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CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES OF CONDUCTION SYSTEM PACING

PROJECT REPORT

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DEPARTMENT OF CARDIOLOGY

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INTRODUCTION

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Cardiac pacing remains the only definitive therapy for non-reversible bradyarrhythmias. RV apical pacing (RVAP) had been the primary pacing strategy since the 1960's. RVAP by virtue of causing electrical and mechanical dysynchrony was found to be associated with increased risk for left ventricular (LV) dysfunction, atrial fibrillation, heart failure over these years. Pacing at alternative right ventricular (RV) sites such as the septum or outflow tract also did not prove to be convincingly superior in this regard. Cardiac resynchronization therapy (CRT) using biventricular pacing (BVP) is another indication for pacing and is aimed at improving cardiac synchrony in advanced heart failure patients with reduced ejection fraction, left bundle branch block (LBBB) and late activation of the lateral left ventricular wall. Though multiple clinical trials on CRT had clearly demonstrated improvements in LV function, clinical outcomes and survival, a significant proportion of patients (30%) are classified as non-responders. Moreover, this pacing modality is also non-physiological, activating ventricular myocardium and not the specialised conduction system. For these reasons, there is an increasing interest in pacing techniques aimed at activating the specialised conduction system over the last decade.

His bundle pacing (HBP) and Left bundle branch pacing (LBBP) are two such physiological pacing techniques introduced more recently. Permanent HBP is considered as the most physiologic form of ventricular pacing. The available scientific data on HBP have convincingly demonstrated its safety and clinical benefits in terms of reduced risk for pacing induced cardiomyopathy, heart failure hospitalisation and atrial arrythmias thereby leading to its rapid worldwide adaptation. However, HBP may not always be possible particularly in patients with infrahisian conduction system disease. Left bundle branch pacing (LBBP) had emerged as an alternative method of achieving physiological pacing in such patients. Multiple observational studies have clearly demonstrated the feasibility, safety and clinical benefits of LBBP as well. we intended to evaluate the outcomes of these pacing techniques in our patient population.

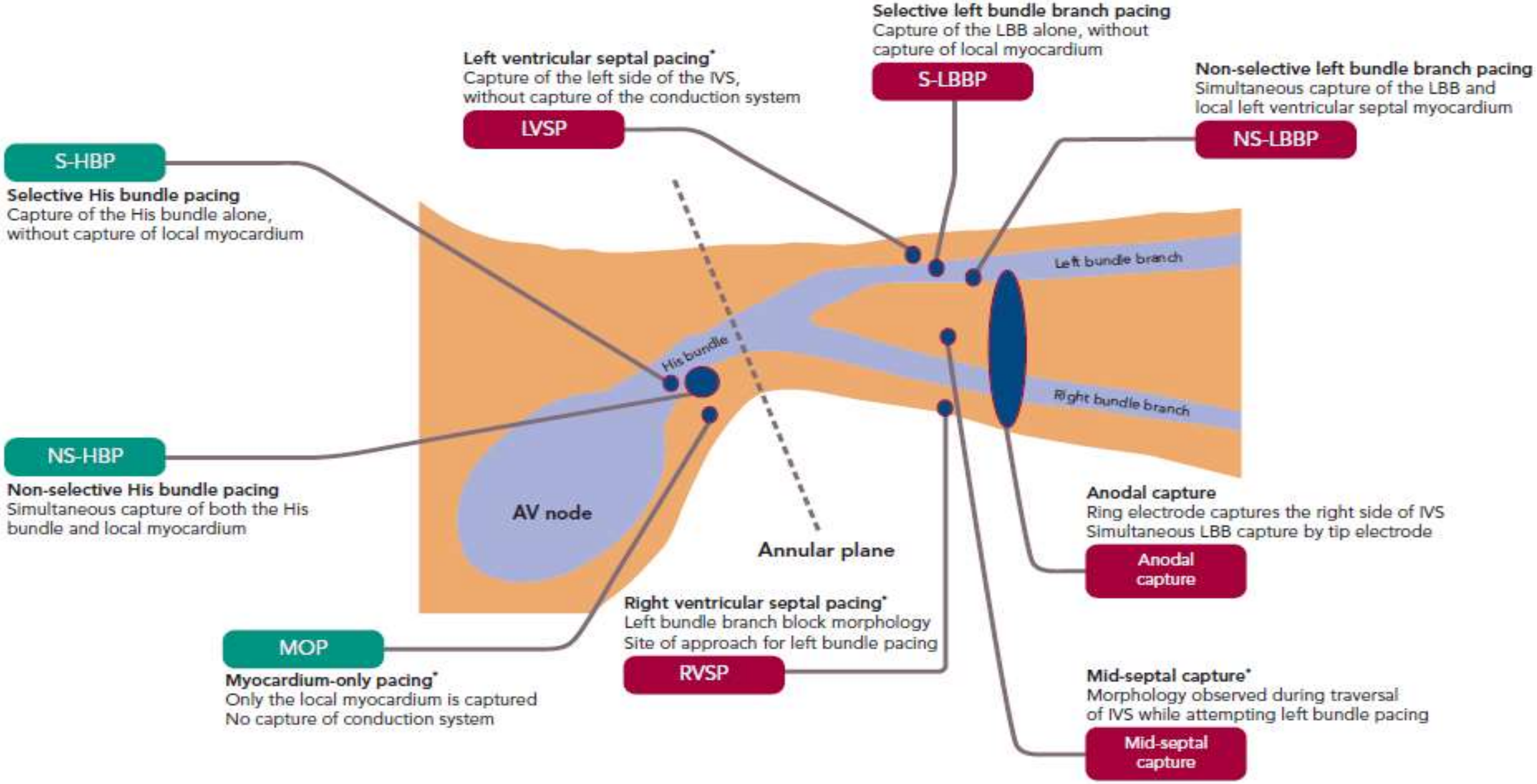
REVIEW OF LITERATURE

Right ventricular apical pacing (RVAP) results in dyssynchronous ventricular activation that can lead to impairment of ventricular function. Alternative myocardial pacing sites such as RV septal pacing (RVSP) and RV outflow tract pacing still rely on myocardial cell-to-cell conduction and have not been shown to prevent pacing-induced cardiomyopathy.[1] Biventricular pacing (BVP) certainly improves upon RVAP, but still produces a non-physiological activation pattern.[2] Direct pacing of the His Purkinje conduction system offers the ability to preserve physiological activation of the ventricles in patients with intrinsically normal, narrow QRS complexes. In patients with bundle branch block (BBB), conduction system pacing can deliver cardiac resynchronisation therapy (CRT) by correcting BBB to synchronise ventricular activation.[3] The originally favoured site of conduction system stimulation is the His bundle, and there is now large global experience of pacing at this site with considerable published follow-up data. More recently, new techniques have pulled focus to pacing of the region of the left bundle branch, which has a growing evidence base.[4]

Indications for Conduction System Pacing

There are three broad categories of indication for conduction system pacing: when a high burden of ventricular pacing is necessary, which includes atrioventricular block (AVB), slowly conducted AF, pacing-induced cardiomyopathy and atrioventricular nodal ablation (AVNA);

Figure 1: Conduction system pacing



Left ventricular septal pacing*
Capture of the left side of the IVS,
without capture of the conduction system
LVSP

Selective left bundle branch pacing
Capture of the LBB alone, without
capture of local myocardium
S-LBBP

Non-selective left bundle branch pacing
Simultaneous capture of the LBB and
local left ventricular septal myocardium
NS-LBBP

S-HBP
Selective His bundle pacing
Capture of the His bundle alone,
without capture of local myocardium

NS-HBP
Non-selective His bundle pacing
Simultaneous capture of both the His
bundle and local myocardium

Anodal capture
Ring electrode captures the right side of IVS
Simultaneous LBB capture by tip electrode
Anodal capture

Right ventricular septal pacing*
Left bundle branch block morphology
Site of approach for left bundle pacing
RVSP

MOP
Myocardium-only pacing*
Only the local myocardium is captured
No capture of conduction system

Mid-septal capture*
Morphology observed during traversal
of IVS while attempting left bundle pacing
Mid-septal capture

[4]

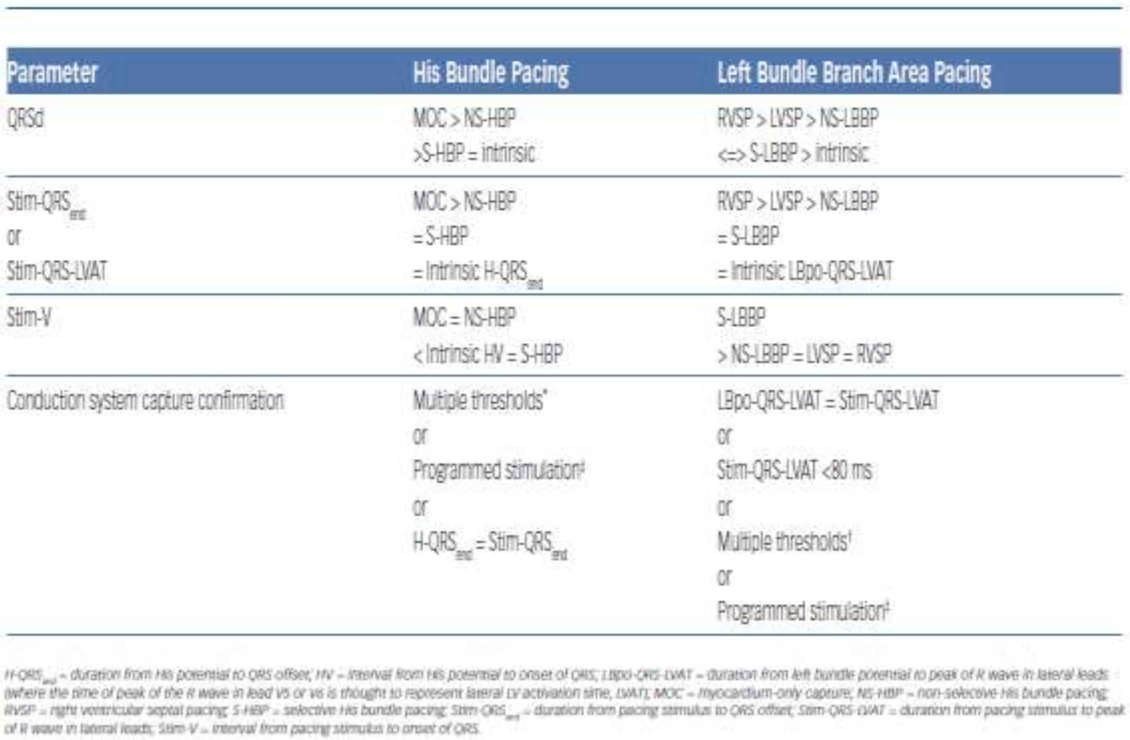
CRT in patients with heart failure and BBB; and sinus node dysfunction (SND), where AV nodal conduction disease may already coexist or develop during follow-up, and operators can gain experience in conduction system pacing because implant failure is less problematic.

Conduction System Pacing Techniques

HBP technique:

In the modern technique, a lumen less lead is steered towards the His bundle, a right atrial structure found at the inferior interatrial septum immediately superior to the tricuspid valve, using a pre-shaped sheath or a deflectable sheath.[7] Although in its infancy this technique was supported by EP catheter mapping of the region, the ability to map signals from the conduction system and adjacent myocardium and using the lead within the sheath was subsequently described by the Geisinger HBP group.[8] The His signal and appropriately balanced atrial and ventricular components (typically, a ventricular signal at least twice the amplitude of the atrial signal) are identified on the lead electrogram (EGM). EGM and ECG characteristics (Table 1) during pacing can confirm the suitability of the location for fixation. The lead is slowly manually rotated through fewer than 10 complete revolutions (typically five). The modern technique utilises the property of the SelectSecure 3830 lead (Medtronic), where the exposed helix is a constituent part of the tip electrode, rather than only the lead tip itself, proximal to the screw, so that when the screw penetrates the fibrous capsule of the His bundle, the conduction system fibres within the His bundle can be captured at relatively low thresholds.

Table 1 Electrical responses in conduction system pacing



Parameter	His Bundle Pacing	Left Bundle Branch Area Pacing
QRSd	MOC > NS-HBP >S-HBP = intrinsic	RVSP > LVSP > NS-LBBP <=> S-LBBP > intrinsic
Stim-QRS$_{end}$ or Stim-QRS-LVAT	MOC > NS-HBP = S-HBP = Intrinsic H-QRS$_{end}$	RVSP > LVSP > NS-LBBP = S-LBBP = Intrinsic LBpo-QRS-LVAT
Stim-V	MOC = NS-HBP < Intrinsic HV = S-HBP	S-LBBP > NS-LBBP = LVSP = RVSP
Conduction system capture confirmation	Multiple thresholds[*] or Programmed stimulation[‡] or H-QRS$_{end}$ = Stim-QRS$_{end}$	LBpo-QRS-LVAT = Stim-QRS-LVAT or Stim-QRS-LVAT <80 ms or Multiple thresholds[†] or Programmed stimulation[‡]

H-QRS$_{end}$ = duration from His potential to QRS offset; HV = interval from His potential to onset of QRS; LBpo-QRS-LVAT = duration from left bundle potential to peak of R wave in lateral leads (where the time of peak of the R wave in lead V5 or V6 is thought to represent lateral LV activation time, LVAT); MOC = myocardium-only capture; NS-HBP = non-selective His bundle pacing; RVSP = right ventricular septal pacing; S-HBP = selective His bundle pacing; Stim-QRS$_{end}$ = duration from pacing stimulus to QRS offset; Stim-QRS-LVAT = duration from pacing stimulus to peak of R wave in lateral leads; Stim-V = interval from pacing stimulus to onset of QRS.

Left Bundle Branch Pacing Technique:

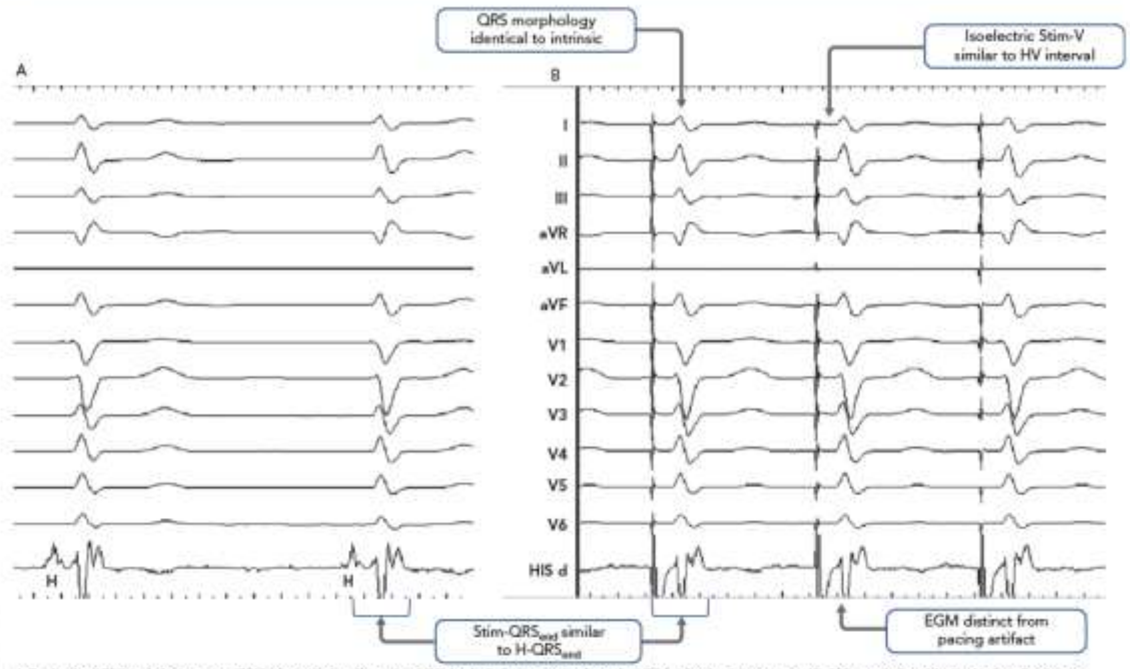
The technique for directly pacing the left bundle branch was first reported by Huang et al. in 2017.[10] The 3830 lead was deployed deep in the IVS, 15 mm distal to the His bundle site in a patient whose LBBB was not corrected by HBP. Pacing at this site successfully narrowed the QRS duration with a response consistent with conduction system capture. The technique for this trans-IVS approach to LBBP is now more firmly established.[11] The HBP technique is used to first identify the distal His bundle, before moving the sheath tip 1–2 cm more distally along the RV septal surface toward the RV apex. Fixating a lead into the His bundle as an anatomical landmark is useful in challenging cases. Pacing at the distal site will produce an LBBB-type pattern including a negative QRS with W-shaped notching in lead V1. Rather than the small number of slow turns recommended for HBP, LBBP requires several bursts of multiple rapid rotations of the SelectSecure 3830 to progress the lead 6–8 mm through the IVS. This may result in a total number of revolutions several times higher than performed in HBP. Periodic checking of the paced QRS characteristics (Table 1) and of lead impedance should be performed after each burst of rotations to confirm if LBB capture has been achieved and to ensure that the lead does not perforate through to the LV cavity, respectively. Contrast injection through the sheath, measuring the point of the lead fulcrum (at the cavity–septum interface) and echocardiography can help to identify the depth of lead penetration through the IVS. The paced QRS will change in morphology as the lead progresses through the mid-septum to the left side of the IVS. In lead V1, the emergence of an RBBB type pattern with a notch/R' wave, thought to represent RV activation, moves later in the QRS complex, the deeper into the septum the lead progresses. The time of peak of the R wave in lead V5 or V6 is thought to represent lateral LV activation time (referred to here as QRS-LVAT to distinguish this measure from LVAT measured using other techniques). The time from the stimulation artefact to QRS-LVAT (Stim-QRS-LVAT) gradually shortens the deeper into the septum the lead is progressed until a step change occurs and Stim-QRS-LVAT substantially shortens to less than 80 ms as left bundle capture is achieved. A left bundle potential may now be seen on lead EGM during intrinsic conduction. In general, the transition from pacing at the RV septum, through the mid-septum to the left septum, where the left bundle can be captured, can be thought of as an LBBB-type paced QRS morphology changing into an RBBB type.

Pacing Characteristics in Conduction System Pacing

Capture Characteristics in His Bundle Pacing:

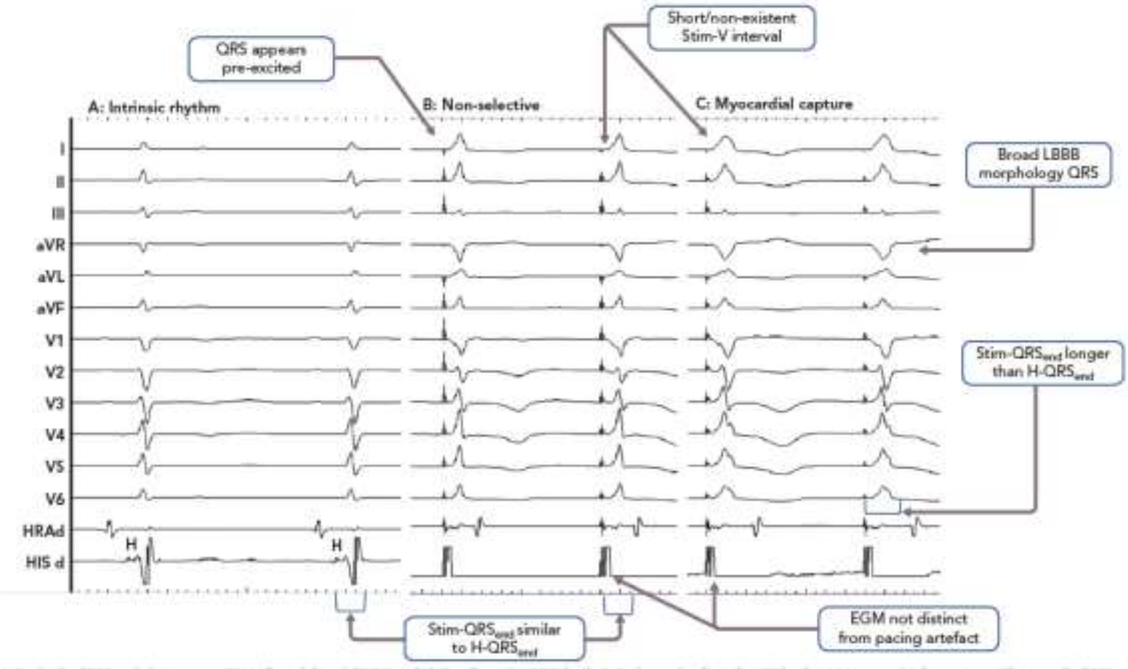
Selective HBP occurs when the His bundle is captured without capture ofsurrounding local myocardium. In patients with a narrow intrinsic QRS complex, this manifests on 12-lead ECG as an iso-electric interval between the pacing stimulus and the QRS onset (Stim-V interval) that is usually approximately equal to the baseline HV interval. The paced QRS duration (QRSd) is equal to intrinsic QRSd, because the LV and RV are activated entirely via the His–Purkinje conduction system, and therefore, the time from the pacing stimulus to the end of the QRS complex (Stim-QRSend) is equal to the time from the His signal to the end of the QRS complex (H-QRSend). The local EGM will be discrete from the pacing artefact, suggesting lack of local myocardial capture. Non-selective HBP occurs when the local septal myocardium is captured alongside capture of the His bundle. During the time where the signal is travelling through the insulated His bundle, local myocardial activation is occurring due to myocardial capture by the pacing stimulus. Therefore, the QRS complex onset occurs very soon, often immediately, after the pacing stimulus, via slow cell-to-cell myocardial conduction through a small region. The remainder of the ventricles are activated rapidly by the His–Purkinje system, therefore ventricular activation (and thus the QRS complex) is completed at an identical duration from the pacing stimulus as in S-HBP, but QRSd is longer in NS-HBP due to early ventricular activation. The slow slurred QRS pre-excitation in NS-HBP is akin to a delta wave in patients with manifest accessory pathways and is referred to as the pseudo-delta-wave. The local EGM is incorporated into the pacing artefact due to local capture (Figure 3).

Figure 2: Selective His bundle pacing



A: Twelve-lead ECG and electrograms (EGMs) from His bundle pacing (HBP) leads. B: During pacing from the HBP lead, selective capture with QRS morphology identical to baseline is seen. Note the discrete local EGM in the HBP lead suggesting absence of direct myocardial capture. H = His potential; H-QRS$_{end}$ = time from the His signal to the end of the QRS complex; HV = His–ventricular; Stim-QRS$_{end}$ = time from the pacing stimulus to the end of the QRS complex; Stim-V = interval between pacing stimulus and QRS onset.

Figure 3: Nonselective HBP versus local myocardial capture



A: Twelve-lead ECG and electrograms (EGMs) from right atrial (HRA) and His bundle pacing (HBP) leads. B: During pacing from the HBP lead at 1.0 V, non-selective capture with pre-excited QRS morphology is seen. C: Pacing at 0.8 V demonstrates myocardial-only capture (MOC) with wider QRS morphology and longer stimulus to QRS offset time compared with during His capture in B. Note that there is no discrete local EGM in the HBP lead, suggesting direct myocardial capture has occurred in both B and C. Short or non-existent Stim-V times are a shared feature between non-selective HBP and MOC. H = His potential; H-QRS$_{end}$ = time from the His signal to the end of the QRS complex; HV = His-ventricular; LBBB = left bundle branch block; Stim-QRS$_{end}$ = time from the pacing stimulus to the end of the QRS complex; Stim-V = interval between pacing stimulus and QRS onset.

When the His bundle is not captured but the pacing stimulus nevertheless, produces ventricular activation, myocardium-only capture

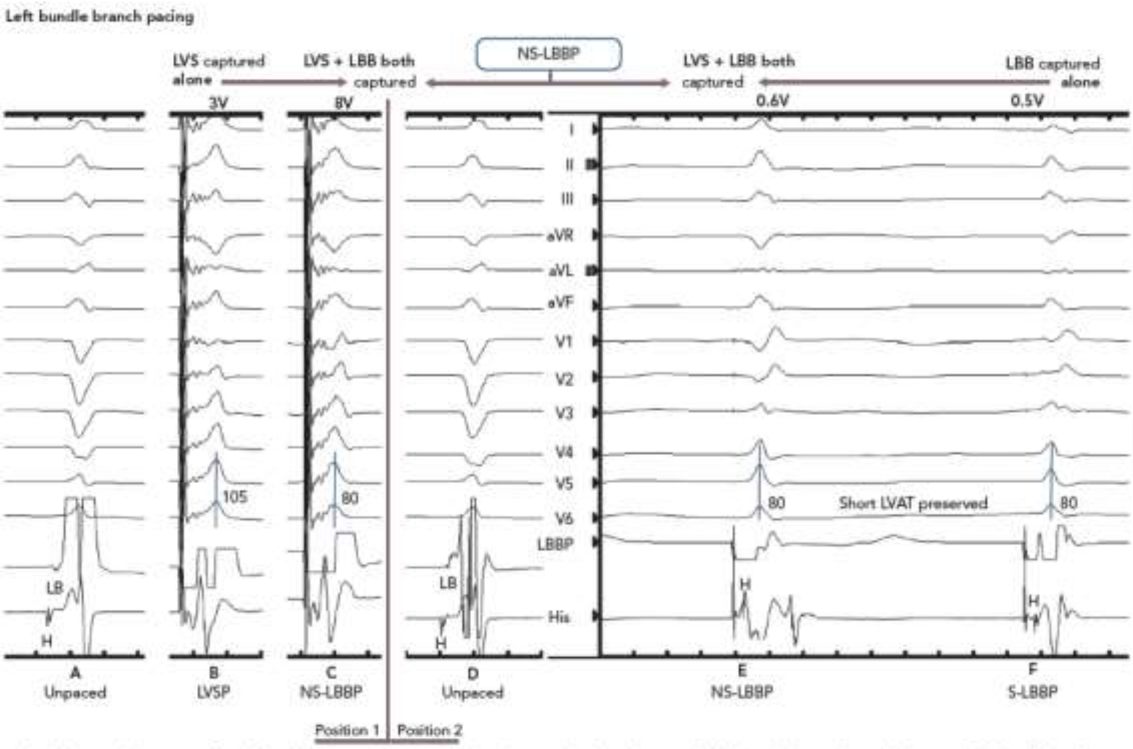
(MOC) occurs. This results in slow cell-to-cell activation of the entirety of both the RV and LV. The measurements that distinguish S-HBP, NS-HBP and MOC are set out in Table 1, showing that H-QRSend is the key reference measurement to distinguish individual NS-HBP complexes from MOC.

Capture Characteristics in Left Bundle Branch Pacing:

LBBP also demonstrates selective and non-selective conduction system capture, and LV septal pacing without direct conduction system capture is the equivalent of MOC. However, capture characteristics of LBBP are more complex than HBP. LBBP will result in an RBBB-type morphology. The second component of the QRS (R') represents RV activation; thus, QRS offset does not demarcate the end of conduction-system activated myocardium. LBBP QRS durations may therefore be longer than intrinsic QRSd. Therefore Stim-QRS-LVAT measurements, using the peak of the R wave in lateral leads, are preferred. This provides a method for assessing the time to lateral LV activation, which is expected to occur via left conduction system capture. The current convention is to assume that left conduction capture has occurred when Stim-QRS-LVAT is shortened to <80 ms. Left bundle potentials are seen with varying frequency (in contrast to the near ubiquity of His potentials in HBP), and the interval from potential to QRS onset is typically 15–35 ms. NS-LBBP can be differentiated from LVSP (without LBB capture) using Stim-QRS-LVAT, but recent evidence from Salden et al. suggests that the importance of this distinction is not as clear cut as the NS-HBP/MOC distinction.[13] LVSP without direct/immediate LB capture has similar electromechanical characteristics to BVP and HBP. This may be due to delayed/indirect penetrance of left-sided conduction system, or due to the balanced position of the LV septum with regard to intra-LV and inter-ventricular synchrony.

In general, during LBBP, lead V1 demonstrates RBBB morphology. To confirm LBB capture, in addition to an RBBB paced pattern one or more of the following criteria should be present: presence of LBB potential; evidence for transition from non-selective LBBP to either selective LBBP or LVSP during threshold testing; short and constant Stim-QRS-LVAT <80 ms at high and low outputs; and direct LBB capture demonstrated by short retrograde His or anterograde distal conduction system potentials or programmed stimulation to demonstrate LBB capture (Figure 4).

Figure 4: LV septal pacing vs LBBP



Twelve-lead ECG and electrograms from His bundle pacing and left bundle branch pacing (LBBP) leads are shown. A: Initial left ventricular septal (LVS) site shows small left bundle branch (LBB) potential prior to pacing. B: Pacing at 3 V shows long Stim-QRS-LVAT of 105 ms without a right bundle branch block (RBBB) pattern, indicating the LVS myocardium is captured alone. C: Pacing at 8 V shows shorter Stim-QRS-LVAT of 80 ms with an RBBB pattern demonstrating simultaneous capture of the LVS and the LBB. D: At final site, the LBBP lead shows a large LBB potential with injury current prior to pacing. E: Pacing at 0.6 V demonstrates non-selective (NS-) LBB capture with short Stim-QRS-LVAT of 80 ms. F: Pacing at 0.5 V shows selective (S-) LBB capture with short Stim-QRS-LVAT of 80 ms. Unlike the transition between left ventricular septal pacing (LVSP) and LBBP, the transition between NS-LBBP and S-LBBP preserves a short Stim-QRS-LVAT. Both E and F demonstrate retrograde His (H) potentials with short stim-H intervals. Stim-QRS-LVAT is the time from stimulus to peak of R wave in lateral 12-lead ECG leads (where the time of peak of the R wave in lead V5 or V6 is thought to represent lateral LV activation time, LVAT). LBB = left bundle branch; LBBP = left bundle branch pacing; LVAT = left ventricular activation time; LVS = left ventricular septal; LVSP = left ventricular septal pacing; NS-LBBP = non-selective left bundle branch pacing; S-LBBP = selective left bundle branch pacing.

Outcomes in Conduction System Pacing

Success Rates and Safety Profile of Conduction System Pacing

Reports of HBP implant success rates range from 72 to 92%, but success definitions have not always been standardised and lower rates are seen with His-CRT.[3,6,19,20] Transient AVB and RBBB can be seen during implant. Macro-displacements are rare but rising thresholds are not uncommon. Combining macro-displacement and high threshold as indications for redo procedures, the re-intervention rate is between 6% and 8% in larger long-term studies.[5,6,19,20] The early indications are that LBBP has a high success rate (>80%) with low re-intervention rates, and that lead perforation of the deeply fixated LBB lead into the LV cavity is very rare.[21] There may, however, be patient populations for whom LBBP is more challenging, such as patients with extensive septal fibrosis or scarring. Longer term follow-up data from large registries are also awaited.

Clinical Outcomes in Conduction System Pacing

Despite more than 20 years of progressively increasing experience of permanent HBP, several years of widespread global interest and uptake there have been no long-term, large-scale, clinical outcome driven randomised controlled trials (RCT) of conduction system pacing. The HOPE-HF trial is due to report in 2020 and is the only large-scale RCT imminent.[22] In the first decade of BVP, more than 6,000 patients were randomised to BVP versus standard-of-care trials, but if current trends continue it is unlikely even a tenth of that population will be randomised in conduction system pacing RCTs.[23] Indeed the established presence of BVP is a key factor that makes trial design for conduction system pacing difficult, alongside disruption by the novel LBBP technique.[23] Therefore, we must rely on observational data to make any inferences about long-term clinical outcomes in conduction system pacing. Improvements in quality of life, 6-minute walk test, LV ejection fraction (LVEF), LV size, heart failure hospitalisations and mortality have been seen with HBP in comparison with RVP. Some of the most compelling evidence comes from a comparison of a hospital performing HBP with a nearby hospital with operators who did not perform HBP, but with otherwise similar populations and standards of care.[24] HBP was associated with a statistically significant 29% reduction in the primary outcome of death, heart failure or upgrade to BVP at 2-year follow-up in that 756 patient study, and the effect was most pronounced in the subgroup with >20% ventricular pacing burden, with the 25% event rate for the primary outcome demonstrating that the difference was clinically meaningful in absolute terms.[24] Small-scale observational studies of LBBP suggest similar clinical and echocardiographic outcomes, but larger, long-term studies and head-to-head comparisons with RVP, BVP and HBP will be required to fully assess LBBP outcomes.[25]

Conduction System CRT

The role of conduction system pacing to resynchronise BBB in patients with heart failure is a particular indication for which recent insights have greatly altered our understanding. El-Sherif et al. observed in the 1970s that pacing the distal portion of the His bundle could correct LBBB to create a narrow QRS complex.[26] Lustgarten et al. demonstrated that this could be achieved with permanent HBP in 2010.[27] Subsequent observational studies show that HBP can shorten QRS duration and improve cardiac function and symptoms in patients with heart failure and LBBB.[28-30] Given these data, His-CRT has gained prominence as a bail-out in cases of failed BVP, but the burning question in this field was whether the physiological nature of resynchronisation by His-CRT produced better outcomes than BVP. In 2019, a pilot head-to-head comparison between the two modalities was published – His Bundle Pacing versus Coronary Sinus Pacing for CRT (HIS-SYNC).[31] His-CRT produced greater QRSd reduction than BVP but a statistically significant difference in LVEF improvement was not found. Unfortunately, the study suffered from a very high rate of cross-over from the HBP arm to the BVP arm, and the reasons for this illustrate the current challenges facing His-CRT. Half of crossovers were attributed to ECGs showing intraventricular conduction delay rather than LBBB. Thirty percent crossed over due to inability to correct LBBB. Arnold et al. have demonstrated, in a within-patient comparison, that when HBP successfully corrects LBBB, the haemodynamic and electrical improvements are greater than with BVP. HIS-SYNC showed that successful His-CRT requires selection of patients with conduction system disease amenable to correction by HBP and that improved implantation tools are required to facilitate correction in these patients. Upadhyay et al. have shown the physiological basis for patient selection. They found, by studying the left-sided conduction system, that patients with 12-lead ECG appearances of LBBB have variation in the nature of conduction disease. The majority had conduction block within the bundle of His, clearly amenable to correction by HBP. A smaller proportion had proximal conduction block within the proximal conduction system but distal to the His bundle: the block was located in the left bundle branch. Such patients may be amenable to HBP correction, but LBBP offers a more plausible corrective method. Importantly, in a sizeable minority of their population of patients attending for ventricular tachycardia ablation (36%), the left-sided conduction system appeared to be intact; QRS widening in these patients were presumed to be due to intramyocardial conduction delay. The

12-lead ECG features of typical LBBB do not seem to reliably discriminate between these groups. Practical methods to distinguish these LBBB phenotypes are required alongside tools dedicated to maximising resynchronisation achieved by conduction system pacing.[40] It should be noted that even though conduction system pacing will not correct it, LV septal pacing may have a role in patients with intra-ventricular conduction delay with intact conduction system. This group includes, for example, a combination of LV hypertrophy and left axis deviation, which can appear on 12-lead ECG as LBBB. LV septal pacing can produce improvements in AV delay in such patients, while activation pattern may be improved compared to the intrinsic pattern.[33]

LBBP is also able to resynchronise LBBB but the literature is sparse. Published series and case reports include few patients with LBBB.[33-35] LBBP is promising for CRT due to its presumed ability to correct block within the His bundle and the proximal left bundle. Furthermore, even if the conduction system is not captured, pacing in the LV septum appears to produce similar electromechanical improvements to BVP.[36] This potentially makes patient selection less of a problem: even intraventricular conduction delay with intact conduction system (including e.g. LV hypertrophy ECG appearances) might be potentially resynchronised to some degree, and furthermore there is scope for AV delay improvement.[36]

Conversely, given that LBBP produces an RBBB pattern, HBP is likely to have an advantage over LBBP for resynchronising RBBB. HBP can resynchronise RBBB in two ways: direct recruitment of the right bundle; and NS-HBP results in a wavefront from the basal RV (local myocardial capture) meeting another wavefront originating more apically (from left bundle mediated activation of the RV).[37] The HOPE-HF study is recruiting patients with long PR intervals and both narrow QRS and RBBB, and will provide evidence in this group. [22]

To summarise, His bundle pacing has rapidly evolved and has been shown to restore physiologic activation of the ventricles and maintain ventricular synchrony. More stable and distal conduction system pacing in the left bundle branch region is a newcomer to the field of physiologic pacing and early evidence suggests it shows promise. Randomised controlled clinical trials of the new forms of pacing for bradycardia and resynchronisation therapy are lacking and are essential to gain additional evidence related to the risks and benefit of this approach.

AIMS AND OBJECTIVES

1. To evaluate the feasibility, safety, pacing characteristics of conduction system pacing techniques.
2. To analyse the short term clinical and echocardiographic outcomes of conduction system pacing techniques.

MATERIALS AND METHODS

STUDY CENTRE: The study was conducted in the Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram

STUDY DESIGN: Prospective observational study design

STUDY PERIOD: May 2020 to December 2020

STUDY POPULATION: All consecutive patients who were taken up for conduction system pacing (His bundle pacing/Left bundle branch pacing) based on their clinical considerations were prospectively enrolled for the study.

SAMPLE SIZE: It was aimed to enrol 20 consecutive patients prospectively. However, the study enrolment was hindered by the occurrence of the Covid 19 pandemic. Hence, by the end of the study period only 10 patients who underwent successful conduction system pacing could be enrolled (from among the 14 attempted patients).

INCLUSION CRITERIA: Adult patients aged > 18 years who have standard indications for permanent pacemaker implantation shall be included in the study.

EXCLUSION CRITERIA: Patients requiring ICD

ETHICAL APPROVAL & INFORMED CONSENT: The study was approved by the Institutional Ethics Committee of SCTIMST, Thiruvananthapuram (See Appendix). Informed consent was obtained from the study patients after explaining to them in detail about the nature of the study.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

METHODOLOGY: From among the patients who were enrolled for the study, all the relevant clinical data were collected by using a standard data collection form (See Appendix). His bundle pacing or Left bundle branch pacing was attempted based on their clinical considerations by the techniques described below. The clinical and electrophysiological parameters observed during the procedure were recorded. All patients were followed up at 3 months and the follow up clinical, echocardiographic and device interrogation data were recorded.

HIS BUNDLE PACING (HBP): HBP was performed using the 3830-pacing lead (Select-Secure, 69cm, Medtronic, Minneapolis, MN) delivered through a fixed curve sheath (C315His sheath, Medtronic, Minneapolis, MN). The His bundle electrogram was initially mapped with a standard quadripolar electrophysiology (EP) catheter placed through femoral venous approach using a EP system (Bard EP, Boston Scientific) to serve as a fluoroscopic roadmap for lead positioning. Through a subclavian venous access, the delivery sheath with the lead tip just beyond the distal part of the sheath in the right anterior oblique (RAO) 30 projection was taken to the region where the His bundle potential was recorded. His capture was assessed by sequential pacing starting at 5V at 1ms of pulse width (unipolar) and once successful, the lead was fixed by rotating typically up to 5 turns with the delivery sheath advanced up to the proximal electrode for support. Procedural success was defined as a pacing threshold of a His capture of <2.5V at 1ms. Selective His bundle capture was considered to be achieved when an isoelectric segment between the pacing stimulus and the onset of the QRS which was equal or shorter than the HV interval with rapid onset of ventricular activation. Nonselective His bundle capture was considered to be present when there is a pseudo delta wave after the stimulus and the overall electrical axis of the paced QRS was concordant with the electrical axis of the intrinsic QRS. Device programming was performed at the end of procedure based on the pacing parameters obtained.

LEFT BUNDLE BRANCH PACING (LBBP): LBBP was performed using the 3830-pacing lead (Select-Secure, 69cm, Medtronic, Minneapolis, MN) delivered through a fixed curve sheath (C315His sheath, Medtronic, Minneapolis, MN) by the trans-ventricular-septal technique. First the His bundle electrogram was mapped with a standard quadripolar electrophysiology (EP) catheter placed through femoral venous approach using an EP system (Bard EP, Boston Scientific) to serve as a fluoroscopic roadmap for left bundle branch mapping. Through a subclavian venous access, the delivery sheath with the lead tip just beyond the distal part of the sheath in the right anterior oblique (RAO) 30 projection was taken to the region where the His bundle potential was recorded. The sheath with the lead was then advanced across the tricuspid valve toward the ventricular septum around 1-1.5cms below the His bundle potential. Once the lead touched the right side of the septum and the paced QRS showed LBBB morphology with an output of 5V at 1ms the lead was pointed toward the left side and screwed perpendicular to the septum in the left anterior oblique (LAO) 40 projection. During the lead advancement, paced QRS morphology and pacing impedance were monitored. Once the paced QRS morphology showed right bundle branch delay or near normal QRS complex, further lead advancement shall be stopped. Selective LBBP was considered if there is an isoelectric interval between pacing spike and ECG QRS complex with pacing spike-QRS interval identical to the left bundle potential-QRS interval (if left bundle potential was recorded) and local ventricular EGM was present as a discrete component. Nonselective LBBP was considered when there was no isoelectric interval between pacing spike and ECG QRS complex and local ventricular EGM shows direct capture of the local tissue by the pacing stimulus. Device programming was performed at the end of procedure based on the pacing parameters obtained.

DATA COLLECTION AND FOLLOW UP: Baseline patient characteristics (including ECG, echo parameters, functional class) and indication for pacing were collected at enrolment. Pacing characteristics (pacing threshold, lead impedance and R wave amplitude, paced ECG pattern, intracardiac EGM pattern, paced QRS duration, LV activation time, interval from the pacing spike to the beginning of the ECG QRS complex, total procedure time and fluoroscopy time) were recorded during implantation. Patients were reviewed before discharge and at 3 months. Clinical parameters (including ECG, echo parameters, functional class), pacing parameters and complications were recorded during follow up.

STATISTICAL ANALYSIS: The data were analysed by the principal investigator with guidance from the statistics department of SCTIMST by utilising appropriate statistical software. Continuous data were presented as mean +/- SD and compared with student t test. Paired t test shall be used to compare the differences between means. Nominal data were presented as frequencies and percentages and compared with the chi square test. A p value of less than 0.05 was taken as significant.

RESULTS

During the study period, 14 adult subjects were enrolled and of them 10 patients underwent successful conduction system pacing (71% success rate). Five patients (50%) underwent His bundle pacing (HBP) while the other five underwent Left bundle branch pacing (LBBP). Of the 10 patients included in the final analysis, five (50%) of them were females. Mean age of the study population was 46.6 years (SD-12.65, Range 24-63). Three (30%) of them had diabetes, two (20%) had hypertension and one (10%) had coronary artery disease. Five of the patients (50%) had a Left ventricular Ejection fraction (LVEF) <50% as assessed by Echocardiography.

Fig 5.1: Subject enrollment

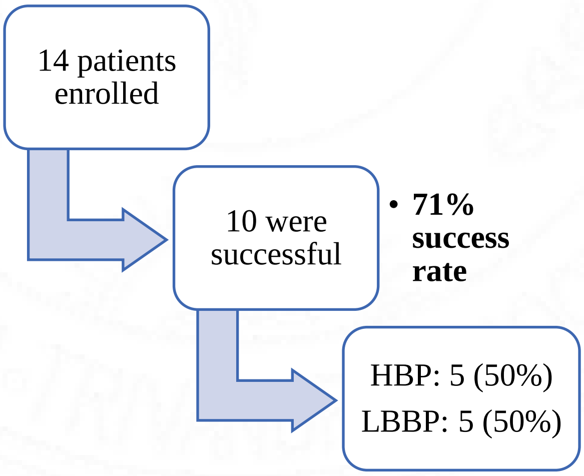


Fig 5.2 Sex distribution of the study subjects

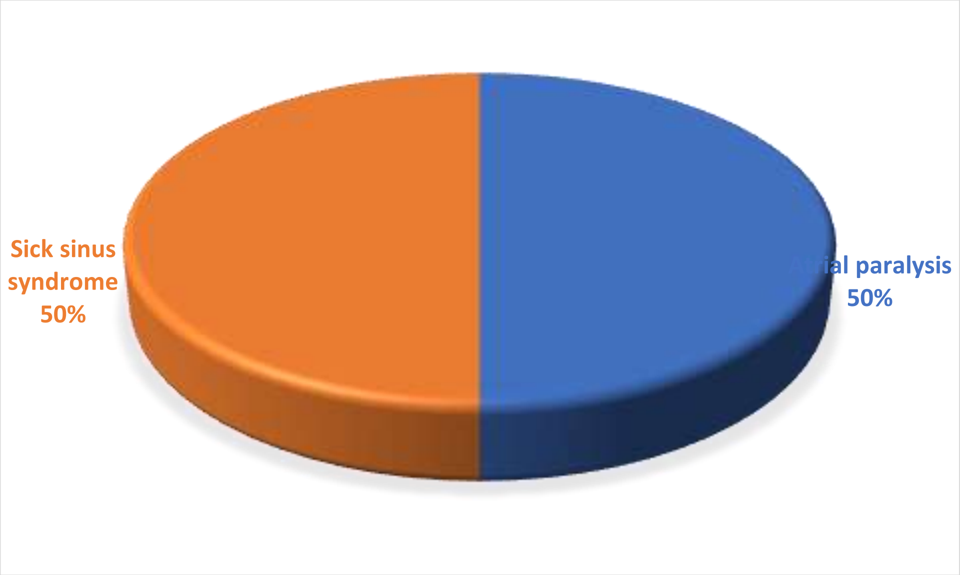
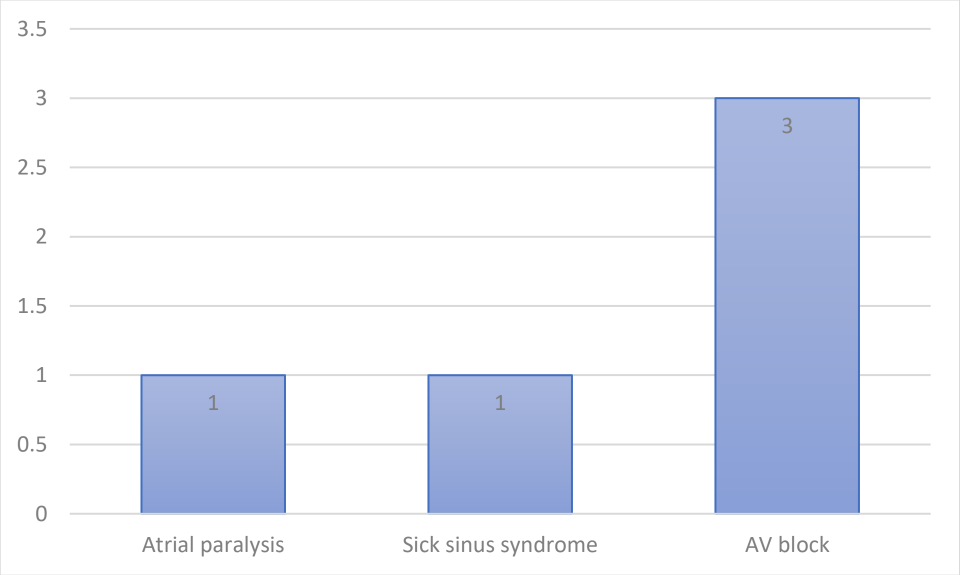
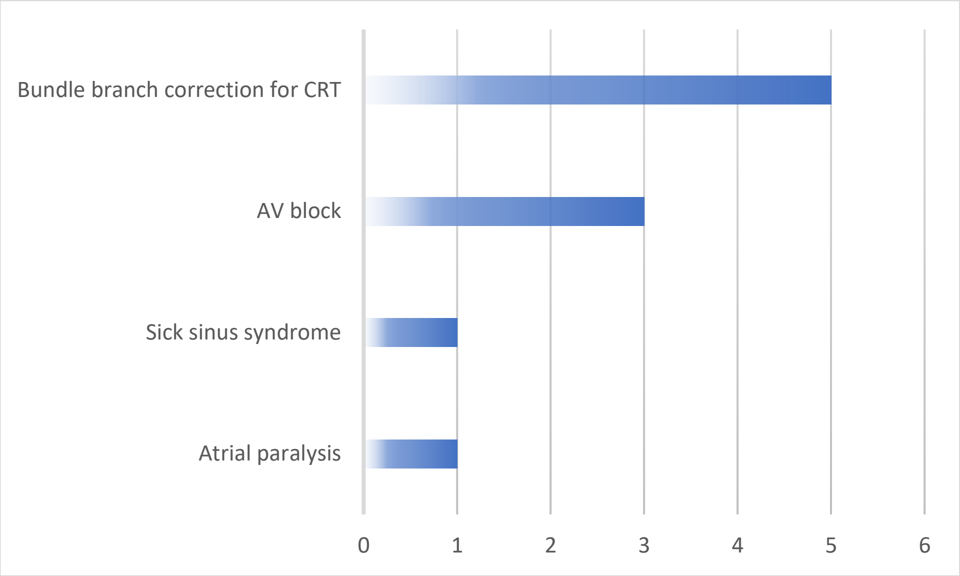


Fig 5.3 Age stratification



The indication for pacing was Atrial paralysis in one patient (10%), Sick sinus syndrome in one patient, AV block in three patients (30%) and bundle branch correction as an alternative to cardiac resynchronisation therapy (CRT) in 5 patients (50%).

Fig 5.4 Indication for pacing



Seven patients (70%) had left bundle branch block morphology at baseline while three patients (30%) had normal QRS morphology. The average fluoroscopy time for the procedure was 29 minutes (SD 5.4) and the average procedure time right from the initiation of procedure was 180 minutes (SD 10.6). There was a trend towards reduction in the mean fluoroscopy and procedure times towards the later part of the project.

Table 5.1: Baseline characteristics of the study population

No. of subjects	10
Females	5 (50%)
Age	Mean 46.6 years (SD-12.65, Range 24-63)
Diabetes	3 (30%)
Hypertension	2 (20%)
CAD	1 (10%)
LVEF <50% >50%	 5 (50%) 5 (50%)
Pacing Indication	Atrial paralysis – 1 (10%) Sick Sinus Syndrome – 1 (10%) AV block – 3 (30%) Bundle branch correction as an alternative to CRT-5 (50%)
QRS morphology	LBBB – 7 (70%) RBBB – 0 IVCD – 0 Normal – 3 (30%)
Mean fluoroscopy time	29 +/- 5.4 minutes
Mean procedure time	180 +/- 10.6 minutes

Electrophysiology parameters:

HBP: His bundle potential was recorded in four out of the five patients who underwent successful HBP (80%). A selective His bundle capture was obtained in four patients (80%) while nonselective His bundle capture was obtained in 1 patient (10%). Mean paced QRS duration after procedure was 106.4 +/- 12.99 ms and the peak LV activation time measured from the stimulus artifact to the peak of the R wave in lead V5 was 78.6 +/- 11.99 ms.

LBBP: Left bundle potential was recorded in only one out of the five patients who underwent successful HBP (10%). A selective left bundle capture was obtained in one patient (20%) while nonselective His bundle capture was obtained in 4 patient (80%). Mean paced QRS duration after procedure was 119.2 +/- 11.49 ms and the peak LV activation time measured from the stimulus artifact to the peak of the R wave in lead V5 was 80.4 +/- 7.94 ms.

Table 2: Electrophysiology parameters

His bundle pacing (n = 5)	His bundle potential recorded – 4 (80%) Selective capture – 4 (80%) Non Selective capture – 1 (20%) Paced QRS duration – 106.4 +/- 12.99 ms Peak LV activation time – 78.6 +/- 11.99 ms
Left bundle branch pacing (n = 5)	Left bundle potential recorded – 1 (20%) Selective capture – 1 (20%) Non Selective capture – 4 (80%) Paced QRS duration – 119.2 +/- 11.49 ms Peak LV activation time in lead V – 80.4 +/- 7.94 ms

Pacing parameters:

HBP: The R wave amplitudes at implantation were 3.12 +/- 1.52 mV and remained stable at 3.14 +/- 1.15 mV at 3 months follow up. Unipolar pacing impedance was 657.8 +/- 51.48 Ohms at implantation and 555.8 +/- 63.34 Ohms at 3 months follow up. There was no major change in the pacing thresholds as well. Mean pacing threshold at implantation was 1.36 +/- 0.62 V and at 3 months follow up were 1.3 +/- 0.58 V.

Table 3: Pacing parameters with HBP

HBP	At Implant	At follow up
R wave amplitude	3.12 +/- 1.52 mV	3.14 +/- 1.15 mV
Unipolar Impedance	657.8 +/- 51.48 Ohms	555.8 +/- 63.34 Ohms
Pacing threshold	1.36 +/- 0.62 V	1.3 +/- 0.58 V

LBBP: The R wave amplitudes at implantation were 10.64 +/- 2.14 mV and remained stable at 10.94 +/- 2.98 mV at 3 months follow up. There were large variations in the unipolar pacing impedance. The impedance was 823.8.8 +/- 126.95 Ohms at implantation and 676.8 +/- 86.6 at 3 months follow up. Mean pacing threshold at implantation was 0.74 +/- 0.19 V. One patient had an elevation in the left bundle capture threshold to 2.25 V at 3 months follow up and the mean threshold at 3 months follow up was 1 +/- 0.63 V.

Table 4: Pacing parameters with LBBP

LBBP	At Implant	At follow up
R wave amplitude	10.64 +/- 2.14 mV	10.94 +/- 2.98 mV
Unipolar Impedance	823.8 +/- 126.95 Ohms	676.8 +/- 86.6 Ohms
Pacing threshold	0.74 +/- 0.19 V	1 +/- 0.63 V

Subgroup analysis: The patients who underwent conduction system pacing with regards to bundle branch correction for cardiac resynchronisation therapy were analysed separately for certain clinical and echocardiographic parameters to study the effect of the pacing procedure on this subset of patients. All these patients had been diagnosed with Nonischemic Dilated Cardiomyopathy with significant LV dysfunction and

QRS duration >150ms. Two patients had undergone HBP for CRT while 3 patients had undergone LBBP for CRT. Mean QRS duration improved from 170 +/- 15.49 ms to 122.4 +/- 11.96 ms and was statistically significant (P=0.0006). An improvement in functional status by one class was observed in all the patients during follow up while the 6-minute walk distance (6MWD) had improved from 256 +/- 104.61 metres to 461 +/- 135.22 metres (P=0.0279). However, this did not reflect as lowering of NTproBNP values as shown in the table (P=0.4484).

With regards to the echocardiographic parameters, the LV ejection fraction improved from 35.2 +/- 1.94 % to 40.8 +/- 4.83 % (P=0.0428), LVIDD improved from 65.2 +/- 7.41 mm to 62 +/- 11.04 mm (P=0.6051). Also, there was significant improvement in the intraventricular dyssynchrony as reflected by the reduction in Septum to Posterior wall delay (S-PW delay) from 274.6 +/- 93.62 ms to 64.4 +/- 28.48 ms (P<0.001). However, there was no significant difference in the interventricular dysynchrony as reflected by the V-V delay (P=0.0762). Similarly there was no significant change in the right ventricular systolic pressure estimated from the TR jet and RA pressure (P=0.1143) and was no change in the degree of mitral regurgitation in these patients.

Table 5: Clinical and Echocardiographic parameters in conduction system pacing for CRT

Parameter	At implant	At follow up	Statistical variables
QRS duration	170 +/- 15.49 ms	122.4 +/- 11.96	Difference -47.600 Standard error 8.752 95% CI -67.7820 to -27.4180 t-statistic -5.439 DF 8 Significance level P = 0.0006
6MWD	256 +/- 104.61 metres	461 +/- 135.22 metres	Difference 205.000 Standard error 76.456 95% CI 28.6918 to 381.3082 t-statistic 2.681 DF 8 Significance level P = 0.0279
NTproBNP	2911.2 +/- 2531.76 pg/mL	1843.6 +/- 2096.57 pg/mL	Difference -1067.600 Standard error 1470.062 95% CI -4457.5695 to 2322.3695 t-statistic -0.726 DF 8 Significance level P = 0.4884
LVEF	35.2 +/- 1.94 %	40.8 +/- 4.83 %	Difference 5.600 Standard error 2.328 95% CI 0.2322 to 10.9678 t-statistic 2.406 DF 8 Significance level P = 0.0428
LVIDD	65.2 +/- 7.41 mm	62 +/- 11.04 mm	Difference -3.200 Standard error 5.946 95% CI -16.9121 to 10.5121 t-statistic -0.538 DF 8 Significance level P = 0.6051
LVIDS	56.2 +/- 6.55 mm	49.2 +/- 9.6 mm	Difference -7.000 Standard error 5.220 95% CI -19.0363 to 5.0363 t-statistic -1.341 DF 8 Significance level P = 0.2167

S-PW DELAY	274.6 +/- 93.62 ms	64.4 +/- 28.48 ms	Difference -210.200 Standard error 12.839 95% CI -239.8071 to -180.5929 t-statistic -16.372 DF 8 Significance level P < 0.0001
V-V DELAY	47.6 +/- 21.53 ms	24.6 +/- 13.22 ms	Difference -23.000 Standard error 11.299 95% CI -49.0550 to 3.0550 t-statistic - 2.036 DF 8 Significance level P = 0.0762
RVSP	42 +/- 12.66 mm Hg	30.4 +/- 7.34 mm Hg	Difference -11.600 Standard error 6.544 95% CI -26.6916 to 3.4916 t-statistic -1.722 DF 8 Significance level P = 0.1143

SAFETY PARAMETERS:

There were no significant complications such as lead dislodgement, septal perforation, pericardial effusion, tricuspid valve injury, infections, thromboembolic episodes in any of the study subjects.

Fig 5.5 ECG Pre and Post HBP

Fig 5.6: HBP lead positioning

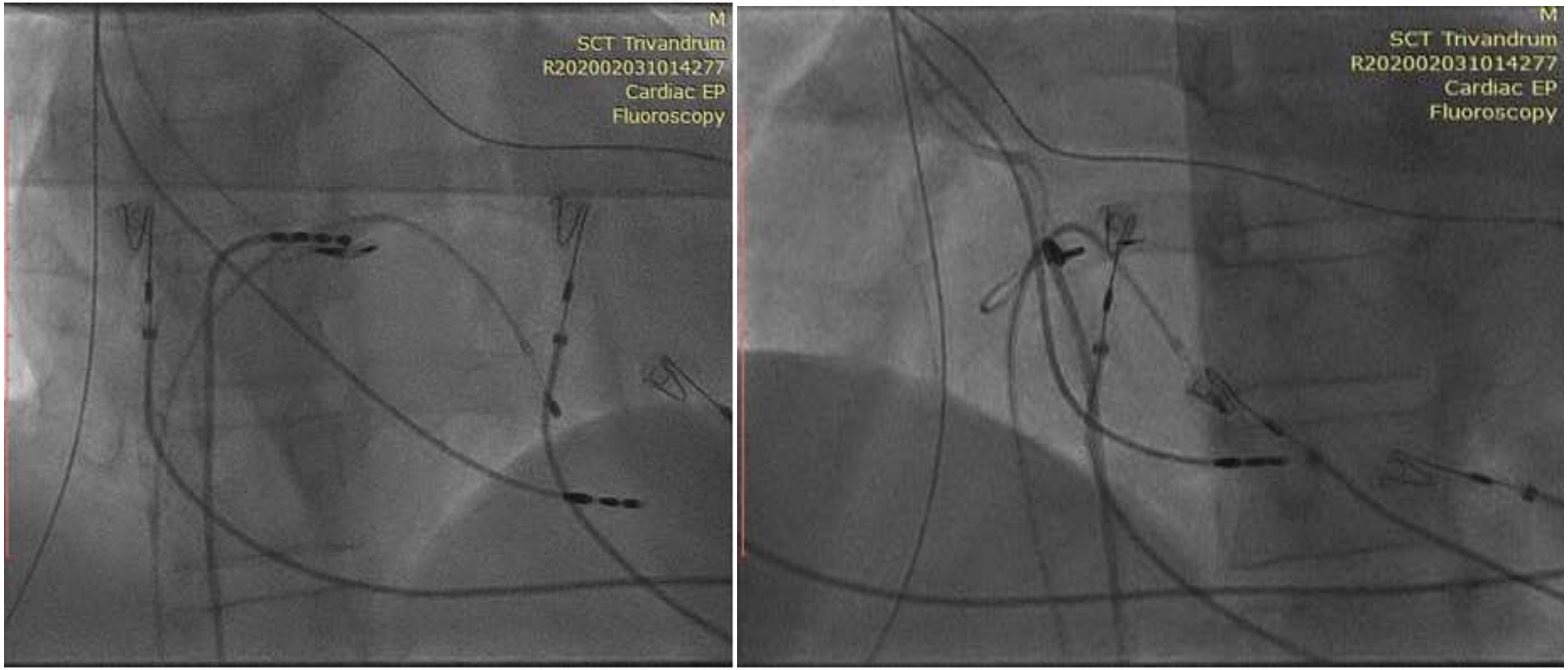


Fig 5.7: ECG Pre and Post LBBP

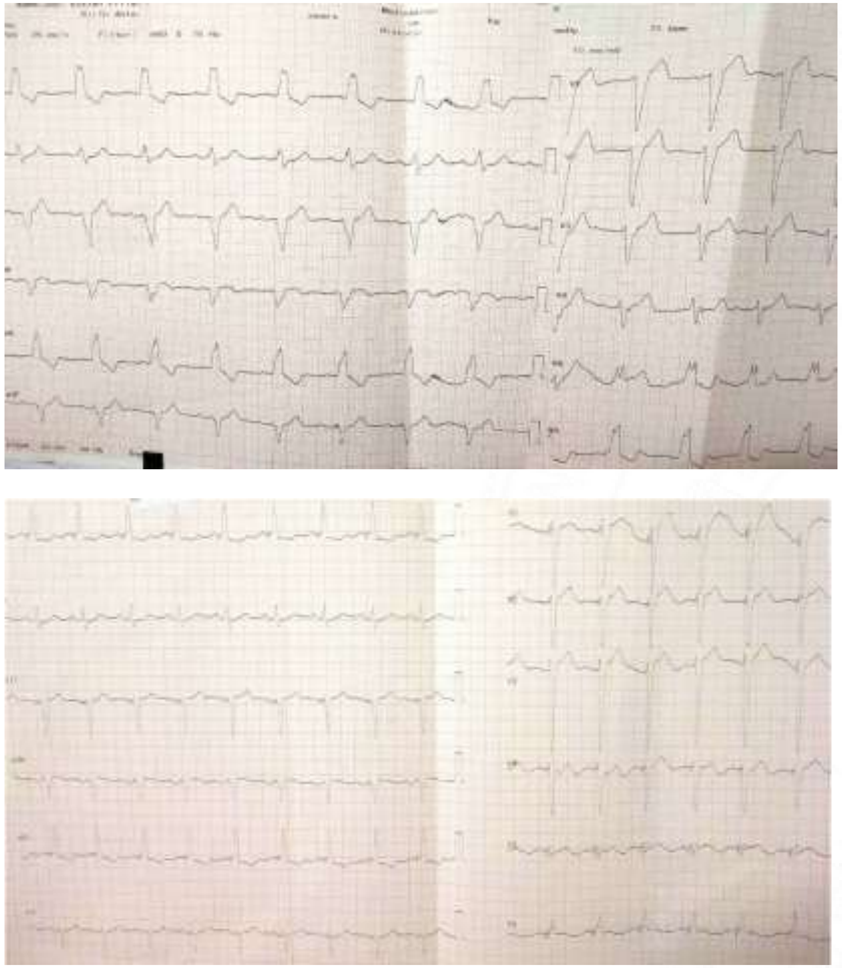
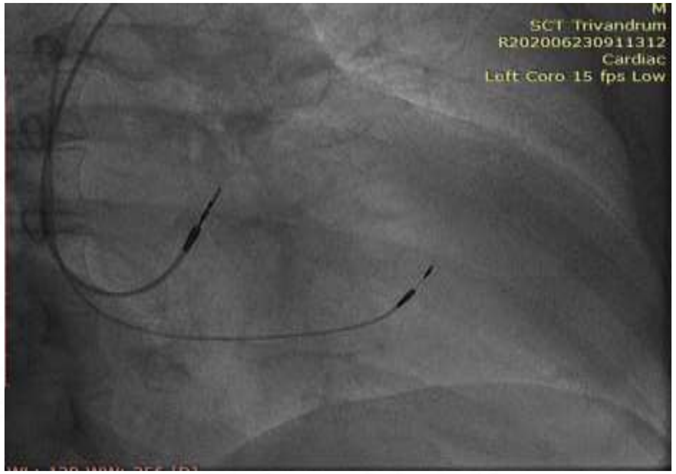


Fig 5.8: LBBP lead position



DISCUSSION

Conduction system pacing can be seen as a collection of techniques: pacing the His bundle, the proximal left conduction system and the region surrounding it. Though initial studies on HBP were only single-centre and observational, widespread interest and uptake of HBP over time has led to large multicentre international registries, long term follow up studies and first RCTs. With these data certain limitations of HBP have come to light such as higher thresholds, smaller R waves, long fluoroscopy times and higher failure rates, but with improvement in operator experience, these limitations could be overcome. LBBP has emerged more recently and much of the limitations of HBP as described above are not shared by this pacing modality as indicated by early evidence.

As HBP is performed more widely, larger registries have provided a picture of contemporary practice including indications.[4,5,6] In the Keene et al. multicentre registry of 529 patients, AV block was the most common indication, seen in half of cases, with slow AF the next most common (27.8%).[6] The remainder of the patients had CRT, SND and AVNA in similar proportions (6.6–8.9%). In the Zanon et al. multicentre experience, AVB (41.2%) and AF (39.7%) were also the most common indications, but fewer patients underwent His-CRT (1.7%).[5] The early experience of LBBP indicates a similar range of indications but with small numbers of patients in published series, the relative proportions are difficult to ascertain. In principle, there is no reason for indications to differ between HBP and LBBP, with the exception of CRT for RBBB where LBBP needs to be carefully studied. In our study, we have performed conduction system pacing was commonly performed for CRT (50%) followed by AV block (30%) and Sinus node dysfunction (20%).

Multiple registries have shown that the stylet-less technique using a SelectSecure 3830 lead is effective in achieving both HBP and LBBP in the vast majority of the cases the C315 fixed curve workhorse sheath (Medtronic) is sufficient to reach the His bundle. [4,5,6,11] In a minority the defectable C304 delivery sheath (Medtronic) had to be used with a yet smaller minority requiring modification to coronary sinus sheaths.[9] In our study, conduction system pacing (HBP/LBBP) was achieved using the SelectSecure 3830 pacing lead and C315 fixed curve sheath in all the cases. In our patients who underwent HBP, selective capture was achieved in 80% of cases, whereas selective LBBP was achieved in only 20% of patients with regard to LBBP. This is a well acceptable result as per available evidence. Beer et al. compared long-term outcomes of heart failure hospitalisation or mortality between S- and NS-HBP and found no significant difference.[12]

Left bundle potentials are seen with varying frequency (in contrast to the near ubiquity of His potentials in HBP), and the interval from potential to QRS onset is typically 15–35 ms. This has been observed in our study as well with His potential recorded in 80% of HBP cases while left bundle potential was recorded in only 20% of LBBP cases.

R wave amplitudes sensed from His leads are generally lower than 5 mV and atrial EGMs of varying amplitudes may also be present.[3] LBBP leads that are surrounded by abundant myocardium have larger R waves, providing one very clear advantage over HBP.[14] The HBP thresholds are typically, higher than for RV myocardial capture, but large contemporary registries suggest that improvements in technique have considerably reduced this issue, with mean His capture thresholds of 1.4 ± 0.9 V at 0.8 ± 0.3 ms, and 1.6 ± 1.0 V at 0.8 ± 0.4 ms observed in the two recent large registries.[5,15] The Keene et al. registry showed that there is a learning curve with HBP and that after 30–50 cases the implant threshold is reduced, as is fluoroscopy time.[6] LBBP thresholds have been noted to be very low (usually, <1 V at 0.5 ms) since its inception and low thresholds are reported in every series.[14,16-18.]

The HBP thresholds are typically higher than for RV myocardial capture, but large contemporary registries suggest that improvements in technique have considerably reduced this issue, with mean His capture thresholds of 1.4 ± 0.9 V at 0.8 ± 0.3 ms, and 1.6 ± 1.0 V at 0.8 ± 0.4 ms observed in the two recent large registries.[5,6,15] LBBP thresholds have been noted to be very low (usually <1 V at 0.5 ms) since its inception and low thresholds are reported in every series.[14,16-18] Post-implant threshold rises are observed in around 7% of cases in HBP and may be due to micro-displacement or fibrosis. They can occur early (prior to initial follow-up) but very late rises have also been seen >6 months or even 1 year after follow up despite stable, low intervening thresholds.[5] Such threshold rises have not been seen yet with LBBP, which is promising, but this is in the context of a much smaller published experience and short-term follow-up. In our study too the His R wave amplitudes were lower than 5mV while the R waves were very good with LBBP. Also, the HBP thresholds were higher when compared to left bundle capture thresholds. In contrary to what has been previously described, the His capture thresholds remained stable at 3 months while there was a marginal increase in Left bundle capture thresholds. The rise in mean left bundle capture threshold was due to the effect of the significant rise in threshold in one patient at 3 months follow up.

Reports of HBP implant success rates range from 72 to 92%, but success definitions have not always been standardised and lower rates are seen with His-CRT.[3,6,19,20] The early indications are that LBBP has a high success rate (>80%) with low re-intervention rates, and that lead perforation of the deeply fixated LBB lead into the LV cavity is very rare.[21] As our experience with conduction system pacing is fairly recent, Our success rate of 71% was comparable.

Among the patients who underwent conduction system pacing for AV block and sinus node dysfunction there was no deterioration in the functional class, 6 min walk distance, NTproBNP, LV function, LV dimensions, degree of mitral regurgitation, Right ventricular systolic pressure as measured by the TR jet. However, these problems usually develop more slowly in patients with RVAP or RV septal pacing and is noted only during long term follow up. Hence the short term follow up of this subgroup of patients cannot not be used to draw meaningful conclusions in this regard.

On the other hand, the role of conduction system pacing to resynchronise BBB in patients with heart failure is a particular indication for which recent insights have greatly altered our understanding. El-Sherif et al. observed in the 1970s that pacing the distal portion of the His bundle could correct LBBB to create a narrow QRS complex.[26] Lustgarten et al. demonstrated that this could be achieved with permanent HBP in 2010.[27] Subsequent observational studies show that HBP can shorten QRS duration and improve cardiac function and symptoms in patients with heart failure and LBBB.[28-30] Given these data, His-CRT has gained prominence as a bail-out in cases of failed BVP, but the important question was whether the physiological nature of resynchronisation by His-CRT produced better outcomes than BVP. In 2019, a pilot head-to-head comparison between the two modalities was published – His Bundle Pacing versus Coronary Sinus Pacing for CRT (HIS-SYNC).[31] His-CRT produced greater QRSd reduction than BVP but a statistically significant difference in LVEF improvement was not found. Unfortunately, the study suffered from a very high rate of cross-over from the HBP arm to the BVP arm, and the reasons for this illustrate the current challenges facing His-CRT. Half of crossovers were attributed to ECGs showing intraventricular conduction delay rather than LBBB. Thirty percent crossed over due to inability to correct LBBB. Arnold et al. have demonstrated, in a within-patient comparison, that when HBP successfully corrects LBBB, the haemodynamic and electrical improvements are greater than with BVP. HIS-SYNC showed that successful His-CRT requires selection of patients with conduction system disease amenable to correction by HBP and that improved implantation tools are required to facilitate correction in these patients. Upadhyay et al. have shown the physiological basis for patient selection. They found, by studying the left-sided conduction system, that patients with 12-lead ECG appearances of LBBB have variation in the nature of conduction disease. The majority had conduction block within the bundle of His, clearly amenable to correction by HBP. A smaller proportion had proximal conduction block within the proximal conduction system but distal to the His bundle: the block was located in the left bundle branch. Such patients may be amenable to HBP correction, but LBBP offers a more plausible corrective method. Literature on LBBP ability in resynchronising LBBB is sparse. Published series and case reports include few patients with LBBB.[33-35]LBBP is promising for CRT due to its presumed ability to correct block within the His bundle and the proximal left bundle. Also, given that LBBP produces an RBBB pattern, HBP is likely to have an advantage over LBBP for resynchronising RBBB. HBP can resynchronise RBBB in two ways: direct recruitment of the right bundle; and NS-HBP results in a wavefront from the basal RV (local myocardial capture) meeting another wavefront originating more apically (from left bundle mediated activation of the RV).[37]

In the current study, certain observations can be made in the subset of patients who had undergone conduction system pacing for bundle branch correction for CRT. This subgroup in the current study improved only patients with LBBB and not with RBBB or IVCD. A significant QRS narrowing (P=0.006) could be achieved in all patients. Almost all the patients had improvement in functional class by one grade during follow up although the increase in their 6MWD did not reach the level of statistical significance desired. There was no significant change (P=0.027) in the NTproBNP however did not occur. With regards to the echocardiographic assessment, a moderate increase in the LV ejection fraction was noted in most of the patients (P=0.0428). As expected, there was a significant reduction in the intra ventricular dysynchrony (P<0.001) while the inter ventricular dysynchrony did not change much. Also, there was no significant change in the grade of mitral regurgitation and the right ventricular systolic pressure at 3 months follow up. Repeat assessments in the medium/long term shall be required to look for further improvements of the clinical and echocardiographic parameters.

LIMITATIONS

The most important limitation of the study is the small sample size. Though the project was originally designed to enrol about 20-25 subjects within the stipulated study period, the same size could not be reached due to the challenges faced during the Covid 19 pandemic.

CONCLUSIONS

Physiological pacing of the conduction system is a feasible and safe method of pacing with stable pacing characteristics during short term follow up. Pacing for bundle branch correction as an alternative to CRT has been associated with both clinical and echocardiographic improvement. This finding needs further validation in a larger cohort.

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