Review

Functional aspects of His bundle physiology and pathophysiology: Clinical implications☆

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Abstract

In this review we present evidence from many experimental studies which challenge the concept of predestination of His bundle fibers. Using both intra- and extracellular His bundle pacing in the context of atrio-ventricular block and the development of bundle branch blocks these experimental studies provide the underlying mechanisms for the recent clinical findings showing the benefits of permanent His bundle pacing.

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Historical background

The structure and function of the His bundle and the Purkinje conduction system (HPS) has been the focus of many investigators since the early pioneering discovery of these structures by Purkinje [1], His [2] and Tawara [3]. In 1919, Kaufman and Rothberger [4] suggested that normal conduction in the HPS was mediated by specific pathways starting in the AV junction that connected to specific right or left ventricular Purkinje-muscle junctions. Several subsequent studies based mainly on electrocardiographic deductions provided indirect evidence supporting the concept of longitudinal dissociation as the basis for physiological functioning of the HPS [5-7].

His bundle physiology

Fig. 1 is a modified illustration of the drawing from the anatomic studies of Tawara showing the structure of the AV node and His bundle as dissected from the right and left side of the atrial/ventricular septa. It should be noted that the His bundle which was measured to be 1.8 cm in length [3] is composed of two distinct sections, the non-branching portion which penetrates the fibrous AV ring and continues as the right bundle branch, seen from the right side of the ventricular septum; and the branching portion of the His bundle from which the branches of the left bundle originate.

This anatomic definition of the His bundle has important functional implications both in normal and pathological states (see below).

In the 1970’s we performed a series of studies designed to investigate the cellular electrophysiology of the His bundle in the dog heart [8,9]. For this purpose we sought to provide an in vitro preparation which would allow the use of extra and intracellular recordings from the exposed His bundle which is sequestered, in part, within the fibrous ring at the crest of the ventricular septum. Briefly, under deep pentobarbital anesthesia, the chest was opened, and the heart was excised and placed in cool oxygenated Tyrode’s solution. The atrial and ventricular free walls were removed leaving the atrial and ventricular septum. The His bundle was exposed by means of a single, strategically placed cut in the atrial septum along the superior aspect of the bundle. The ventricular septum was split to the crest, allowing the left and right ventricular surfaces to be aligned in a 2 dimensional plane along with the His bundle. The split ventricular septum encompassed the left and right bundle branch systems (Fig. 2). The flaps of the split ventricular septum were pinned in a lucite chamber and continuously superfused with oxygenated Tyrode’s solution at 36.5 ºC. Using this preparation, Lazzara et al. [8], in a large number of iterations detailed the normal sequence of activation when the proximal His bundle was stimulated with a close bipolar pair of electrodes. Of interest, the earliest area of ventricular muscle activation of the left side was mid-septal (27 ± 2 ms) and was temporally matched by activation at the same mid-septal activation on the right side at the junction of the right bundle branch and the base of the anterior papillary. However, the area of earliest activation on the left (shaded

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area) was much larger than on the right; this finding would appear to be the functional basis for the Q wave as seen in inferior ECG leads providing a strong left to right vector.

Since the His bundle itself was now exposed this allowed insertion of microelectrodes into individual His bundle cells for recording of single cell action potentials. Furthermore, current injected through the microelectrode within randomly selected His bundle cells showed the same sequence and timing of the His Purkinje-muscle activation as was found when stimulation was initiated by close bipolar electrodes to the proximal His bundle. Importantly when the microelectrode was removed from the cell and the same current applied to the cell surface no excitation occurred. We, therefore concluded that functional transverse interconnections are relatively numerous within the normal His bundle allowing a uniform wave front to proceed from the His bundle to the bundle branch/Purkinje network. If the normal His bundle does not show dissociation then under what circumstances and what pathophysiological conditions could His bundle dissociation occur? Moreover what are the clinical consequences of His bundle dissociation?

His bundle pathophysiology: in vivo studies

To study the electrophysiology of the His bundle after ischemic injury, in vivo studies were conducted in pentobarbital anesthetized dogs. Plunge wires and electrode catheters were utilized to record from proximal (Fig. 3A), mid (B) and distal (C) portions of the His bundle [9]. In the baseline state, under relatively physiological conditions, during sinus rhythm (120/min) or atrial pacing (150/min) the H-V interval from proximal to distal His bundle recording was 4 ms. His bundle pacing at 200/min at each of the His bundle sites corresponded to those values shown during sinus rhythm and atrial pacing. Also, QRS morphology in ECG leads was unchanged (Fig. 3D, E F).

In order to induce ischemic damage to the area of the His bundle, the anterior septal artery (first septal perforator) was dissected as it exited from the main left coronary artery. A ligature placed around the vessel could be used for ligation providing ischemic injury of myocardium at the crest of the septum underlying the AV junction. One to two hours after anterior septal artery ligation, His bundle damage manifested...
as split His bundle potentials (H, H’, Fig. 4A). Atrial pacing at a cycle length of 300 ms (180/min) exacerbated the intra-His bundle delay (Fig. 4B) and showed an incomplete right bundle branch block in the ECG leads. Decreasing the pacing cycle length to 250 ms (240/min) induced 2:1 A-V block between the proximal and distal His bundle potentials (Fig. 4C). As ischemia progressed, complete right bundle branch block was observed at during sinus rhythm at a rate of 130/min (Fig. 4D). However, distal His bundle pacing at comparable or even at higher rates (240/min) resulted in normal QRS complexes, with ST changes due to myocardial ischemia.

Myocardial ischemia was not the only intervention which allowed us to show the direct relationship between Intra His bundle delay and block with distal patterns of bundle branch blocks. In our in vitro preparation we were able to induce localized damage with a needle point inserted into the His bundle while action potentials were being recorded from microelectrodes in the proximal (PH, ME1) and distal (DH, ME2) to the damaged zone (hatched area, see diagram at upper left in Fig. 5). In addition we recorded close bipolar electrograms from the right (Rb) and left bundle (Lb) branches distal to the His bundle. Panel A. Pacing impulses (PI) applied at the very proximal His bundle were sequentially followed by the action potentials of the proximal and distal His bundle. Panel B. After traumatic injury to the bundle, both action potentials showed depolarization and marked diminution of their upstrokes indicative of slowed conduction which was associated with delay to the Lb electrograms and complete block of conduction to the Rb electrograms. Panel C. Several minutes later partial recovery of resting action potential and upstroke were observed as well as restoration of conduction to Lb and Rb electrogram recordings.

It is interesting to note, that a recent clinical report by Vijayaraman et al. [10] induced acute injury to the His bundle during electrode attachment by a screw-in lead. These authors stated that, “...two patients...developed transient right bundle branch block that resolved within 24 hours.”

**Permanent His bundle pacing**

Although the ability of His bundle pacing (HBP) to normalize conduction in conditions of pathology localized in the His bundle was demonstrated both experimentally [9,11,12] and clinically [13,14], the incidence of His bundle disease was unknown and there was no established technique for maintaining HBP similar to standard forms of permanent ventricular pacing. More than 2 decades later, Deshmukh et al. in 2000 [15] used a fixed screw-in lead to achieve direct HBP in 12 of 14 patients with chronic atrial fibrillation and dilated cardiomyopathy. During a mean follow-up period of 2 years, there was a significant improvement in several hemodynamic functions including reduced end-diastolic volumes and ejection fraction. In 2006, Zanon et al. [16] tested a newly developed deflectable sheath and 4.1 Fr. screw-in electrode catheter (Medtronic, Select Secure) which was successfully implanted in 92% of the 26 patients with

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**Fig. 3. Recording and pacing from proximal, mid and distal sites within the His bundle. Panels A–C show the following traces: ECG leads II (L-2) and aVR; plunge wire electrograms recorded from the different sites within the His bundle and distal His bundle activity recorded by an electrode catheter in the aortic root (Hbeg). The His bundle potentials in these traces are labeled H (proximal), H’ (mid) and H” (distal). Panels D–F show pacing from each His bundle site with pacing impulse (PI-V = 35, 34 and 31 ms, equal to the measured H-V, H’-V and H”-V intervals, respectively. (Reproduced by permission, J Electrocardiology, 1978;11: 343–354).**
Fig. 4. Ischemia induced intra-His bundle block manifested as split His bundle potential H and H’. ECG traces, Lead II (L-2) and AVR are shown and a His bundle electrogram (HBeg) from an electrode catheter in the aortic root. In panel A, at a cycle length of 450 ms the H-H’ interval equals 25 ms. In B with atrial pacing at a cycle length of 300 ms the H-H’ interval increases and an incomplete right bundle branch block pattern emerges. In panel C, pacing at a cycle length of 250 ms 2:1 A-V block was induced which was localized distal to the H potential. Note that the H-H’ interval is further prolonged in conducted beats (40 ms). With progressive ischemia complete right bundle branch was recorded during sinus rhythm which was normalized by distal His bundle pacing. Panel D. The interval between time lines equals one second. (Reproduced by permission, J Electrocardiology. 1978;11: 343–354).

Fig. 5. Mechanically induced localized damage in the His bundle, in vitro. A diagrammatic representation of the preparation is shown at the upper right. Microelectrode recordings (ME1 and ME2) were made from the proximal (PH) and distal (DH) His bundle. Extracellular electrograms were made from the right (1st two traces) and left (last 3 traces) bundle branches at comparable distances from the His bundle. In panel A, (Control) prior to needle induced damage to the His bundle. Panel B. (After Trauma). Panel C. During recovery. See text for further discussion. (Reproduced by permission, J Electrocardiology. 1978;11: 343–354).
conserved His-bundle conduction. Over a follow-up of 3 months direct HBP showed an unchanged pacing threshold.

Lustgarten et al. [17] provided a crossover comparison of permanent HBP versus biventricular (BIV) pacing in a larger number of patients. Twenty eight of the 29 patients enrolled showed left bundle branch block (mean duration, 169 ± 16 ms) which decreased with selective HBP to 131 ± 35 ms. At 6 month follow-up several measures of significant improvement were noted with both HBP and BIVP including ejection fraction; NYHA level, 6 min walk values and quality of life assessment. The narrowing of the QRS with selective HBP, in the 28/29 cases with left bundle branch block would indicate that many ECG bundle branch block patterns are indicative of His bundle dissociation and represent a larger population of patients who would benefit from HBP.

In conclusion, the recent recognition of HBP as a feasible alternative for CRT appears to be gaining momentum as a means of inducing normal physiological activation of the His Purkinje system although peripheral pathologies, i.e., ischemic etiologies of heart failure, may diminish the overall therapeutic effect. Beyond CRT, permanent HBP has also been shown to significantly reduce heart failure hospitalizations compared to standard right ventricular pacing over a 2 year follow-up period [18].

References
