clinical data regarding pLV pacing

effects on RV function (assessed by means of e.g., two-dimensional speckle tracking-based longitudinal strain, cardiac magnetic resonance imaging, or even right-sided ventriculoarterial coupling), despite that theoretically it is a vantage point for pLV pacing and historically it constituted the rationale for the latters' development.

Conclusion - Future Perspectives

Significant clinical research is being conducted regarding pLV pacing. The contemporary AdaptResponse trial (70) aims to elaborate on metaanalyzes' findings regarding superiority of pLV pacing over BVP (65) and aims to recruit and randomize approximately 3000 patients in 200 centers with a worldwide scope (between subject design). Randomization lies in activation or not of the AdaptivCRT® algorithm, allowing for comparison of pLV pacing and standard BVP. Primary endpoint includes all-cause mortality and intervention for HF decompensation (not necessarily mandating hospitalization), being more general but also more clinically relevant. On the other hand, enrollees will have to not only meet CRT eligibility criteria but also exhibit "true" LBBB, as defined per the Strauss criteria (QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads) (71) – a restriction not present in the Adaptive CRT trial (61). Moreover, BVP optimization will be left to treating physicians' discretion, again diverging from the design of previous trials in the field, but closer to daily practice. Once more, RV function alterations do not explicitly constitute a study endpoint. However, following a planned follow-up period of 2.5 years and projected primary endpoint occurrence in 1100 participants, the aforementioned trial will be powered to demonstrate pLV superiority to BVP, at least in that more selected CRT-eligible patient group.

Consequently, trials aiming to assess global cardiac effects of pLV pacing, especially in comparison with standard BVP are in order, examining both components of circulation–pulmonary and systemic–and estimating improvements in exercise capacity, potentially linking them to better bilateral VAC. On a more advanced notion, combination of pLV and multisite LV pacing, a modality further boosting chamber resynchronization (72, 73), would potentially represent combinational use of the most advanced forms of cardiac pacing to improve outcomes in patients with advanced dyssynchronous systolic HF.

Conflict of interest: None declared.

Peer-review: Internally peer-reviewed.

Authorship contributions: Concept – P.D., C.K.A., P.M., I.S., K.K., N.M., P.X., C.C., K.G., D.T.; Design – P.D., I.S., C.C., K.G., D.T.; Supervision – P.D., I.S., C.C., K.G., D.T.; Fundings – None; Materials – None; Data collection &/or processing – None; Analysis &/or interpretation – None; Literature search – C.K.A., P.M., K.K., N.M., P.X.; Writing – C.K.A., P.M., K.K., N.M., P.X.; Critical review – P.D., I.S., C.C., K.G., D.T.

References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al.; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140-50. [CrossRef]
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al.; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539-49.
3. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol 2006; 21: 20-6. [CrossRef]
4. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008; 117: 2608-16. [CrossRef]
5. Gerber TC, Nishimura RA, Holmes DR Jr., Lloyd MA, Zehr KJ, Tajik AJ, et al. Left ventricular and biventricular pacing in congestive heart failure. Mayo Clin Proc 2001; 76: 803-12. [CrossRef]
6. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013; 34: 2281-329. [CrossRef]
7. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al.; Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013; 368: 1585-93. [CrossRef]
8. Chalil S, Stegemann B, Muhyaldeen S, Khadjooi K, Smith RE, Jordan PJ, et al. Intraventricular dyssynchrony predicts mortality and morbidity after cardiac resynchronization therapy: a study using cardiovascular magnetic resonance tissue synchronization imaging. J Am Coll Cardiol 2007; 50: 243-52. [CrossRef]
9. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA 2007; 297: 2502-14. [CrossRef]
10. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003; 89: 54-60.
11. Holland RP, Brooks H. The QRS complex during myocardial ischemia. An experimental analysis in the porcine heart. J Clin Invest 1976; 57: 541-50. [CrossRef]
12. Cardone-Noott L, Bueno-Orovio A, Minchole A, Zemzemi N, Rodriguez B. Human ventricular activation sequence and the simulation of the electrocardiographic QRS complex and its variability in healthy and intraventricular block conditions. Europace 2016; 18(suppl 4): iv4-iv15. [CrossRef]
13. Auricchio A, Fantoni C, Regoli F, Carbucicchio C, Goette A, Geller C, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 2004; 109: 1133-9. [CrossRef]
14. Galeotti L, van Dam PM, Loring Z, Chan D, Strauss DG. Evaluating strict and conventional left bundle branch block criteria using electrocardiographic simulations. Europace 2013; 15: 1816-21. [CrossRef]
15. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989; 79: 845-53.

Anatol J Cardiol 2019; 22: 132-9
DOI:10.14744/AnatolJCardiol.2019.35006

16. Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. Am J Physiol 1980; 238: H858-67. [CrossRef]
17. Tian Y, Zhang P, Li X, Gao Y, Zhu T, Wang L, et al. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. Europace 2013; 15: 1499-506.
18. Antoniou CK, Manolakou P, Magkas N, Konstantinou K, Chrysohoou C, Dilaveris P, et al. Cardiac Resynchronisation Therapy and Cellular Bioenergetics: Effects Beyond Chamber Mechanics. Eur Cardiol 2019; 14: 33-44. [CrossRef]
19. Chrysohoou C, Antoniou CK, Kotrogiannis I, Metallinos G, Aggelis A, Andreou I, et al. Role of right ventricular systolic function on long-term outcome in patients with newly diagnosed systolic heart failure. Circ J 2011; 75: 2176-81. [CrossRef]
20. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999; 99: 1567-73. [CrossRef]
21. Blanc JJ, Etienne Y, Gilard M, Mansourati J, Munier S, Boschat J, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. Circulation 1997; 96: 3273-7. [CrossRef]
22. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999; 99: 2993-3001. [CrossRef]
23. Bernier M, Josephson ME. RV electrical activation in heart failure during right, left, and biventricular pacing. JACC Cardiovasc Imaging 2010; 3: 576-7. [CrossRef]
24. Varma N, Jia P, Ramanathan C, Rudy Y. RV electrical activation in heart failure during right, left, and biventricular pacing. JACC Cardiovasc Imaging 2010; 3: 567-75. [CrossRef]
25. Lee KL, Burnes JE, Mullen TJ, Hettrick DA, Tse HF, Lau CP. Avoidance of right ventricular pacing in cardiac resynchronization therapy improves right ventricular hemodynamics in heart failure patients. J Cardiovasc Electrophysiol 2007; 18: 497-504. [CrossRef]
26. Antonini L, Auriti A, Pasceri V, Meo A, Pristipino C, Varveri A, et al. Optimization of the atrioventricular delay in sequential and biventricular pacing: physiological bases, critical review, and new purposes. Europace 2012; 14: 929-38. [CrossRef]
27. Jones RC, Svinarich T, Rubin A, Levin V, Phang R, Murillo J, et al. Optimal atrioventricular delay in CRT patients can be approximated using surface electrocardiography and device electrograms. J Cardiovasc Electrophysiol 2010; 21: 1226-32. [CrossRef]
28. Skinner NS Jr., Mitchell JH, Wallace AG, Sarnoff SJ. Hemodynamic effects of altering the timing of atrial systole. Am J Physiol 1963; 205: 499-503. [CrossRef]
29. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91: 2D-8D. [CrossRef]
30. Tolosana JM, Hernandez Madrid A, Brugada J, Sitges M, Garcia Bolao I, Fernandez Lozano I, et al.; SPARE Investigators. Comparison of benefits and mortality in cardiac resynchronization therapy in patients with atrial fibrillation versus patients in sinus rhythm (Results of the Spanish Atrial Fibrillation and Resynchronization [SPARE] Study). Am J Cardiol 2008; 102: 444-9. [CrossRef]
31. Barold SS, Herweg B. Cardiac Resynchronization in Patients with Atrial Fibrillation. J Atr Fibrillation 2015; 8: 1383.
32. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol (1985) 2008; 105: 1342-51. [CrossRef]
33. Ky B, French B, May Khan A, Plappert T, Wang A, Chirinos JA, et al. Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure. J Am Coll Cardiol 2013; 62: 1165-72. [CrossRef]
34. Antoniou CK, Chrysohoou C, Lerakis S, Manolakou P, Pitsavos C, Tsioufis K, et al. Effects of ventriculoarterial coupling changes on renal function, echocardiographic indices and energy efficiency in patients with acute decompensated systolic heart failure under furosemide and dopamine treatment: a comparison of three therapeutic protocols. Int J Cardiol 2015; 199: 44-9. [CrossRef]
35. Gorter TM, van Veldhuisen DJ, Voors AA, Hummel YM, Lam CSP, Berger RMF, et al. Right ventricular-vascular coupling in heart failure with preserved ejection fraction and pre- vs. post-capillary pulmonary hypertension. Eur Heart J Cardiovasc Imaging 2018; 19: 425-32. [CrossRef]
36. Sagawa K, Maughan WL, Suga H, Sunagawa K. Cardiac contraction and the Pressure-Volume relationship. New York: Oxford University Press; 1988.
37. García Guerrero JJ, Fernández de la Concha Castañeda J, Doblado Calatrava M, Redondo Méndez Á, Lázaro Medrano M, Merchán Herrera A. Left ventricular endocardial pacing in the real world: Five years of experience at a single center. Pacing Clin Electrophysiol 2019; 42: 763. [CrossRef]
38. Auricchio A, Delnoy PP, Butter C, Brachmann J, Van Erven L, Spitzer S, et al. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. Europace 2014; 16: 681-8. [CrossRef]
39. Nishimura RA, Hayes DL, Holmes DR Jr., Tajik AJ. 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: 281-8. [CrossRef]
40. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015; 65: 1231-48. [CrossRef]
41. Manfra O, Frisk M, Louch WE. Regulation of Cardiomyocyte T-Tubular Structure: Opportunities for Therapy. Curr Heart Fail Rep 2017; 14: 167-78. [CrossRef]
42. Auricchio A, Klein H, Tockman B, Sack S, Stellbrink C, Neuzner J, et al. Transvenous biventricular pacing for heart failure: can the obstacles be overcome? Am J Cardiol 1999; 83: 136D-42D. [CrossRef]
43. Touiza A, Etienne Y, Gilard M, Fatemi M, Mansourati J, Blanc JJ. Long-term left ventricular pacing: assessment and comparison with biventricular pacing in patients with severe congestive heart failure. J Am Coll Cardiol 2001; 38: 1966-70. [CrossRef]
44. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, et al.; Pacing Therapies in Congestive Heart Failure II Study Group; Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003; 42: 2109-16. [CrossRef]
45. Turner MS, Bleasdale RA, Vinereanu D, Mumford CE, Paul V, Fraser AG, et al. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block: impact of left and biventricular pacing. Circulation 2004; 109: 2544-9. [CrossRef]
46. Gasparini M, Bocchiardo M, Lunati M, Ravazzi PA, Santini M, Zardini M, et al.; BELIEVE Investigators. Comparison of 1-year effects of

left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: the Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. Am Heart J 2006; 152: 155. [CrossRef]
47. van Gelder BM, Bracke FA, Meijer A, Lakerveld LJ, Pijls NH. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. Am J Cardiol 2004; 93: 1500-3. [CrossRef]
48. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. Circulation 2002; 106: 2078-84. [CrossRef]
49. Porciani MC, Dondina C, Macioce R, Demarchi G, Pieragnoli P, Musilli N, et al. Echocardiographic examination of atrioventricular and interventricular delay optimization in cardiac resynchronization therapy. Am J Cardiol 2005; 95: 1108-10. [CrossRef]
50. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52: 1834-43. [CrossRef]
51. Bax JJ, Gorcsan J 3rd. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. J Am Coll Cardiol 2009; 53: 1933-43. [CrossRef]
52. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, et al.; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007; 357: 2461-71. [CrossRef]
53. Sirker A, Thomas M, Baker S, Shrimpton J, Jewell S, Lee L, et al. Cardiac resynchronization therapy: left or left-and-right for optimal symptomatic effect--the LOLA ROSE study. Europace 2007; 9: 862-8.
54. Boriani G, Kranig W, Donal E, Calo L, Casella M, Delarche N, et al.; B-LEFT HF study group. A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: the Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. Am Heart J 2010; 159: 1052-8. [CrossRef]
55. Thibault B, Ducharme A, Harel F, White M, O'Meara E, Guertin MC, et al.; Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex ≥120 milliseconds. Circulation 2011; 124: 2874-81. [CrossRef]
56. Skaf S, Thibault B, Khairy P, O'Meara E, Fortier A, Vakulenko HV, et al.; EARTH Investigators. Impact of Left Ventricular vs Biventricular Pacing on Reverse Remodelling: Insights From the Evaluation of Resynchronization Therapy for Heart Failure (EARTH) Trial. Can J Cardiol 2017; 33: 1274-82. [CrossRef]
57. Boriani G, Gardini B, Diemberger I, Bacchi Reggiani ML, Biffi M, Martignani C, et al. Meta-analysis of randomized controlled trials evaluating left ventricular vs. biventricular pacing in heart failure: effect on all-cause mortality and hospitalizations. Eur J Heart Fail 2012; 14: 652-60. [CrossRef]
58. Chen A, Chen X, Shen Y, Li W. Modalities of ventricular pacing for cardiac resynchronization therapy in patients with heart failure: a meta-analysis and systematic review. Arch Med Sci 2017; 13: 1006-17.
59. Garrigue S, Bordachar P, Reuter S, Jais P, Haissaguerre M, Clementy J. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: a prospective hemodynamic study. Card Electrophysiol Rev 2003; 7: 315-24. [CrossRef]
60. Rai MK, Prabhu MA, Sharma A, Vekariya R, Kamath P, Pai N, et al. 'Optimized' LV only pacing using a dual chamber pacemaker as a cost effective alternative to CRT. Indian Pacing Electrophysiol J 2017; 17: 72-7. [CrossRef]
61. Krum H, Lemke B, Birnie D, Lee KL, Aonuma K, Starling RC, et al. A novel algorithm for individualized cardiac resynchronization therapy: rationale and design of the adaptive cardiac resynchronization therapy trial. Am Heart J 2012; 163: 747-52. [CrossRef]
62. Martin DO, Lemke B, Birnie D, Krum H, Lee KL, Aonuma K, et al.; Adaptive CRT Study Investigators. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. Heart Rhythm 2012; 9: 1807-14. [CrossRef]
63. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail 2001; 7: 176-82. [CrossRef]
64. Birnie D, Lemke B, Aonuma K, Krum H, Lee KL, Gasparini M, et al. Clinical outcomes with synchronized left ventricular pacing: analysis of the adaptive CRT trial. Heart Rhythm 2013; 10: 1368-74. [CrossRef]
65. Singh JP, Abraham WT, Chung ES, Rogers T, Sambelashvili A, Coles JA Jr., et al. Clinical response with adaptive CRT algorithm compared with CRT with echocardiography-optimized atrioventricular delay: a retrospective analysis of multicentre trials. Europace 2013; 15: 1622-8. [CrossRef]
66. Birnie D, Hudnall H, Lemke B, Aonuma K, Lee KL, Gasparini M, et al. Continuous optimization of cardiac resynchronization therapy reduces atrial fibrillation in heart failure patients: Results of the Adaptive Cardiac Resynchronization Therapy Trial. Heart Rhythm 2017; 14: 1820-5. [CrossRef]
67. Hsu JC, Birnie D, Stadler RW, Cerkvenik J, Feld GK, Birgersdotter-Green U. Adaptive cardiac resynchronization therapy is associated with decreased risk of incident atrial fibrillation compared to standard biventricular pacing: A real-world analysis of 37,450 patients followed by remote monitoring. Heart Rhythm 2019; 16: 983-9. [CrossRef]
68. Malagoli A, Rossi L, Bursi F, Zanni A, Sticozzi C, Piepoli MF, et al. Left Atrial Function Predicts Cardiovascular Events in Patients With Chronic Heart Failure With Reduced Ejection Fraction. J Am Soc Echocardiogr 2019; 32: 248-56. [CrossRef]
69. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al.; CASTLE-AF Investigators. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med 2018; 378: 417-27.
70. Filippatos G, Birnie D, Gold MR, Gerritse B, Hersi A, Jacobs S, et al.; AdaptResponse Investigators. Rationale and design of the AdaptResponse trial: a prospective randomized study of cardiac resynchronization therapy with preferential adaptive left ventricular-only pacing. Eur J Heart Fail 2017; 19: 950-7. [CrossRef]
71. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011; 107: 927-34. [CrossRef]
72. Pappone C, Calovic Z, Vicedomini G, Cuko A, McSpadden LC, Ryu K, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: Twelve-month follow-up study. Heart Rhythm 2015; 12: 1250-8. [CrossRef]
73. Chrysohoou C, Dilaveris P, Antoniou CK, Skiadas I, Konstantinou K, Gatzoulis K, et al. Heart failure study of multipoint pacing effects on ventriculoarterial coupling: Rationale and design of the HUMVEE trial. Ann Noninvasive Electrocardiol 2018; 23: e12510. [CrossRef]