European Heart Journal Supplements (2023) **25** (Supplement C), C227–C233
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad046

Cardiac resynchronization therapy: present and future

Marco Schiavone[1,2], Roberto Arosio[1], Simone Valenza[1], Diego Ruggiero[1], Gianfranco Mitacchione[1], Leonida Lombardi[1], Maurizio Viecca[1], and Giovanni Battista Forleo[1]*

[1]Cardiology Unit, Luigi Sacco University Hospital, Via G.B. Grassi 74, Milan 20157, Italy; and [2]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

KEYWORDS
Cardiac resynchronization therapy;
Biventricular pacing;
Left ventricular pacing;
Conduction system pacing;
His-bundle pacing;
Left bundle branch area pacing

Cardiac resynchronization therapy (CRT) via biventricular pacing (BVP) is a well-established therapy for patients with heart failure with reduced ejection fraction and left bundle branch block, who remain symptomatic despite optimal medical therapy. Despite the long-standing clinical evidence, as well as the familiarity of cardiac electrophysiologists with the implantation technique, CRT via BVP cannot be achieved or may result ineffective in up to one-third of the patients. Therefore, new alternative techniques, such as conduction system pacing and left ventricular pacing, are emerging as potential alternatives to this technique, not only in case of BVP failure, but also as a stand-alone first choice due to several potential advantages over traditional CRT. Specifically, due to its procedural characteristics, left bundle branch area pacing appears to be the most convincing technique, showing comparable efficacy outcomes when compared with traditional CRT, not increasing short-term device-related complications, as well as improving procedural times. However, transvenous leads remain a major limitation of all these pacing modalities. To overcome this limit, a leadless left ventricular endocardial pacing has been developed as an additional tool to achieve a left endocardial activation, although being still associated with non-negligible pitfalls, limiting its current use in clinical practice. This article focuses on the current state and latest progresses in cardiac resynchronization therapy.

Cardiac resynchronization therapy: state of the art and current pitfalls

Cardiac resynchronization therapy (CRT) is a treatment cornerstone for patients with heart failure with reduced ejection fraction (HFrEF), who remain symptomatic despite optimal medical therapy (OMT).[1] Apart from reducing intraventricular conduction delay, thus preventing the subsequent mechanical dyssynchrony, CRT may induce cardiac reverse remodelling, potentially improving left ventricular (LV) function, reducing morbidity and mortality, as well as enhancing functional clinical status.[2]

Therefore, according to current guidelines, CRT might be recommended, on top of OMT, in symptomatic HFrEF patients, with different level of evidence according to QRS duration and underlying rhythm (sinus rhythm or atrial fibrillation, AF).[1] Moreover, CRT might also be considered as an upgrade from conventional pacemaker (PM) or implantable cardioverter defibrillator (ICD) in HFrEF patients with a high burden of pacing, or as a first-line treatment in patients with an expected high burden of pacing, undergoing PM or ICD implantation, with initial LV dysfunction. Despite the heterogeneous definitions of non-response to CRT among the different studies, approximately one-third of patients demonstrate a lack of echocardiographic reverse remodelling or poor clinical outcomes following traditional CRT implantation.[3]

*Corresponding author. Tel: +39 02 3904 4171, Fax: +39 02 3904 2311, Email: forleo@me.com

Table 1 Patient selection for cardiac resynchronization therapy implantation

	Best candidate	Worst candidate
QRS duration	>150 ms	<120 ms
QRS morphology	LBBB	Non-LBBB
Scar and dyssynchrony	(−)	(+)
Aetiology	CAD (−)	CAD (+)
Gender	Female	Male
Atrial fibrillation	(−)	(+)
CKD	(−)	(+)

CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block.

To address the challenge of CRT non-responsiveness, a careful selection of patients is mandatory, and several characteristics have been proposed as potential predictors of optimal or suboptimal CRT response (*Table 1*). The best candidates are known to present QRS duration >150 ms with left bundle branch block (LBBB) morphology, whereas there it is acknowledged that there is less benefit in non-LBBB morphology and shorter QRS durations.[4] Whether these two features represent the main predictors of a beneficial response to CRT is still a matter of debate, and other clinical characteristics, such as CRT implantation timing, have been considered as potential predictors during the last decade. Specifically, early CRT is considered to result into better outcomes whenever LBBB is judged to be the predominant cause of LV dysfunction, while CRT implantation in a 'bystander' LBBB-associated cardiomyopathy is possibly associated with unsatisfactory results. Regarding the underlying aetiology, ischaemic disease with large myocardial scar is associated with worse reverse remodelling and less improvement in LV function, when compared with non-ischaemic cardiomiopathy.[5] Moreover, women may respond to CRT better than men, possibly due to the smaller volume of ventricular chambers. Baseline cardiac rhythm is another parameter that has be considered in this regard; although recommended in sinus rhythm, CRT could also be an option in selected AF patients, who exhibit appropriate QRS duration and morphology.[1] This is because AF may interfere with adequate biventricular pacing (BVP) delivery because of its irregularity, fast ventricular rate, and the induction of fusion or pseudo-fusion beats. Thus, strategies to achieve rhythm control, or at least adequate rate control, are mandatory to ensure a satisfactory pacing rate. Finally, regarding comorbidities, chronic kidney disease is a strong and independent predictor of long-term mortality among patients undergoing CRT implantation.[6] Indeed, CRT provides a cardiac reverse remodelling across all CKD stages, although to a lesser extent in those with severe renal dysfunction.[7] These predictors have commonly been studied in the traditional CRT implantation setting, when physiological pacing is achieved via the coronary sinus, as the primary target for a left epicardial stimulation, in combination with a right-side endocardial pacing.[8]

However, several pitfalls still exist with this current approach. Indeed, although CRT via BVP is a well-established technique in common practice, it still results in a non-physiological cardiac activation and its clinical effectiveness is limited by the need to access the LV epicardial surface via the coronary sinus and its venous tributaries. First, optimal device implantation requires a suitable coronary sinus branch (usually posterolateral), allowing a sufficient myocardial recruitment without diaphragmatic capture. If the introduction of quadripolar leads and multipoint pacing techniques have been associated with higher implant success rates, lower risk of LV lead displacements or phrenic nerve stimulation,[9,10] there is still a non-negligible rates of patients with coronary sinus morphology unsuitable for CRT (up to 15% of patients),[11] conditioning an implantation failure of the LV lead. Thus, the venous anatomy (more than physician dexterity) dictates the choice of pacing site, risking possible suboptimal electrical pacing parameters and phrenic nerve stimulation. Moreover, after the implantation, the rate of 'CRT non-response' with the traditional BVP technique is ∼30%,[3] and BVP implantation might also be a particular time-consuming technique in the electrophysiology laboratories, even in tertiary centres with substantial expertise. Lastly, the risk of lead fractures and infections when positioning three catheters required for traditional CRT implantation in sinus rhythm is considerable, in a 'pacing world' that is going leadless, whenever possible, both for pacing[12] and defibrillation[13] techniques. To overcome these issues, several alternatives have been currently proposed, not only to treat patients in whom BVP cannot be achieved with traditional CRT, but also as a first-line alternative to this well-established technique (*Figure 1*).

Left ventricular pacing: time for a new era?

Left ventricular endocardial pacing

Left ventricular endocardial pacing can be achieved through an atrial transseptal approach, deploying the lead directly into the left ventricle. This technique guarantees the access to all LV regions, ensuring a faster impulse propagation and assuring a physiological and direct LV stimulation, preserving the sequence of transmural LV activation and subsequent repolarization.[14] The recent ALSYNC study was the first prospective multicentre trial which investigated the feasibility and the safety of an LV endocardial CRT delivered through the atrial transseptal approach. The 6-month implant success rate was achieved in 89.4% patients, with 82.2% of patients being free from complications at follow-up (mean follow-up: 17 + 10 months), showing stable pacing parameters as well. A clinical and echocardiographic improvement was detected in 59 and 55% patients, respectively, and no death was related to the primary safety endpoint (defined as: any transseptal implant tool, transseptal implant procedure, or left ventricular endocardial pacing (LVEP) lead-related adverse event resulting in patient death, confirmed stroke, termination of significant device function, or any invasive intervention, including administration of intramuscular and parental fluids).[15] A subsequent large meta-analysis analysing all current trials on this topic has reinforced these results.[16] The main concerns about LVEP are related to lead-related complications, and mainly to thromboembolic events. Thus, the LV lead can be the source of systemic embolic accidents, while a residual atrial septal orifice may predispose to paradoxical

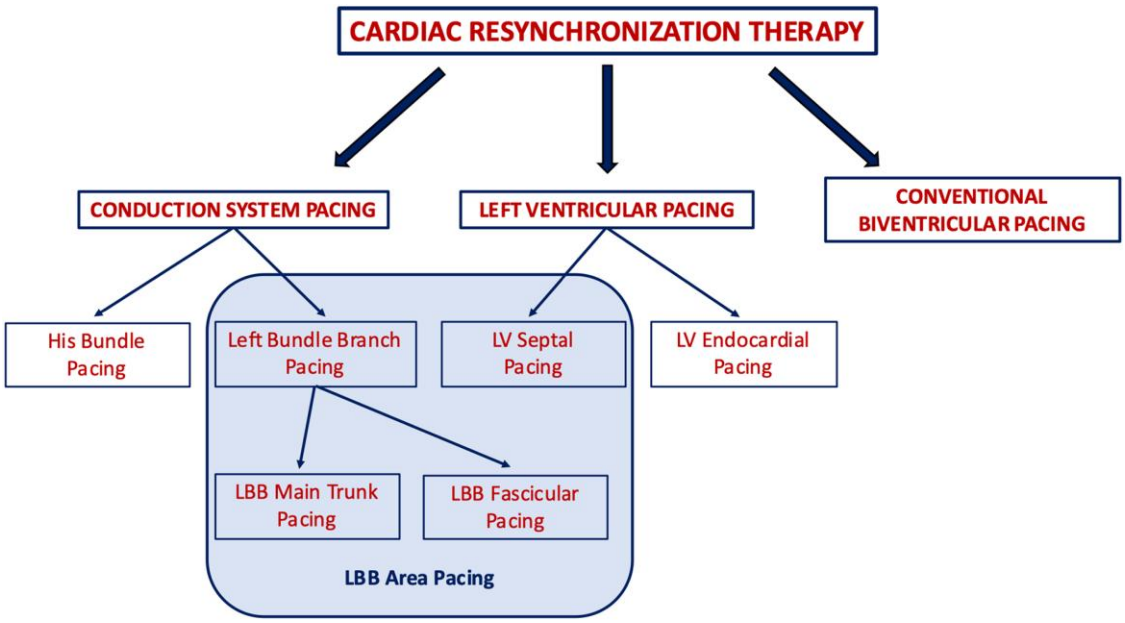

Figure 1 Novel pacing approaches for cardiac resynchronization therapy. New alternative techniques to conventional biventricular cardiac resynchronization therapy include conduction system pacing, such as His-bundle pacing and left bundle branch pacing (main trunk or fascicular branches), and left ventricular pacing, encompassing left ventricular septal pacing and left ventricular endocardial pacing. Left bundle branch pacing and left ventricular septal pacing fall into the left bundle branch area pacing.

embolization, facilitated by pulmonary hypertension, often already present in HF patients. To prevent these events, a long-term anticoagulation therapy, with its associated bleeding risk, is required after device positioning.[14] Indeed, in the previously mentioned ALSYNC study, transient ischaemic attacks and non-disabling strokes occurred in 6.8 and 3.8% of cases, respectively.[15] Moreover, when crossing mitral valve, LV lead could interfere with valvular function, increasing the risk of severe regurgitation and endocarditis. However, case reports and the ALSYNC study reported a stable grade of mitral regurgitation during follow-up, whereas endocarditis was an uncommon complication.[14,15] Lastly, there was no systematic experience of long-term LV endocardial pacing lead extraction in the context of thromboembolic complication or system infection.[15]

To overcome the limitations of a transeptal lead, a novel wireless LVEP system (WiSE-CRT system; EBR Systems, Sunnyvale, CA, USA) has been developed. This system is composed by an ultrasound pulse generator, implanted subcutaneously in an intercostal space, and a small receiver electrode, deployed percutaneously into the LV cavity, being able to convert ultrasound waves into electrical energy. After 1 month, the electrode is fully endothelialized, avoiding the need for long-term anticoagulation. The right ventricular pacing triggers the LV stimulation, ensuring a near simultaneous endocardial activation on both sides. In the first multicentre experience, the system was successfully implanted in 94.4% of non-CRT responder patients, improving functional class in 70% of subjects at 6 months. Complications rates were reported to be low, and five deaths (5.6%) were described, with three procedure-related deaths, occurring within 6 months from system implantation. Regarding procedural complications, it is mandatory to perform the implantation by appropriately trained operators at centres with immediately available cardiothoracic and vascular surgical support.[17] Besides the atrial transseptal approach, transaortic and transapical LV lead implantations have been theorized and reported in anecdotical cases. The feasibility and safety of a transaortic approach, via carotid artery, has been successfully studied in a pig model. No thromboembolic events occurred despite the lack of anticoagulation therapy and aortic valvular regurgitation. Few case reports described a transapical method so far, requiring a surgical approach, but possibly reducing the risks of mitral valve regurgitation. The long-term safety and efficacy of these techniques, as well as the target population, need to be examined in larger human studies.

Left ventricular septal pacing

Left ventricular septal pacing (LVSP) is another promising alternative to achieve a more direct LV electrical activation, by pacing the LV endocardial side of the interventricular septum (IVS). During sinus rhythm with a normal interventricular conduction through the His-Purkinje system, the activation of the LV starts in the LBB. The impulse exits at the LV endocardial surface of the IVS, then proceeding from the left to the right septal side and in an apico-basal direction. LV function depends on both QRS duration and the sequence of ventricular activation. Therefore, pacing near this exit site has been proved to ensure a physiological activation pattern with only a slight delay related to the RV free wall involvement. Although LVSP and RV septal pacing sites are very close, the significant delay in transseptal conduction during RV stimulation defers LV electrical and mechanical activation, potentially causing dissynchrony.[18] Because of its positive haemodynamic effects, LVSP has been investigated as alternative to BVP for CRT. Specifically, in animal studies, the LV septal

lead was deployed by introducing a pacing lead with extended helix into the RV and then placing it through the IVS into the LV septum. These findings have been then confirmed by Mafi-Rad *et al.*[19] in the first-in-man study (2016), demonstrating the feasibility of this technique using a transvenous approach. These authors highlighted that LV septal pacing has the potential to reduce electric dyssynchrony, while improving the acute haemodynamic performance compared with RV pacing, both apical and septal. The results of this study suggest that LV septal pacing may represent a valid alternative for antibradycardia pacing, even in patients with narrow QRS. Furthermore, LVSP ensured an improvement in LV pacing that was comparable with BVP and His-bundle pacing, when a proper haemodynamic evaluation was performed.[20] With a further long-term validation, LVSP might be able to offer a physiological solution for patients undergoing CRT, even if the magnitude of these potential risks of a possible LVS lead extraction. Indeed, extractions of a deep septal lead, due to infections or lead malfunction, pose significant concerns of creating a ventricular septal defect. Also, the temporary protrusion of the extraction sheath in the LV cavity could potentially enhance the risk of systemic embolization, especially in infective cases.

Conduction system pacing: back to the future?

Conduction system pacing is obtained deploying permanent pacing leads along different sites of the cardiac conduction system, both including His-bundle pacing (HBP) and left bundle branch pacing. In the last years, this technique has come to light to achieve cardiac resynchronization in patients with HFrEF and interventricular dyssynchrony, when compared with traditional CRT achieved via BVP (*Table 2*).

His-bundle pacing

The HBP stimulates the His-Purkinje system and restores the physiological activation of both ventricles. Described for the first time in 1970s,[26] this technique has demonstrated to be feasible and safe in different settings, improving functional NYHA class, reversing cardiac remodelling and increasing ejection fraction.[27] After some observational studies on this topic, the His-SYN Pilot Trial was the first randomized trial comparing HBP and BVP for CRT: HBP-CRT ensured a greater QRS narrowing and a non-significant trend towards a better echocardiographic response, while cardiovascular hospitalization or mortality did not differ significantly.[22] Compared with BVP-CRT, HBP-CRT provides these similar outcomes at the expense of higher pacing thresholds, as showed in His-Alternative Trial,[23] posing significant concerns especially during follow-up, due to premature battery depletion. Thus, HBP effectiveness is hampered by several factors. First, the implantation technique is challenging due to the narrow anatomic target zone, determining a moderate success rate. Second, HBP is often associated with high unstable pacing thresholds, shortening the longevity of device battery. Due to low R-wave amplitudes recorded, both an atrial oversensing and a ventricular undersensing are possible, configuring a potential atrial-ventricular crosstalk phenomenon. Finally, when the conduction system conduction delay is distal or more extensive, HBP alone may not achieve to shorten QRS duration, failing to restore the biventricular synchronous activation, thus not achieving adequate results in terms of CRT.[18]

Left bundle branch area pacing

Considering HBP limitations, pacing the conduction system distal to His bundle has been proposed to bypass the potential block region and achieve a more distal and profound cardiac resynchronization. Thus, pacing the LBB has been more recently introduced as a valid method to achieve LV synchrony in this scenario. In the CRT setting, left bundle branch area pacing (LBBAP) is appearing to be a feasible, safe, and promising alternative, not only in patients with unsuccessful BVP-CRT implantation or non-responders, but also as a first-line alternative to achieve intraventricular conduction delay resolution.[28] LBBAP techniques include both LBB (main trunk or anterior/posterior fascicles) pacing, with the main trunk representing the selected target in LBBB patients, and LVSP, previously described (*Figure 2*). At the same time, in patients without conduction disturbances (narrow QRS), the retrograde activation of the right bundle branch can rapidly activate the right ventricle with less time delay, thus maintaining interventricular synchrony and potentially achieving a physiological ventricular synchrony, proving an adequate pacing strategy also in the setting of pure antibradycardia pacing without intraventricular conduction disturbances. LBB capture is defined by several parameters: a LBB potential recording during intrinsic rhythm, a paced right bundle branch block morphology, a constant LV activation time during different pacing outputs, and the documentation of a transition from non-selective LBBP to selective LBBP or non-selective LBBP to LVSP (with LV endocardial capture). The main difference between LVSP and LBBP is that a proper capture of the LBB is reached in LBBP, while the myocardial capture is prevalent in LVSP. Thus, if LBBP allows to obtain a synchronous electrical activation of the LV, by involving the conduction system directly, LVSP results in a more abrupt left-to-right transseptal depolarization but also in a delayed LV lateral wall depolarization.[29] However, according to current literature, the LBB capture rate varies from 60 to 90%, meaning that many patients undergoing LBBP are indeed unintendedly treated with LVSP, especially if several mechanical rotations of catheter with extended helixes needs to be performed in thicker septa. Therefore, caution should be taken with this approach. A terminal R/r or rs/Rs morphology in lead V1, more than pseudo-RBBB morphology with the terminal r/R in lead V1, may represent an electric marker of LVSP capture. Moreover, when decreasing the pacing output from 5 V to loss of capture, either no changes or only minor changes in QRS morphology and V5 R-wave peak time (<10 ms) are usually observed when capturing in-depth the LV. However, both techniques allow to get adequate pacing of the LBB area.

Apart from slight differences in the pacing site, compared with BVP-CRT, LBBAP-CRT was associated with a significantly shortened QRS duration, improved NYHA class, reduced LV dimensions and increased LV ejection fraction.[28,30] On the other hand, in comparison with HBP, LBBAP showed similar clinical outcomes, with better

Table 2 Conduction system pacing vs. conventional biventricular pacing for cardiac resynchronization therapy: randomized trials

Authors	Year	CSP target	Total patients	Population characteristics	Follow-up (months)	Endpoints
Lustgarten *et al.*[21]	2015	HBP	29	71 years, NYHA I-III, LVEF 26.5%, LBBB, QRSd 162 ms, CAD 55%	6	Similar improvement in NYHA class, 6MWT, LVEF
Upadhyay *et al.* (HIS-SYNC)[22]	2019	HBP	41	65 years, NYHA II-IV, LVEF 28%, QRSd 168 ms, CAD 65%	12.2	Greater QRSd reduction for HBP (−20 vs. −1 ms) No difference in LVEF improvement, freedom from CV hospitalization and mortality
Vinther *et al.* (HIS-alternative)[23]	2021	HBP	50	66 years, symptomatic HF, LVEF ≤ 35%, LBBB, QRSd 166 ms, CAD 25%	6	No difference in NYHA class and LVEF improvement. Similar reduction on NT-proBNP, QRSd, and LVESV. Higher pacing thresholds for HBP at implant (1.8 vs. 1.2 V) and follow-up (2.3 vs. 1.4 V)
Wang *et al.*[24]	2022	LBBP	40	64 years, NYHA Class 2.4, LVEF 29%, QRSd 174 ms, CAD 0%	6	Higher improvement in LVEF for LBBP (+5.6%). Favourable reduction in LVESV and NT-proBNP for LBBP. No difference in NYHA class and 6MWT improvement.
Pujol-Lopez *et al.* (LEVEL-AT)[25]	2022	HBP (11%) LBBP (89%)	70	67 years, NYHA Class 2.4, LVEF 28%, QRSd 178 ms, CAD 31%	6	Similar decrease in LVAT. No difference in LVESV reduction and freedom from HF hospitalization and mortality

CAD, coronary artery disease; CSP, conduction system pacing; HBP, His-bundle pacing; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LVAT, left ventricular activation time; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; QRSd, QRS duration; V, volts; 6MWT: 6 min walk test.

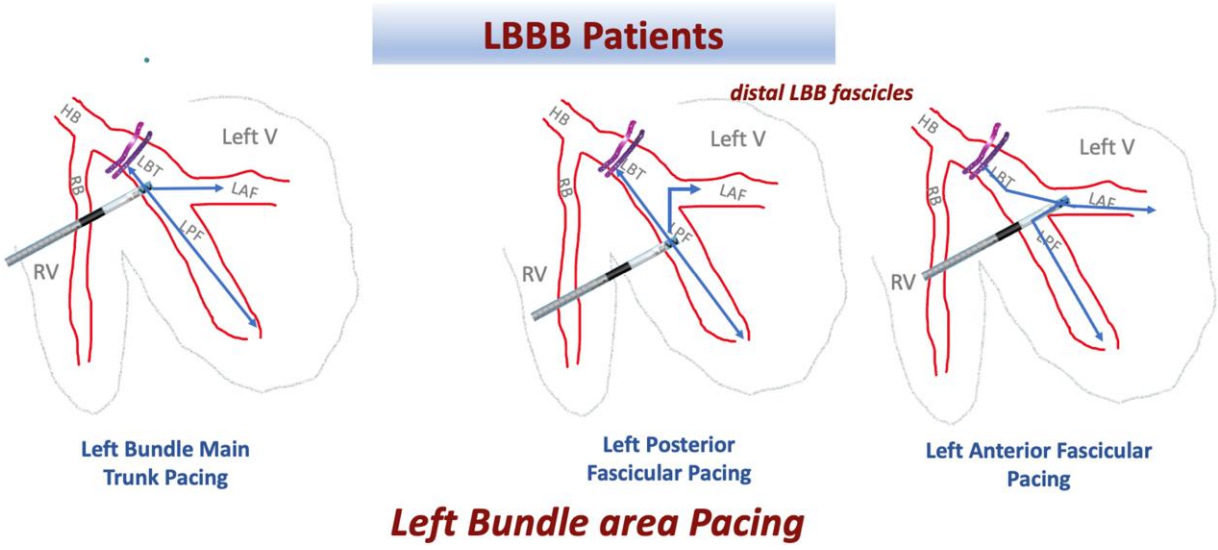

Figure 2 Left bundle area pacing in left bundle branch block patients: target zones.

results in terms of higher success rates of implantation, lower and stable capture thresholds, and longer battery longevity. However, it has to be highlighted that several complications could be associated with this procedure. In the acute setting, since the lead advances into the deep IVS, an LV perforation could occur, while, in a long-term perspective, the safety of lead extraction after a long duration has not been widely explored yet, as previously mentioned for the LVSP technique. Given the exciting results of recent studies on LBBAP, this technique is emerging as an optimal alternative to BVP-CRT in patients with LV dysfunction and conduction disturbances, and also in patients needing ventricular pacing due to atrioventricular blocks. Data on long-term effects are lacking and needed to confirm the potential role of these pacing modalities and deepen the knowledge about their similarities and differences.

Conclusions

Cardiac resynchronization therapy is a well-established therapy for patients with HFrEF and LBBB, who remain symptomatic despite OMT. The long-standing clinical evidence data, as well as the habits to achieve cardiac resynchronization via biventricular pacing, still give to this technique the leading role in common clinical practice in this scenario. However, new alternative techniques, such as conduction system pacing (HBP and LBBAP) and left ventricular pacing (either endocardial or septal), are emerging as potential alternatives to BVP, not only in case of failure or non-response, but also as a stand-alone first choice due to several potential advantages. Specifically, due to its procedural characteristics, LBBAP appears as the most convincing technique, showing comparable efficacy outcomes, not increasing short-term device-related complications, as well as improving procedural times. More studies are necessary to better understand these new techniques, in comparison with traditional BVP, especially regarding long-term efficacy and safety data.

Acknowledgement

The past must be known to understand the present and to guide the future (Tucidide, 460-404 a.C.).

Funding

No funding has been used for this work.

Conflict of interest: None declared.

Data availability

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

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