Conduction System Pacing: How far are we from the "electrical" bypass?

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Abstract

Conduction system pacing is an alternative practice to conventional right ventricular apical pacing. It is a method that maintains physiologic ventricular activation, based on a correct pathophysiological basis, in which the pacing lead bypasses the lesion of the electrical fibers, and the electrical impulse transmits through the intact adjacent conduction system. For this reason, it might reasonably characterized by the term "electrical bypass" compared to the coronary artery bypass in revascularization therapy. In this review reference is made to the sequence of events that conventional right ventricular pacing may cause adverse outcomes. Furthermore, there is a reference to alternative strategies and pacing sites. Interest focuses on the modalities for which there is data from the literature, namely for the Right Ventricular (RV) septal pacing, the His Bunde pacing (HBP), and the Left Bundle Branch pacing (LBBP). A more extensive reference is about the HBP, for which there are the most updating data. We analyze the considerations that limit HBP wide application in three axes, and we also present the data for the implantation and follow-up of these patients. Then, the indications with their most important studies to date are described in detail, not only in their undoubtedly positive findings but also in their weak aspects, because of which, this pacing mode has not yet received a strong recommendation for implementation. Finally, there is a report on LBBP, focusing mainly on its points of differentiation from HBP.

1. Introduction

Conduction system pacing (CSP) was a subject of intense discussion at the European Society of Cardiology (ESC) Congress 2021 due to an ever-growing interest in the past five years, both in the literature and clinical practice.[1] This is because of the deeply established knowledge that chronic conventional right ventricular (RV) pacing is responsible for an increased risk of provoking and worsening heart failure with hospitalizations, as also atrial fibrillation or even causing death.[2] The fact that conventional RV apical pacing (RVA pacing), through inter-ventricular dyssynchrony, promotes the appearance rather sooner than later of Pacing-Induced Cardiomyopathy makes it responsible for the disturbance of the diastolic and systolic function of both right and left ventricle, with the subsequent adverse impact on patients. (**Figure 1**)

For the prevention of this phenomenon, alternative pacing strategies and sites have been proposed. On the one hand, pacing different areas of the myocardium outside the apex of the RV (non-apical RV pacing) by targeting the interventricular septum at various higher positions, such as this happens with the Right Ventricular Outflow Tract (RVOT) septal pacing, the Mid and High RV Septal (RVS) pacing, but also Para-Hisian pacing, and from the other attempt pacing parts of the conduction system (Conduction System Pacing - CSP), as with Left Bundle Branch Area pacing (LV Septal pacing or Left Bundle Branch pacing), but also His Bundle pacing (HBP). (**Figure 2**)

2. Non-apical RV pacing

RV septal pacing is the only one during the last decade for which randomized studies have been conducted both for indications of high-grade atrioventricular (AV) block disorders and cardiac resynchronization therapy. Regarding the first indication, the Protect-Pace study compared RV apical and septal pacing.[3] There were randomized 240 patients with preserved Left Ventricular Ejection Fraction (LVEF) > 50%, requiring high-burden RV pacing > 90%, for two years of follow-up. The study concluded that LVEF decreased in both groups (apical and septal) to the same non-statistically significant degree. At the same time, there was no significant difference in heart failure hospitalizations, mortality and atrial fibrillation burden as well as biomarkers levels, such as Brain Natriuretic Peptide (BNP). On the contrary, a longer time was required for the RV septal implantation procedure with an increase up to doubling the fluoroscopy time.

Regarding RV septal pacing compared to RVA for the application of cardiac resynchronization therapy (CRT), the randomized study performed was the SEPTAL CRT study.[4] 263 patients were randomized for septal and apical pacing in the CRT context. The results showed non-inferiority of septal, compared to the apical position of the RV electrode, in terms of reduction of echocardiographically determined left ventricular end-systolic volume (LVESV) and composite clinical endpoint of deaths and hospitalizations for heart failure, at a 6-month follow-up. The above two studies were the cause that RV septal pacing did not officially approve for routine implementation in permanent pacemaker implantations.

The precise placement of the RV electrode in a septal position is a matter that is not easy to ascertain through the fluoroscopy currently used. Nevertheless, in addition to the above two randomized studies, a meta-analysis of all available studies demonstrated a benefit of non-apical RV pacing, compared to apical, in patients who had pre-implantation reduced LVEF <40%.[5]Furthermore, in an observational study, in 2200 patients having 3822 active-fixation pacing and defibrillation leads, the apical location of the RV lead, especially for female gender and age >80 years, appeared to be statistically associated with cardiac perforation.[6] Therefore, the effort to place the electrode in a non-apical position with the data so far is not systematically recommended for every patient needing pacing therapy but should perhaps be considered for these specific categories. The summarized data for non-apical RV pacing instead of RV apical pacing is in **Table 1** .

3. Conduction system pacing: An "Electrical Bypass"

Therefore, given that the pacing of the RV myocardium beyond the apex is not always associated with favorable clinical endpoints, the effort to find and pace the conduction system in order to avoid Pacing-Induced Cardiomyopathy is deemed essential. CSP comprises His bundle pacing (HBP) and Left Bundle Branch Area pacing (LBBAP). This technique is based on a pathophysiologically correct theory and could be considered an "Electrical Bypass". (**Figure 3**) The role of the venous graft used in revascularization therapy is represented in this setting by the pacing lead. By bypassing a lesion of the native pacing system, which usually occurs in the area of the AV node, with the pacemaker lead and transmitting the stimulus downward through the remaining intact part of the system, results in faster transmission of the electrical impulse with the normal mode, but also simultaneous stimulation of both ventricles, and therefore the avoidance of the unfavorable phenomenon of dyssynchrony. As a result, CSP could be characterized as an "ideal" form of pacing. Speaking of an ideal pacing method, this should be easily applicable to all patients with AV system disorders, without complications, and with long-term beneficial clinical endpoints, namely, a form of pacing where the answer to the question "when and to whom patients" is "always and to everyone"!

This idea is not new. More than half a century before, in 1970, Narula et al. in a series of 30 patients with conduction disturbances in the AV node, through the transvenous technique, found the His Bundle, mapped it, measured the corresponding intervals, and successfully induced pacing.[7] Nevertheless, permanent HBP has applied 30 years afterward, in 2000, in a series of 18 patients, with impaired left ventricular systolic function and atrial fibrillation before AV node ablation.[8] Successful pacing was achieved in 14 patients, with satisfactory results as far as the improvement of left ventricular dimensions and LVEF from 20 to 31%. However, despite the good outcomes, the HBP procedure did not proceed on a large scale, recording a plateau in clinical application and literature research. That is because of the following three considerations, schematically illustrated in **Table 2** .

4. HBP: "Why not always and to everyone"?

4.1. Anatomical Considerations

The first reason this pacing method does not apply widely until now is the formation and anatomical location of the AV conduction system. The AV node is located from the perspective of the right atrium within the triangle of Koch, an area defined by heterogeneous structures. On one side is the tendon of Todaro in the Eustachian ridge, just below is the ostium of the coronary sinus, and on the other side is the constantly moving septal leaflet of the tricuspid valve.[9] From this position, the AV node, as it converts into the His Bundle, enters the electrically inactive fibrous cardiac skeleton, then passes to the membranous portion of the interventricular septum, where its two bundles, right and left, after their separation, advance into the myocardium of the corresponding areas of the septum.

Additionally, it is not only the complex path of the conduction system but also the dimensions of these formations: the mean length, width, and thickness of the compact AV node are 3.5 ± 1.2 mm, 4.5 ± 1.1 mm, and 1.2 ± 0.3 mm, respectively, and the tubular His Bundle has only a length of 20 mm and a diameter of 4 mm.[10] But even the placement of the His Bundle within the myocardium anatomically varies and can be distinguished into three types: His bundle may run under the membranous portion of the interventricular septum, it may run within the muscular portion of the interventricular septum beyond the lower border of its membranous portion, so in this case, it is hard to achieve pure selective pacing, and also it may be located beneath the endocardium with no surrounding myocardial fibers.[11] Therefore, the position and course, the minuscule size, and the anatomic variations of the conduction system are a challenge to be confronted with fluoroscopy to reveal electrical signals and give a stimulation. That is precisely where the second consideration for HBP lies.

4.2. Technical Considerations

Fluoroscopy is inaccurate for localizing lead positions compared with other imaging methods, such as cardiac computed tomography (CT). Indeed, in a series of 59 heart failure patients undergoing CRT, the agreement for the left ventricular lead position was observed in 35% and for the right ventricular lead position in only 22% of the patients with fluoroscopy, respectively.[12] The agreement within and between observers was much better and more accurate for cardiac CT (kappa 0.87 and 0.85 for both left and right ventricular lead position, respectively). Further, another technical limitation is the implantation tools for HBP. Although several companies in the pharmaceutical industry have created pacing leads for His Bundle, the most commonly used HBP lead is the 69 cm Select Secure 3830 (Medtronic), a non-stylet-driven active fixation lead.[13] This lead can be delivered to the His bundle region using either the specially-designed non-deflectable His delivery sheath (C315 43 cm; Medtronic) or a deflectable sheath (C304 69 cm; Medtronic). A characteristic of this 4.1 Fr (French gauge) bipolar lead is that the 1.8 mm exposed-helical-screw design forms part of the tip electrode, with 9 mm tip to ring spacing, allowing easier detection and thus pacing of His Bundle fibers. It has unipolar mapping capabilities and minuscule size, reducing flow stresses and valvular motion effects, thus giving maximum stability in that demanding area.[14] This lead has the best features after 50 years of trying pacing His Bundle using primarily fluoroscopic guidance and afterward electrical mapping for its placement.

As a technique, it does not have any critical complications for the patient, apart from those related to the vein puncture, as with conventional pacemakers implantation. However, there are two main troubles: the possibility of an increase in pacing threshold, which is observed at about 10% of the patients, leading to shorter battery-life duration, as well as the higher rate of lead revisions in an actual percentage ranging from 6.7 - 8.9 %, due to loss of capture or increased threshold. In order to avoid the above two concerns, a 'backup' right ventricular lead can be used. The use of a 'backup' lead is recommended in HBP in cases of the inexperience of the implanter, acceptable threshold achieved at the upper limit, at about 2V/1ms, possible schedule of an AV node ablation shortly, but also in cases of high-degree or infranodal block, especially in entirely pacemaker-dependent patients.[1] Undoubtedly, an extra third lead for pacing has the advantage of safety, especially in cases of loss of capture, and it has better sensing compared with the HBP lead. However, more transvenous hardware for pacing (three versus two leads) increases the procedure's cost, along with the risk of complications, both during implantation (ventricular perforation or vein thrombosis) and after, such as lead damage or risk of endocarditis. From all the anatomical and technical limitations mentioned, which may lead to a possible increase in pacing threshold and the need for lead revisions, arises the third consideration, which is also restrictive of HBP widespread application.

4.3. Programming Considerations

Minimal dimensions of both the structures and the HBP lead cause a variety of expressions of attempted CSP.[15] During the implantation process, the pacing lead may achieve exclusive stimulation of the intrinsic conduction system (selective pacing), may stimulate a part of the system and part of adjacent myocardial fibers (non-selective pacing) or the neighboring myocardial fibers only, failing directly stimulate the conduction system (myocardium-only pacing). These combinations may occur for both the His Bundle and the Left Bundle Branch area, presenting nine patterns of pacing: Selective HBP, Non-Selective HBP, Myocardium-Only (Para-hisian) Pacing, Selective Left Bundle Branch Pacing (LBBP), Non-Selective LBBP, Left Ventricular Septal Pacing, Right Ventricular Septal Pacing, Mid-septal capture, and Anodal capture (simultaneous capture of the interventricular septum and left bundle branch from lead's ring and tip, respectively). Of course, the arisen question is whether Selective pacing is superior to Non-Selective pacing in terms of clinical endpoints. In a study of 350 consecutive patients with successful HBP and [?]20% ventricular pacing burden, Selective and Non-Selective HBP have associated with similar outcomes of death and heart failure hospitalizations together as a primary endpoint. However, when heart failure hospitalizations and all-cause mortality were studied as secondary endpoints separately, Selective pacing appeared to be superior in the latter.[16]

Selective and Non-Selective pacing can be recognized through the His bundle lead threshold check electrocardiographic parameters during the implantation. These parameters are mainly related to the morphology and duration of the intrinsic QRS. These electrical responses are hard to assess by only the implanter, so an additional familiar with the procedure person needs to estimate these changes, and that's another reason that makes this procedure demanding.[15] In situations with narrow QRS, Selective HBP is easily distinguished with an isoelectric interval (corresponding to the H-V interval) between the pacing spike and QRS onset, whereas in Non-Selective HBP, a 'pseudo-delta' wave is observed due to the capture of local myocardium, before the onset of paced QRS.[17, 18] In situations of Bundle Branch Block (BBB) presence, correction of BBB may be observed during these electrical tests at the pacing threshold.[19] Another characteristic of the transition with reduction of pacing output is that Myocardium only capture instead of Selective HBP is observed before the loss of capture (LOC).[17] Some examples follow for the beneficial effect of HBP on the electrocardiographic duration of ventricular depolarization compared to biventricular pacing and conventional apical RV pacing. The loss of pacemaker capture during threshold control, and the recording of selective and nonselective pacing on the electrocardiogram, are also shown. In addition, the position of the three electrodes in the fluoroscopic view during HBP implantation is apparent. (**Examples 1-4**) Except for QRS duration, other electrocardiographic parameters are examined, such as H-QRSend = duration from His potential to QRS offset, LBpo-QRS-LVAT = duration from left bundle potential to peak of R wave in lateral leads (where the time of the peak of the R wave in lead V5 or V6 is thought to represent lateral LV activation time, LVAT), Stim-QRSend = duration from pacing stimulus to QRS offset, Stim-QRS-LVAT = duration from pacing stimulus to the peak of R wave in lateral leads, and Stim-V = interval from pacing stimulus to the onset of QRS.[15]

Moreover, in cases of conduction system disease with BBB, it is examined whether or not there is a correction of the pre-existing disorder in the branches of the His Bundle. Even in cases where there is no complete correction of the block, the width of the QRS with HBP is narrower than the initial.[11] Thus, electrocardiographic criteria have been proposed based on the various types of pacing in combination with the intrinsic electrocardiogram, and that is undoubtedly more demanding than simple conventional pacing.[20]

In HBP, there are also troubleshooting issues to take care of because they cause programming considerations, not only during implantation but also at outpatient follow-up.[21] Two issues that should be taken care of during implantation, and have to do with the position of the His lead, are those of atrial oversensing and ventricular undersensing. Attention should be paid to cases of atrial capture with the His lead due to loss of His Bundle capture, as there may be morphologies with a short PR interval (due to proximity to the AV node) but also with a narrow P-wave morphology (due to simultaneous bi-atrial activation).[17] In addition, His leads may produce pacing artifacts, especially at high pacing thresholds, and morphologies that may be confusing when reading the electrocardiogram, such as retrograde P-wave and anodal capture.

Atrial ovesensing should be checked at each follow-up visit, as should any threshold increases that may occur during the follow-up period. HBP thresholds are usually higher when compared with other pacing sites, not only because His Bundle is encased in a fibrous sheath which is electrically non-conducting but also because of the concomitant His area disease, including local fibrosis and degeneration. Underlying conditions, such as right atrial dilatation, septal hypertrophy, or infiltrative situations, as in sarcoidosis or amyloidosis, should be considered for threshold issues, as well. Finally, the ports that His lead is placed in, especially at CRT devices (atrial, right ventricular, or left ventricular port), should be taken into account so that the timing intervals are accurately measured, and the correct algorithms are appliable.[22, 23] For these reasons, a specialized Pacemaker Technician is required, who will actively participate with knowledge and suggestions during the implantation process. In conclusion, HBP associates with more clinical and technical issues, and an every six months closer surveillance, which for many elderly patients may not be so practical, unlike conventional pacemakers, where the in-office follow-up oughts to be annual.[1]

5. HBP: Implantation and follow-up

Despite the described difficulties of HBP, there are data from a small number of centers indeed that show encouraging results for this implantation technique, as well as for the follow-up of these patients regarding the variation of the pacing parameters within the time. In a recently published study including a total of 529 patients, in five years, with a mean 7-month follow-up, a relatively short learning curve was recorded, with an overall implant success rate of 81%, which improved to 87 % after completion of 40 cases.[24] The mean fluoroscopy time was 11.7 ± 12.0 min, and His capture threshold decreased. HBP lead re-implantation occurred in 7.5% of successful procedures mainly due to threshold rise. It is worth noting that the QRS duration decreased by 26 msec in patients with an intrinsic QRS $>$ 120 msec, while on the contrary, an insignificant increase in the QRS width by 12 msec observed in the patients with a narrow QRS.

Regarding the efficacy of HBP, in QRS duration change with non-selective or selective pacing, in the absence of BBB, selective and non-selective pacing minimally affected QRS duration, whereas, in the presence of BBB, QRS duration markedly decreased with both patterns of HBP.[18] AV block morphology seems to affect the procedural success and needs to be considered before applying this type of pacing. In a recently published meta-analysis of 1438 patients, the implant success rate of the lead in the bundle of His averaged 84.8%, considerably higher than that with older stylet-driven leads with which the success rate reached up to just 70%. LVEF improved by an average of 5.9% during follow-up and even more in ventricles with impaired systolic performance $<$50%, while in preserved LVEFs, no statistically significant change recorded. Average pacing thresholds were 1.71 V at implant and 1.79 V at $>$3 months follow-up, with various pulse widths.[25]

Also, according to recently published data, both the intermediate-term and the long-term performance of HBP leads seem to be quite encouraging for the implantation success rate and the threshold maintenance. Nevertheless, threshold increase and the loss of selective pacing have not been overcome in this study, too, during a follow-up period of 1.5 years, and that may cause a lead revision in rates up to 10%.[26] Additionally, in patients' follow-up data for five years, HBP proved superior to RV pacing in paced QRS duration and LVEF improvement with significantly lower rates of occurrence of Pacing-Induced Cardiomyopathy, findings affecting clinical endpoints, such as death and heart failure hospitalizations, especially in patients with $>$40% ventricular pacing.[27] A summary of published trials conducted in the last 15 years on HBP with clinical and/or echocardiographic follow-up is included in the 2021 ESC Guidelines' supplementary data on cardiac pacing and cardiac resynchronization therapy.[1] Therefore, according to all mentioned, the question of "when and in which patients" it is worth applying the HBP could be answered based on the following four axes, as shown in summary in **Figure 4** .

6. Indications of His Bundle Pacing: When and to whom?

6.1. Pacing for bradycardia

Several small studies have demonstrated the superiority of HBP over RV pacing in avoiding Pacing-Induced Cardiomyopathy. Even though upgrading simple RV to biventricular pacing could be a highly effective solution in patients with post-implant LVEF <35%, nevertheless, it is significantly underutilized even in those with lower preimplant LVEF.[28] The echocardiographically estimated LVEF is used as a study indicator of Pacing-Induced Cardiomyopathy, knowing, of course, the limitations of this indicator in terms of the impact of clinical endpoints and mortality in patients with heart failure.[29] The older studies by Zanon et al. (2008), Barba-Pichardo et al. (2010), and Kronborg et al. (2014) recorded an LVEF improvement in 12, 59, and 32 patients, respectively, mainly with atrioventricular block, with relatively short follow-up of 3-12 months, in single-center trials.[30-32] Sharma et al. (2015) and Vijayaraman et al. (2018) included 75 patients in each study, recording less heart failure hospitalization and a trend in lower mortality in patients with >40% ventricular pacing, as well as no difference in patients with atrial fibrillation, in HBP group.[27, 33]

The largest study is that of Abdelrahman et al. (2018), a two-center study that included 304 consecutive patients with HBP and 433 patients with RV pacing at a sister hospital. In a 2-year follow-up, the study showed the superiority of HBP in terms of the combined endpoint of all-cause mortality, heart failure hospitalization, or upgrade to biventricular pacing. The HBP superiority was even great in patients with ventricular pacing >20% (HR 0.71 and 0.65, respectively).[34] Additionally, two recently published studies with a small number of patients with bradycardia have documented the adequacy of HBP in maintaining LVEF after transcatheter aortic valve implantation, as well as in comparison with LBBAP.[35, 36] The commonality of all the above studies is that the data came from observational, single, or two-center studies, with few patients, with short follow-up periods. For that reason, most authors emphasize the need to conduct large, prospective, randomized control trials (RCTs) comparing HBP to RV pacing to prove beneficial clinical endpoints, such as reduction in hospitalizations and mortality attributable to HBP in patients with bradycardia.

6.2. "Ablate and pace" strategy

As already mentioned, the first clinical study for HBP was by Deshmukh et al. (2000), an observational, single-center study. In 18 patients scheduled for AV node ablation, with narrow QRS and LVEF <40%, with atrial fibrillation, using stylet-driven leads without a guiding catheter, improvement in LVEF, LV dimensions, and New York Heart Association (NYHA) Functional Classification achieved.[8] Afterwards, Occhetta et al. (2006) conducted another small study with 16 patients, trying to achieve HBP again using stylet-driven leads without a guiding catheter, succeeding only in four of them HBP, while in the rest, para-Hisian pacing only recorded. In a follow-up period of 6 months, comparing HBP to RV pacing, the study recorded a better NYHA class, and a 6-min walk test (6MWT), while no difference observed in LVEF and LVESV.[37]

Because of the difficulty in approaching the His bundle, subsequent studies with improved leads conducted by Huang et al. (2017), Vijayaraman et al. (2017), and Wang et al. (2019) in 42, 40, and 44 patients, respectively.[38-40] In all three of these studies, an improvement was noticed in LVEF, left ventricular dimensions, and NYHA class compared with baseline. The authors pointed out that AV node ablation may result in capture thresholds increase or lead dislodgments in a minority of patients and should be taken into account before implantation since patient safety comes first. Similar results were shown in the study by Su et al. (2020), who applied HBP combined with AV node ablation to 81 patients. Additionally, pre-procedure values of high pulmonary artery systolic pressure (PASP) [?]40 mmHg, serum creatinine levels [?]97 µmol/L ([?]1.1 mg/dl), or reduced LVEF <40% pointed out as independent predictors of the composite endpoint of all-cause mortality and heart failure hospitalization.[41] Finally, Zweerink et al. (2020) compared HBP with AV node ablation in 44 patients, applying either radiofrequency ablation or cryoablation. Although the results regarding the improvement in LVEF were similar to the previous studies regarding the ablation technique, cryoablation appeared as more procedural time-consuming, may require more redo procedures, and does not avoid the risk of compromising His capture thresholds.[42] Be that as it may, all studies in the "ablate and pace" indication of HBP until now have been observational, single-center studies with few patients and a short follow-up of a few months. Most authors of all these studies underline the need to conduct large RCTs for this indication, as for the previous one.

6.3. Role in CRT

The electrocardiographic feature of inter-ventricular dyssynchrony is the QRS widening, which manifests as either Right BBB (RBBB) or Left BBB (LBBB). On the other hand, there is the intra-ventricular dyssynchrony, which refers to the late activation of the lateral regions of the left ventricular chamber as compared to the interventricular septum, existing in patients with heart failure, regardless of QRS duration. Especially for patients with LBBB, the role of biventricular pacing is proven beneficial, both in narrowing the QRS duration and in clinical endpoints. In 1977, Narula in 27 patients showed that by pacing the His bundle, LBBB is corrected, suggesting a longitudinal dissociation in the His Bundle and proposing the concept of "sinoventricular conduction".[43] Narula's theory is based on the hypothesis that stimulation at a constant cycle length, at a slightly distal site, can abolish the LBBB (constant or rate related) due to synchronous impulse conduction to both the bundle branches. These early conclusions confirmed by a recent mapping study from Upadhyay et al. (2019) with 85 patients. This study reported that LBBB patterns comprise a set of partial disorders that can range from complete conduction block when this is intrahisian to no discrete block and intact Purkinje activation, when the block is more peripheral, in the left anterior and posterior fascicles. In patients to whom HBP attempted, block correction achieved in 94% of patients with left intrahisian block and none with a peripheral disorder at the level of the fascicles confirming thus the theory of intracardiac delineation of the septal conduction system, proposed almost half a century ago.[44]

The achievement of block reversal with HBP is reached either by placing the His lead further from the lesion if it is relatively proximal to the His bundle or by remote electrical activation, considering higher outputs, with all that this implies for the battery longevity. Moreover, the same may be achieved by retrograde activation of the His-Purkinje system via capture of an upper septal branch when His lead is fortuitously placed in close proximity with one of these many left bundle septal branches.[45] Especially when the pacing is selective, the corrected morphology of paced QRS can be maintained even with chronic pacing, as also happens with mean thresholds. Subsequently, this electrocardiographic notification of BBB correction with HBP in those patients led to studies that attempted to demonstrate and correlate this correction with clinical benefits.

Several studies, though with few patients, showed non-inferiority of HBP in CRT compared to biventricular pacing. Barba-Pichardo et al. (2013) in 9 patients, Lustgarten et al. (2015) in 12 patients, Ajijola et al. (2017) in 16 patients, and Shan et al. (2018) in 16 patients recorded an improvement in LVEF and LV dimensions and reduction in NYHA class compared with baseline. [46-49] In these studies, in addition to LVEF, an improvement was observed in other echocardiographic parameters, such as the disappearance of a significant septal-to-posterior wall delay in colour tissue Doppler, as well the reduction in isovolumic contraction time, and increase in peak systolic velocity in Pulsed-wave tissue -Doppler. Secondary endpoints were also studied, such as the quality of life (QoL), 6MWT, and mitral regurgitation jet area, with a trend of improvement.

HBP especially gained remarkable worth in CRT as a solution in the case of failed LV lead implantation. This indication first studied by Giraldi et al. (2011), wherein 20 patients with unfavorable cardiac veins anatomy, an alternative CRT was attempted with a surgical minithoracotomic approach.[50] The utilization of HBP lead as a general CRT alternative was also highlighted by Upadhyay et al. (2019) in a secondary analysis of the His-SYNC Pilot Trial. The study initially underlined the role of HBP in the QRS duration improvement and LBBB correction but failed to determine the advantage in hospitalizations and mortality.[51] However, in cases of failure to place the LV lead in the coronary sinus, due to absence, tortuosity, or diameter <3mm of lateral or posterolateral vein or angle <60* of the lateral vein, HBP could be a reliable alternative to conventional CRT.

Another promising application of HBP in CRT was studied by Vijayaraman et al. (2019), with good results regarding QRS duration narrowing in the His-Optimized CRT study (HOT-CRT). In this study, in 27 heart failure patients presenting LBBB with QRS duration >140 msec and LVEF [?]35%, the RV lead placed in the His Bundle area and the LV lead synchronized in a time equal to the H-V interval with the His Bundle lead.[52] An impressive reduction of QRS duration was recorded (from 183±27 msec to 120±16 msec), improvement of LVEF from 24±7% to 38±10%, and a change in NYHA functional class from 3.3 to 2.04, in 14- month follow-up. Similar results of this method observed in 11 patients with permanent atrial fibrillation and LVEF <40% by Boczar et al. (2019).[53]

Finally, the application of HBP showed the same good results in patients with RBBB, where the conventional CRT has a weaker class of recommendation. Sharma et al. (2018), in 39 heart failure and RBBB patients with QRS duration [?] 120 msec and LVEF [?]50%, demonstrated a significant narrowing of QRS from 158+-24 msec to 127+-17 msec, an increase in LVEF from 31+-10% to 39+- 13%, and improvement in NYHA class from 2.8 to 2 with HBP in 15-month follow-up.[54] All the above results for the beneficial effects of HBP in CRT come from observational, single-center studies, with a limited number of patients and for a relatively short follow-up period. As in the studies of the previous indications, for proof of these beneficial effects in primary clinical outcomes, such as hospitalizations and mortality, the authors also emphasize the need to carry out large RCTs.

6.4. Heart Failure with Narrow QRS and PR Prolongation

A less studied but significant indication is the application of HBP in heart failure patients with narrow QRS and atrio-ventricular dyssynchrony, namely an extensive PR prolongation. Except for inter-ventricular dyssynchrony, caused by RV pacing, the long prolongation of the atrial emptying phase also drives to non-optimal ventricular filling and, therefore, non-optimal application of the Frank-Starling law. Especially in heart failure patients, that is important not only for symptoms but also for their adequate cardiac function, affecting their mortality. After all, in addition to the simultaneous activation of the two ventricles, the benefit of biventricular pacing is also due to PR interval optimization.[45]

And for this indication of HBP, the data is limited. The randomized, crossover HOPE-HF trial (His Optimized Pacing Evaluated for Heart Failure Trial), which is still conducting, includes 160 patients with PR prolongation ([?]200 msec), impaired LVEF [?]40%, and either narrow QRS [?]140 msec or RBBB. The clinical impact of HBP on reducing the PR interval is studied.[55] As primary endpoint is considered the change in exercise capacity. Secondary endpoints include changes in LVEF, QoL scores, B-type natriuretic peptide values, and daily patient activity levels. In another recently published study, Strocchi et al. (2020), in 24 LBBB heart failure patients recruited for CRT upgrade (96% males, mean LVEF 34% +- 10%), have compared HBP with LBBAP, LV septal pacing, biventricular endocardial and biventricular epicardial pacing, regarding ventricular activation changes. HBP showed clear superiority over the other pacing methods in ventricular synchrony, while noteworthy is that for left bundle pacing, AV delay optimization resulted in a reduction of RV activation times.[56] Undoubtedly, for these studies, as well as for all the above related to HBP, the lack of large RCTs that would relate the impact of these findings on hospitalizations or mortality is a disadvantage and should be investigated in the coming years.

7. Left bundle branch area pacing: just an alternative to HBP or an independent pacing method?

LBBAP is considered an alternative, so far, to HBP, with both these methods constituting the two components of CSP. LBBAP includes LV septal pacing and LBBP. There are no studies to date for LV septal pacing, having a clinical follow-up, as opposed to RV septal pacing. Left bundle branch pacing, compared to HBP, presents several differentiations.**(Figure 5)** Mostly this is due to anatomical reasons. As opposed to the small size of the His bundle, the left bundle branch extends comparatively to a much larger area in the interventricular septum, which has two anatomical explanations. That is because, on the one hand, the left bundle branch subdivides into two main fascicles, the left anterior and the left posterior fascicle. At the same time, other sources divide the left bundle branch into three fascicles concluding with the left septal fascicle. On the other hand, there is a rich network of fibers among these structures, creating a wide range of variations. As a result, this part of the conduction system can be stimulated in an easier way successfully than the His bundle area.[10, 57]

In addition to the anatomical ones, there are technical reasons making LBBP easier. The infrahisian conduction system and the proximal right and left bundle branches are enveloped in an insulating sheath of lesser thickness than the penetrating bundle of His. In contrast, most peripheral branches are located in the myocardium, thus requiring a much smaller threshold for selective stimulation, with a consequent significant impact on battery longevity. Also, for LBBP, as in HBP, the method used for the pacing lead implantation is fluoroscopy. The only difference is the wider target area in the interventricular septum and, therefore, the fewer requirements for lead placement accuracy.[58] Other technical issues differentiate the LBBP implantation procedure from HBP's. In challenging cases, fixing a lead into the His bundle as an anatomical landmark may be helpful.[15] Special technical feature of the implantation technique of LBBP is the fulcrum sign of the pacing lead, which makes the lead and its subsequent parameters more stable. Sheath angiography is also helpful by gently pulling back the catheter and administering a contrast agent to establish the correlation of lead and septum positions and identify the depth penetrated by the bipolar lead with its active helix. The most commonly used lead is Select Secure 3830, as in HBP, with 9 mm tip to ring spacing and 1.8 mm the exposed helix. The w-shaped QRS configuration of pacing the right ventricular septum at the initial fixation site indicates LBBP.

This technique is also demanding to program. Apart from the threshold, better parameters are recorded regarding sensing, which is also maintained in the follow-up, especially concerning atrial oversensing and ventricular undersensing, in contrast to HBP. In addition, LBBP offers ease in the need for future AV node ablation in heart failure patients with refractory atrial fibrillation and a rapid average heart rate despite optimal medical therapy in contrast with HBP that this may not be possible. LBBP, as an alternative method, may be successful in blocks that are too distal to be treated with HBP, although these blocks are not that frequent. A recent publication, in a series of 333 consecutive patients with AV block referred for pacemaker implantation, recorded the prevalence of the site of conduction block.[59] The study found that the exact site of conduction block was nodal in 55% and infranodal in 45% of the cases, which in turn, distributed in intra-Hisian 89%, infra-Hisian 4%, and indeterminate 7% of the patients. Therefore, although infra-Hisian blocks are rare, LBBP is an alternative pacing modality for these patients.

Compared to HBP, where complications are minimal, the LBBP technique's complications may be life-threatening to the patient. There have been reported cases of septal perforation to the LV chamber (during the procedure, but also post-procedure in case of excessive slack of the pacing lead), LBBP lead dislocation, especially when there is not adequate slack of the lead, right bundle branch injury, septal injury or hematoma, and coronary artery injury, especially when the pacing lead is placed deep in the proximal septum, causing even myocardial infarction.[60] Moreover, LBBP lead fracture may occur, causing loss of pacing, with unpleasant consequences, especially for pacemaker-dependent patients. However, the rate of all these procedure-related complications of LBBP is still low.

Therefore, LBBP is currently being tested not only as an alternative method to HBP in case of technical difficulties, such as a high HBP threshold at implant, but also as a primary pacing method, with all the corresponding indications described for HBP.[61] Success rate is very high (>90 %), and the achieved capture thresholds are low (< 1 Volt at 0.4 msec), which maintain in the follow-up. At the same time, beneficial results have also been found in echocardiographic parameters, such as LVEF and left ventricular volume measurements. Various studies have pointed out this in the last few years. The main indications for LBBP concern bradycardia and CRT. Zhang et al. (2019) in 11 patients, Wu et al. (2020) in 32 patients, Huang et al. (2020) in 61 patients, and Vijayaraman et al. (2021) in 277 patients with impaired LVEF <50% and LBBB found a notable improvement in LVEF, NYHA class, BNP plasma level, but also lower capture threshold and higher R-wave sensing amplitude in comparison to HBP patients.[62-65] Padala et al. (2020) in 305 patients showed low rates of lead dislodgement over two weeks with LBBP, while similar findings of complications were also recorded by Su et al. (2021) in 632 patients, with a follow-up of 8.6 months.[66, 67] Finally, LBBP was even tested in cases after unsuccessful or suboptimal HBP but also after TAVR implantation in a few patients, with encouraging results regarding improvement in LVEF and reduction in QRS duration over follow-up, respectively.[35, 61]

All the above results, as also the recorded post-procedure stability of electrical parameters, suggest that LBBP is a feasible and effective pacing method with promising results for the near future. Nevertheless, the fact that these data come from observational, single-center studies with a small number of patients and a short follow-up explains why LBBP is not included as an official indication in the latest 2021 ESC Guidelines on cardiac pacing. That's why it's highlighted, as for HBP, the need to conduct large RCTs, which will correlate these findings with clinical endpoints such as heart failure hospitalizations and mortality.

8. Looking to the Future

The great interest in CSP in recent years logically directs towards the issues that make difficulties so that this type of pacing prevails as the dominant one for all prospective patients who may need this type of intervention.[15] Given the complicated anatomy of the area where the conduction system locates, new tools are tested by all manufacturers, both for HBP and LBBP. The tests concern the sheaths that guide the pacing lead and the lead model itself. Stylet-driven leads, tested in the past, are already being tested again to locate the area of interest with greater precision and stability, bypassing the existing anatomical and hemodynamic difficulties.[68] Moreover, efforts to circumvent the difficulties of locating the conduction system with fluoroscopy are being made by testing new 3D electro-anatomical mapping systems.[69] Recently published data is also encouraging for an electrogram-only guided approach to HBP with minimal fluoroscopy and high success rates compared to the classical method.[70] But of course, the need for data collection through conducting large RCTs, which will prove the significant benefit of this pacing in clinical endpoints of hospitalizations and mortality, should not be overlooked. For this reason, studies are constantly conducted in this direction. Thus, for the question concerning CSP "when and to whom", the answer one day may be "always and to all".

9. Conclusion

Classic RV pacing may induce the systolic and diastolic dysfunction of both ventricles with consequent adverse clinical endpoints. CSP is a method that maintains physiologic ventricular activation. It has a correct pathophysiological basis, and for a long time, the scientific community has been interested in circumventing its anatomical and technical difficulties. The knowledge is there, and as the interest is there, the only thing missing is the right tool so that it is possible to access this area whenever needed, with satisfactory pacing parameters, without complications, and of course, with indisputable proof of its good clinical outcomes. Thus, after coronary artery bypass grafting, which revolutionized the field of coronary artery revascularization, electrical lesions in the conduction system might be dealt with a corresponding "electrical bypass" feasible for all indications and in all patients who need this pacing treatment.

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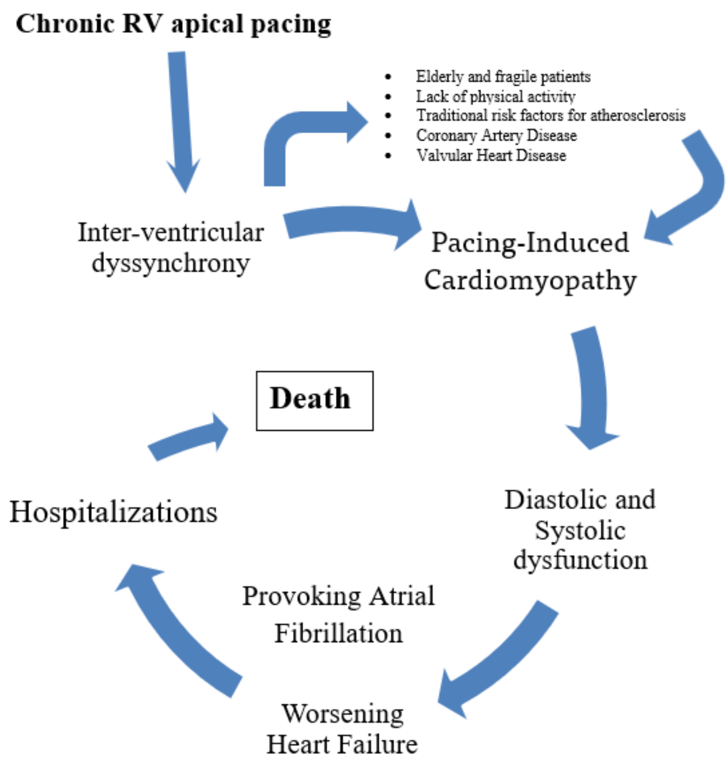
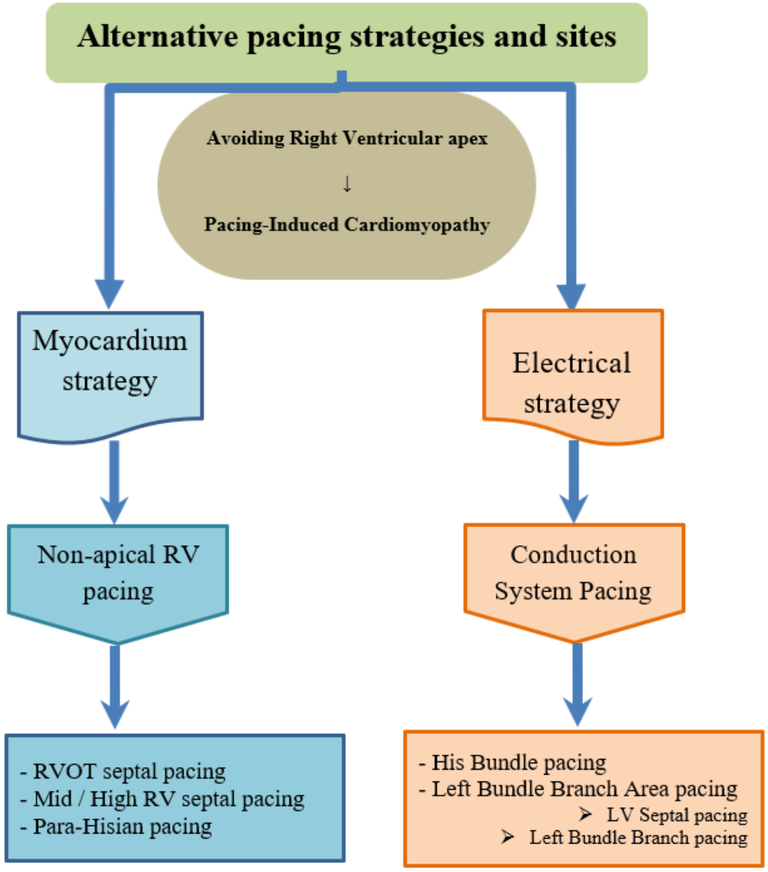
Figures

Figure 1. The detrimental effects of chronic RV apical pacing



RV: right ventricular

Figure 2 : Alternative pacing strategies and sites



RV: right ventricular, RVOT: Right Ventricular Outflow Tract, LV: left ventricular

Figure 3: An "Electrical Bypass"

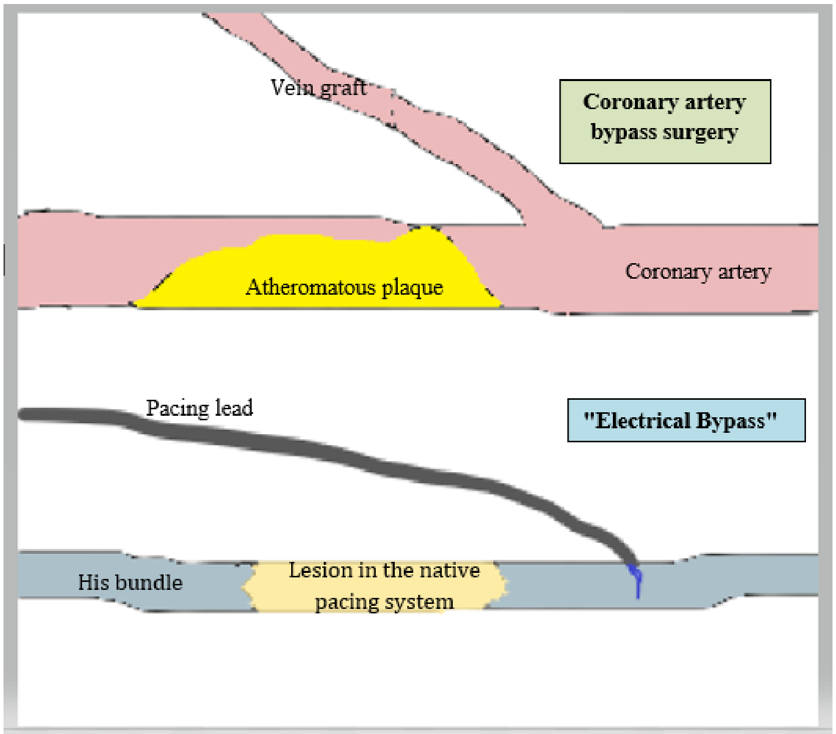
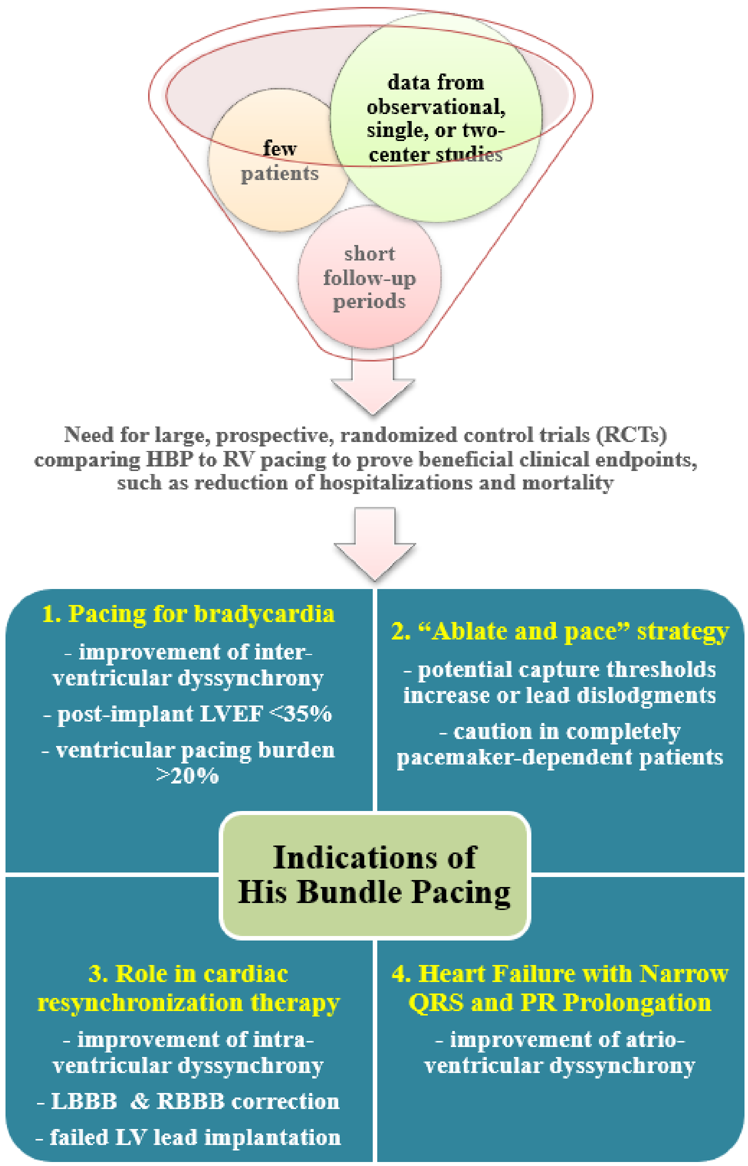
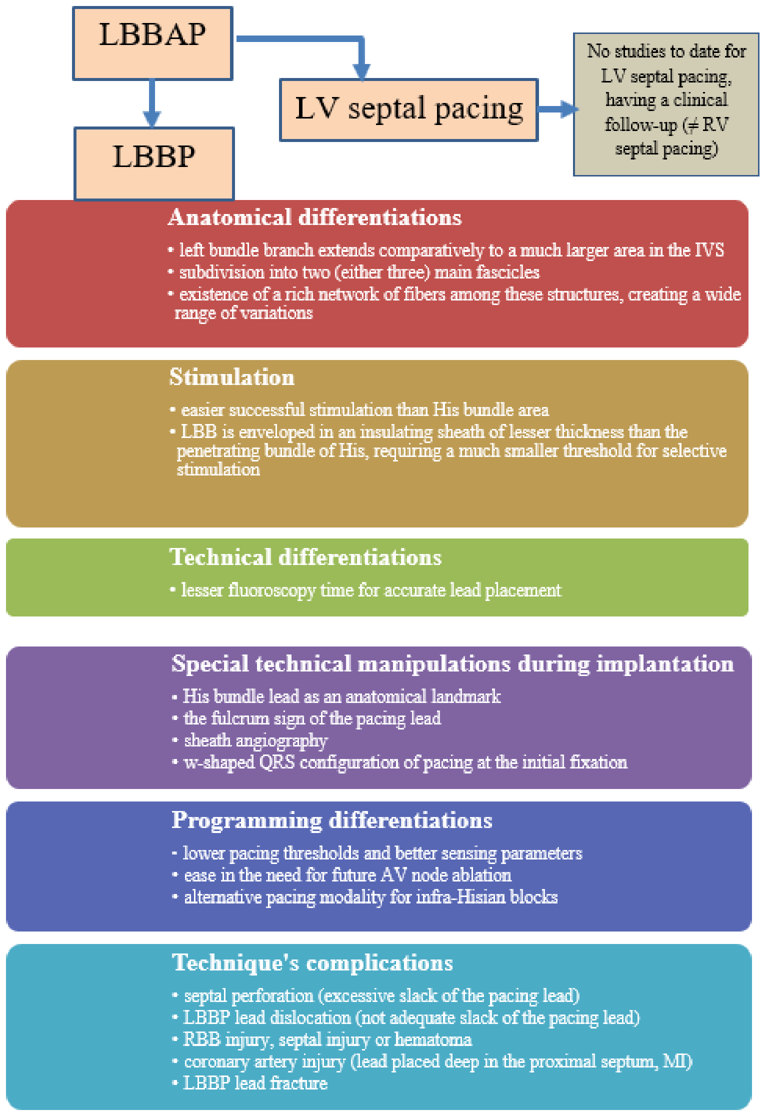


Figure 4: Indications of His Bundle Pacing



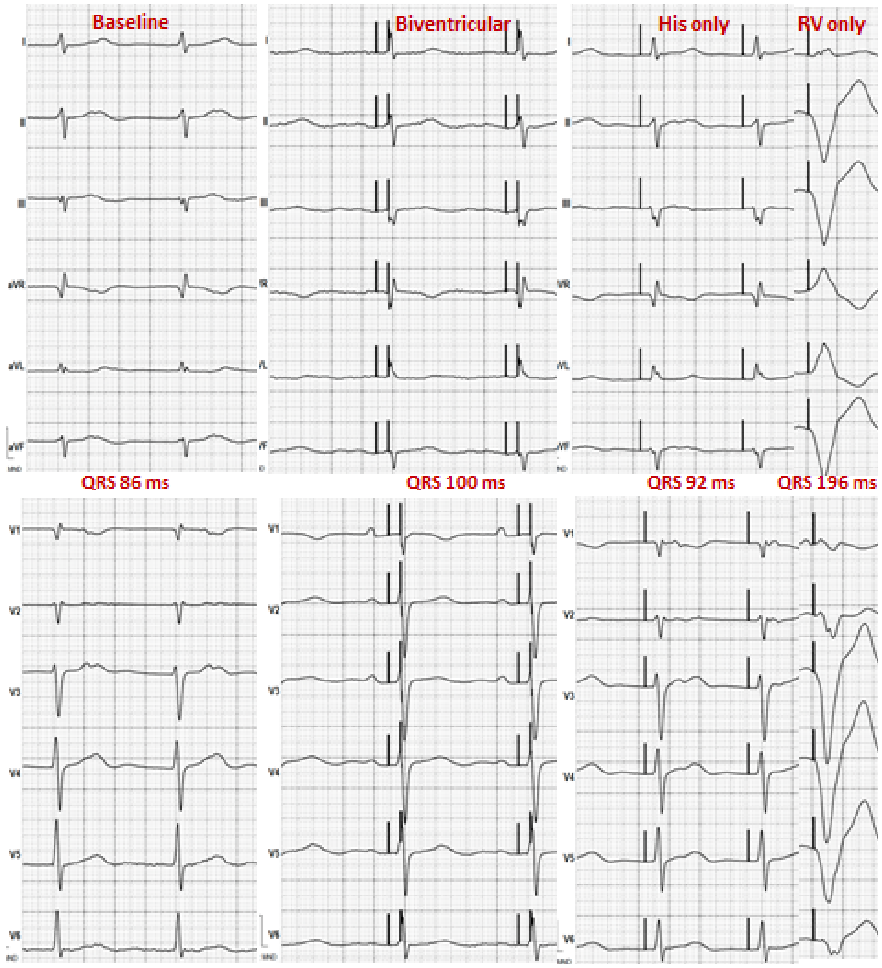
HBP: His bundle pacing, RV: right ventricular, LVEF: Left ventricular ejection fraction, LBBB: Left bundle branch block, RBBB: Right bundle branch block, LV: left ventricular

Figure 5: Differentiations of LBBAP compared to HBP

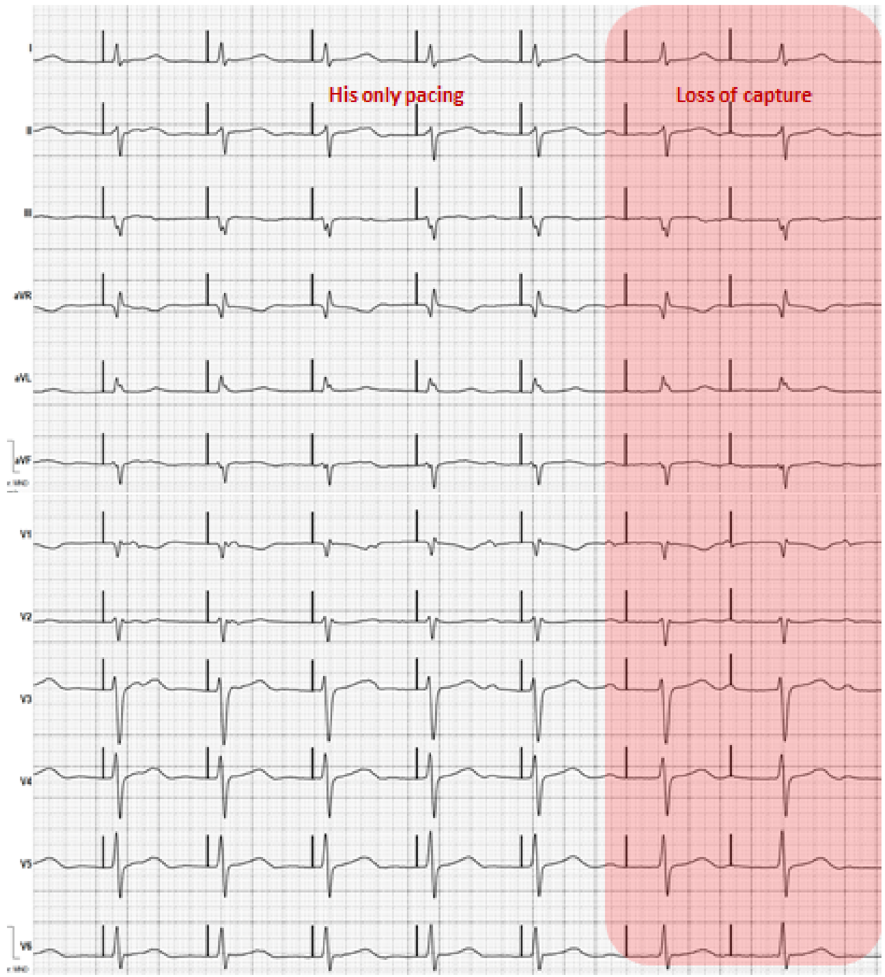


LBBAP: Left bundle branch area pacing, LBBP: Left bundle branch pacing, LV: left ventricular, RV: right ventricular, IVS: interventricular septum, LBB: Left bundle branch, RBB: Right bundle branch, MI: myocardial infarction

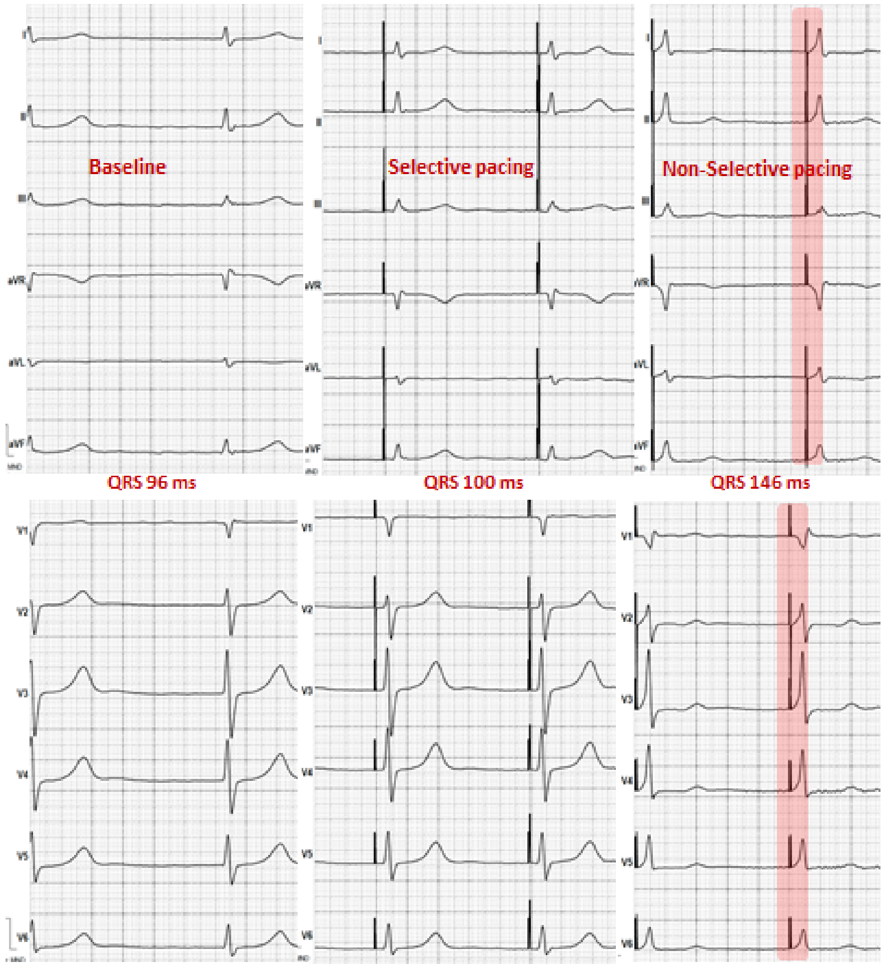
Example 1: Twelve-lead electrocardiogram (ECG) at baseline and following BVP, HBP and apical RV pacing. The baseline ECG demonstrates a QRS duration of 86 ms. During BVP and HBP the QRS duration remains narrow, 100ms and 92ms, respectively, in contrast to its significant widening during apical RV pacing, where it reaches 196ms. BVP; biventricular pacing; HBP; His Bundle pacing; RV; Right ventricular



Example 2: Twelve-lead electrocardiogram (ECG) of His Bundle Pacing. Loss of capture is demonstrated during threshold check.



Example 3: Twelve-lead electrocardiogram (ECG) shows the QRS morphology at baseline, as well as with Selective and Non-Selective His Bundle Pacing. The noted QRS duration widening during Non-Selective Pacing is due to the existence of the pseudo-delta wave, which is not observed in Selective Pacing (146 ms versus 100 ms, respectively).



Example 4: Fluoroscopic projection showing the position of the leads. RA, right atrium; HB, His bundle; RV, right ventricle; AP, Anteroposterior; LAO, Left Anterior Oblique

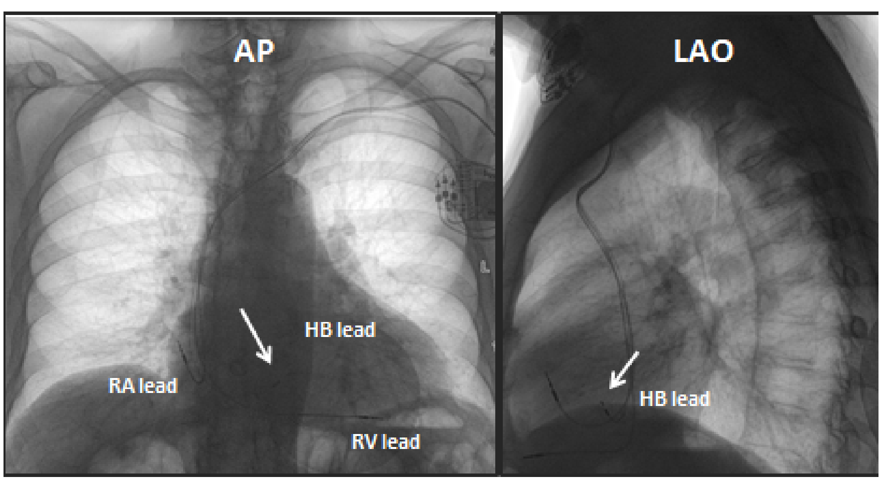


Table 1: Data for non-apical RV pacing

Data only for RV Septal pacing

Drawbacks (-)	Drawbacks (-)	Drawbacks (-)	Benefits (+)
Indications	high-grade atrioventricular block	cardiac resynchronization therapy	meta-analysis results: pre-implantation LVEF <40% females age >80 years
Randomized studies	Protect-Pace study	SEPTAL CRT study	
Patients	240	263	
Results	Decrease in LVEF, no difference in HF hospitalizations, AF, BNP, and mortality	No difference in reduction of LVESV and composite clinical endpoint of deaths and HF hospitalizations	

RV: right ventricular, CRT: cardiac resynchronization therapy, LVEF: left ventricular ejection fraction, HF: heart failure, AF: atrial fibrillation, BNP: brain natriuretic peptide, LVESV: left ventricular end-systolic volume

Table 2: His bundle pacing: "Why not always and to everyone"?

His bundle pacing's considerations

Anatomical	complex formation and anatomical location of AV conduction system minuscule dimensions His bundle asso - within the muscular portion of IVS - beneath the endocardium
Technical	Procedure related: - fluoroscopy for localizing lead positions - implantation tools - HBP lead (stylet, non-stylet driven) - His delivery sheath (deflectable, non-deflectable) Parameters related: - increase in pacing threshold - lead stability – dislodgement
Programming	Selective pacing Non-Selective pacing Myocardium-only pacing Selective HBP Non-Selective HBP Myocard - ventricular undersensing - pacing artifacts which port the His lead is placed in (especially at CRT) specialized Pacemaker Technician

AV: atrioventricular, IVS: interventricular septum, RV: right ventricular, HBP: His bundle pacing, LBBAP: Left bundle branch area pacing, LBBP: Left bundle branch pacing, ECG: electrocardiographic, BBB: bundle branch block, CRT: cardiac resynchronization therapy