European Heart Journal Supplements (2025) **27** (Supplement 3), iii126–iii130
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suaf030

ESC
European Society
of Cardiology

The advantages of physiological pacing

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KEYWORDS
Pace-induced cardiomyopathy;
Conduction system;
His pacing;
Left bundle branch pacing

The evidence that conventional right ventricular pacing can result in the development of cardiomyopathy and heart failure over time has prompted the search for alternative pacing sites. Conduction system pacing (CSP) represents an attempt to overcome the limitations of conventional pacing and to provide an alternative for patients with reduced EF and various degrees of dyssynchrony for whom resynchronization therapy is not feasible for technical or anatomical reasons. In particular, His bundle pacing and left bundle branch area pacing (LBBAP), with their advantages and disadvantages, have been shown to meet the criteria of physiological pacing. The former, although technically more challenging and less satisfactory in terms of electrical parameters, allows to obtain a QRS complex that is identical to the spontaneous one. The latter produces a wider paced QRS and although the technical complexity at the time of implantation is significantly reduced, is subject to a series of mechanical complications related to the trans-septal positioning of the lead. Careful patient selection along with an adequate learning curve for the operators make CSP a safe and effective procedure, although burdened by a higher complication rate compared with conventional pacing. Future studies will clarify its role, which is currently limited by current ESC guidelines to His Pacing only as an alternative procedure in case of failure of resynchronization therapy (class of recommendation IIa), after the 'ablate and pace' procedure or as an alternative to right ventricular pacing in patients with AV block, left ventricular ejection fraction <40% and an expected right ventricular pacing percentage >20% (class of recommendation IIb).

Introduction

In its sixty-year-old history, cardiac pacing has become an essential therapy for many patients in various clinical situations. Nevertheless, it has been demonstrated that a high percentage of right ventricular pacing is associated with an increased risk of developing pacing-induced cardiomyopathy and heart failure. A meta-analysis of 26 studies showed that the incidence of pacing-induced cardiomyopathy ranged from 5.9% to 39%, depending on the adopted definition, in a follow-up period of 0.7 to 16 years.[1] Electromechanical dyssynchrony resulting from right ventricular pacing can be considered similar to the one observed in left bundle branch block. The onset of cardiomyopathy is influenced by numerous factors such as the degree of dyssynchrony, pre-existing ventricular dysfunction, functional mitral insufficiency, and the burden of right ventricular pacing.[2] The search for alternative right ventricular pacing sites (interventricular septum and outflow tract) has not yielded substantial benefits, whereas biventricular pacing has emerged as the gold standard for patients with heart failure with reduced ejection fraction and various degree of

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interventricular dyssynchrony. However, this option is not always technically feasible, moreover approximately one-third of patients are considered non-responders. Conduction system pacing (CSP) represents therefore an attempt to provide an alternative option to conventional pacing in order to avoid its potential long-term consequences and to overcome the limitations of biventricular pacing when this is not a viable or effective solution.[3]

Conduction system pacing

Conduction system pacing refers to the stimulation of the conduction system at any level, including the bundle of His, the right bundle branch, the left bundle branch, and its fascicles.

The initial approach to CSP was obtained through His bundle pacing, which can be intuitively considered the most physiological modality of ventricular activation. In His pacing, the activation of the conduction system occurs distally to the distal portion of atrioventricular node but proximally to the bifurcation of His bundle into its branches.

However, positioning of the lead at the exact location of the His bundle is not always easy to achieve and can be technically extremely challenging. In addition, electrical parameters are often unsatisfactory at the time of implantation and remain unstable over time, necessitating the placement of an additional ventricular backup lead.

In light of these limitations, the evolution of CSP has continued towards the search for additional pacing sites.

When the lead is positioned at the level of the distal His, right bundle branch stimulation is obtained. However, this modality is sub-optimal due to the wider QRS which does not fulfil the criteria for physiological stimulation.[4] Therefore, the left bundle branch area pacing (LBBAP) was proposed as an alternative. This pacing modality involves positioning of the lead deeply into the interventricular septum at a distance of 1–2 cm from the His bundle. The lead is positioned in the area proximal to the bifurcation of the left bundle branch into its fascicles which are then simultaneously activated.

Conversely, if the lead is positioned more distally, it is possible to obtain a fascicular stimulation or alternatively a deep septal stimulation in case the subendocardial layer is not reached.

Anatomy

Knowledge of the anatomy and its variations is essential for a proper understanding of the physiopathology of conduction disorders and correct implantation technique.

The His bundle is a structure of ~2 cm in length, isolated from the surrounding atrial and ventricular myocardium by fibrous tissue that encapsulates it. The His bundle contains the fibres that become the right and left bundle branches with their fascicles. It originates from the atrioventricular node, runs along the posterior and inferior edge of the membranous septum in the right atrium and remains undivided for a few millimetres. At the level of the crest of the muscular interventricular septum, the His bundle begins to divide into the right and left bundle branches.[4] The stem of the left bundle branch often divides into two fascicles with numerous ramifications and connections after about 2 cm.

Recent evidence has identified three anatomical variants of the His bundle in relation to the membranous septum: in the first and most common, it runs along the lower edge of the membranous septum and is covered by a thick layer of fibres coming from the muscular septum; in the second variant, it runs in the membranous septum and then crosses the muscular septum; in the third, it is located immediately below the endocardium and runs over the membranous part of the septum.[5]

Implantation techniques and electrocardiographic criteria

The role of the 12-lead electrocardiogram in the organization of the EP lab when approaching the conduction system implantation technique is of paramount importance when compared with conventional pacing. Electrocardiogram enables the identification of the optimal pacing site and confirmation of conduction system capture. It is essential to interpret both filtered and unfiltered signals. The latter serves to visualize the current of injury, which exerts a significant influence on both the acute and long-term capture parameters. To correctly differentiate the conduction system potentials, a tracing speed of 50–100 mm/sec should be used. In patients with atrioventricular block or left bundle branch block and an indication for dual-chamber pacemaker implantation, it may be advisable to temporarily deploy the atrial lead in the ventricle as a backup lead. Similarly, if a defibrillator is implanted, the defibrillation lead should be implanted first. In order to accurately determine the optimal lead placement site, it is crucial to consider a number of factors, including the anatomical and fluoroscopic landmarks, the morphology of the paced QRS complex and the intracavitary signals. It should be noted, however, that these factors have some limitations. First, the assessment of correct lead positioning through fluoroscopy may prove to be imprecise. Second, the morphology of the paced QRS complex may be influenced and modified by the substrate. Finally, the intracardiac signal of conduction system potential may not be easily detected.[4]

It is not necessary to use an electrophysiology catheter to map the His bundle. The use of a pacing lead in unipolar mode, inserted in a special introducer with a fixed curve or a deflectable release system oriented posteriorly towards the interventricular septum is sufficient for the purpose of this procedure. Once the lead has reached the region of the tricuspid annulus at an angle of 20–30° in the right anterior oblique view, mapping can be initiated. Subsequently, the system can be advanced towards the septum in the left anterior oblique view at an angle of 30–40°. If the His potential is not discernible, a high-output pace mapping procedure may be undertaken until narrow stimulated complexes are obtained. In cases where the anatomy is particularly complex, the use of electro-anatomical mapping may be indicated.[4]

His bundle pacing can be performed with conventional or dedicated leads (leads with stylet and retractable screw or lumen-less leads with exposed screw); if the former avoids screw entrapment in the chordae tendineae, the exposure of the helix when the target is found may lead to micro-dislodgments that alter the electrical parameters.

Fixation is a critical phase of the implantation procedure as it has a decisive influence on the short- and long-term electrical parameters. Irrespective of the type of catheter used, the rotational movements applied by the operator are transmitted along the body to the tip of the lead to facilitate its penetration through the fibrous layer covering the His bundle. Once fixation is complete, the electrical parameters are checked to confirm the capture of the His bundle.[4] Before cutting the dedicated delivery, it is advisable to position the atrial lead so as not to dislocate the His bundle lead and, at the end of the procedure, a further check of the electrical parameters must be carried out.

A sensing value > 2 mV in bipolar and > 4 mV in unipolar and a pacing threshold <1.5 V × 0.5 msec can be considered optimal for His pacing. However, a higher threshold may be acceptable in different clinical scenarios.

During threshold testing, it is possible to observe a change in the morphology of the paced QRS when moving from non-selective to selective capture. In non-selective capture, the myocardium surrounding the His bundle is also stimulated, whereas in selective capture only the conduction system is activated. Electrocardiographic criteria can be used to distinguish between the two.[6] In non-selective capture, a pseudo-delta or local potential may be observed on the surface electrocardiogram, fused with the pacing spike. In contrast, with selective capture, myocardial depolarization occurs after a latency period with respect to the pacing stimulus, resulting in an isoelectric line on the surface electrocardiogram. This interval corresponds to the HV interval and the QRS complex is identical to the spontaneous one. Although similar in outcome, non-selective capture appears to be safer due to the presence of backup myocardial activation and the presence of better electrical parameters.[7] The appearance of a notch, slur or plateau in the midst of the QRS complex in the left leads (I, V5, and V6) is the first clear evidence of loss of selective His bundle capture and ventricular activation by the slow cells of the working myocardium. Another noteworthy electrocardiographic criterion is the V6R wave peak time (V6RWPT), also known as left ventricular activation time (LVAT). This is the time taken for the depolarizing wave front to reach the epicardial surface of the lateral wall of the left ventricle. A V6R wave peak time of 100 milliseconds or less is a specific indicator of His bundle capture[8] (*Table 1*).

Similar assumptions are held with regard to the stimulation of the left bundle branch area compared with His bundle pacing; however, notable differences are also evident. First, it is of great importance to conduct a preliminary assessment of the echocardiographic data, paying particular attention to right atrial and ventricular volumes and septal thickness. In terms of materials, either conventional leads (with a stylet and removable screw) or dedicated lumen-less lead with a fixed screw along with dedicated introducers (preformed or with an adjustable curve), can be employed.

Table 1 **Electrocardiographic criteria for His bundle nonselective and selective pacing**

	Non-selective His stimulation	Selective His stimulation
Between spike and QRS	Pseudo-delta	Isoelectric, equal to HV interval
QRS	Wider than the spontaneous one, possible presence of notch/slur/plateau in the left leads	QRS identical to the spontaneous one
V6RWPT	>100 msec	<100 msec

In the early days of this technique, the distal His potential was used as a reference to locate the target area; today, the tricuspid annulus is used as a reference and, in a 30–45° right anterior oblique view, the system is advanced towards the His region and then advanced 1.5–2 cm towards the apex. In a 30–45° left anterior oblique view; while applying a counter-clockwise rotation, the interventricular septum is approached with the exposed lead tip at the point where the left bundle branch is thought to be located. The PSA (pacing system analyser) is then connected in a unipolar configuration to assess the morphology of the stimulated QRS.[4]

A favourable starting position is one in which a W-shaped appearance is obtained, with a notch in lead V1 and QRS discordance in lead II (isodiphasic or predominantly positive) and lead III (isodiphasic or completely negative). Once the target site has been identified, septal penetration can be performed. This represents the crucial step in the entire procedure. In a left anterior oblique view, an injection of iodinated contrast medium can be used to outline the profile of the interventricular septum, allowing for verification of perpendicularity before lead screwing. This is pivotal for the correct advancement of the screw and for assessing the depth reached by the lead during penetration.

Ideally, a gradual advancement of the lead should be achieved by gentle, continuous, and progressive rotation and pushing.[4] During lead screwing, the disappearance of the notch in lead V1, the appearance of an r’ wave (indicating a delay in right ventricular activation) and the shortening of the peak time of the V6-R wave (<75 msec or 80 msec in the presence of pre-existing left bundle branch block)[9] are observed in the unipolar modality paced QRS. Other indirect signs of successful penetration include the occurrence of fixation beats, i.e. ventricular pre-mature beats that occur after mechanical trauma that show an r’ wave or a morphology similar to that of left bundle branch stimulation[10] and the characteristic trend of the impedance curve, which, after an initial rise and subsequent plateau, begins to fall.[11] Occasionally, the appearance of a left bundle branch potential is also noted (*Table 2*).

If the lead is situated at a greater distance from the His area, fascicular stimulation can be achieved. In this instance, if the paced QRS is positive in leads II and III,

Table 2 Electrocardiographic signs of left bundle branch penetration

Signs of left bundle branch penetration
Transition from W in V1 to the appearance of terminal R′
V6RWPT < 75 msec (80 msec in the presence of LBB)
Fixation beats
Impedance rise, plateau and subsequent decrease
Appearance of the left bundle branch potential

the stimulation site would be the left anterior fascicle; if it is isodiphasic/positive in II and isodiphasic/negative in III, the stimulation site would be the middle part of the septum; finally, if the QRS complex is negative in leads II and III, the stimulation site would correspond to the left posterior fascicle. Conversely, if the lead is positioned deeply within the septum but does not reach the subendocardium, this is referred to as deep septal pacing. In this instance, the QRS complex is relatively narrower than that observed in right ventricular pacing, yet the criteria for conduction system pacing are not met (there are no notches in the left leads and the terminal R in lead V1 is absent).

The pros and cons of conduction system pacing

According to recent studies, the success rate of His pacing was 92%, and that of LBBAP, according to the Multicentre European Left Bundle Branch Pacing Outcomes Study, was 92.4% in patients with an indication for anti-bradycardic therapy and 82.2% in patients with heart failure.[12]

Both techniques have advantages and disadvantages. For instance, LBBAP yields superior and more stable electrical parameters over time compared with His pacing. Conversely, His pacing results in a narrower QRS complex, which increases the likelihood of improving the LV ejection fraction.[13] This is because narrowing of the QRS complex is a key factor in terms of advantage of CSP over conventional pacing. Moreover, while LBBAP may be sufficient to restore physiological and synchronous ventricular activation, in more complex patients such as patients with heart failure and severely reduced ejection fraction, the delay in left ventricular free wall activation may also be influenced by other factors, including the presence of a scar or a dysfunction in the more distal conduction system, which can result in electrical uncoupling.

In terms of complications, the most common with His pacing are related to the electrical parameters, which are not always optimal at implantation (low sensing and high capture threshold) and are often variable and unstable over time (ventricular undersensing or oversensing of His or atrial signals, threshold rise or loss of capture). A complication rate of 11.7% has been reported with LBBAP (similar to CRT). However, the trans-septal position of the pacing lead resulted in a range of complications in 8.3% of cases: periprocedural septal perforation (3.7%), occurrence of right bundle branch block or complete block, acute coronary syndrome, coronary fistula, septal haematoma, helix rupture or fracture; post-operatively, late perforation, dislocation, loss of left bundle branch capture, increased threshold, and worsening tricuspid regurgitation.[12]

Conclusions

In conclusion, in the absence of large randomized clinical trials, it can be stated that, despite a peri-procedural complication rate that is two to three times higher than that observed with conventional pacing, Conduction system pacing is safe in the majority of patients if performed by experienced operators after an adequate learning curve.[12] The long-term benefits of this para-physiological pacing in terms of heart failure, arrhythmias and reduced mortality remain to be demonstrated. The current evidence does not support the use of conduction system pacing as an alternative to biventricular pacing. However, the latest European guidelines recommend considering this approach in patients who are eligible for biventricular pacing but fail to receive a left ventricular lead for different reasons (class IIa recommendation) and following an 'ablate and pace' procedure. Conduction system pacing should also be considered as an alternative to right ventricular pacing in patients presenting with AV block, LVEF <40% and in whom a ventricular pacing percentage of more than 20% can be reasonably expected (recommendation class IIb).[14]

Conversely, the ACC guidelines categorize CSP as a class IIa indication for patients with reduced EF (36-50%) and a class IIb indication for those with normal EF, both with an anticipated high percentage of right ventricular pacing. Further research will shed light on the function of CSP within the broader context of cardiac pacing, with a particular focus on its role in the management of complex heart failure cases.[15]

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

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

Disclaimer

This paper was originally published in the Italian language as 'I vantaggi dell'ettrostimolazione fisiologica', in the Volume degli Atti del Congresso "Conoscere e Cuare il Cuore 2025", published by Centro per la Lotta contro l'Infarto for distribution at the CCC Conference. This paper was translated by Dr. Mario Albertucci, representative of the CLI Foundation, and republished with permission.

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