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The infrahisian conduction system and endocavitary cardiac structures: relevance for the invasive electrophysiologist

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1 Introduction

With the increasing acceptability and use of catheterization ablation for ventricular tachycardia, detailed anatomic studies have been done to improve the safety and efficacy for energy delivery in and around critical cardiac structures [1–7]. More recently, ventricular fibrillation and certain forms of monomorphic ventricular tachycardia have required ablation in either the infrahisian conduction system or endocavitary cardiac structure, such as the papillary muscle, false tendons, and the right ventricular moderator band [8–13]. In this review, we explain the critical details of structure and structure–function relations of the infrahisian tissue and the cardiac endocavitary structures. We approach the structures as a single unit with endocavitary structures routinely having a rich network of the distal His-Purkinje system. In addition, several commonly applied cardiac mapping maneuvers, including parahisian pacing and pacemapping, rely on understanding conduction tissue

anatomy and active myocardium within the cavity for correct interpretation. Throughout the text are interspersed boxes that tabulate and summarize key anatomic pieces of information for the invasive electrophysiologist.

2 Infrasisian conduction system and endocavitary structures

The infrasisian conduction system is a complex network of specialized Purkinje fibers that serves to coordinate ventricular contraction in synchrony with atrial activation. From its origin at the bundle of His to individual Purkinje cell–ventricular myocyte junctions, it is insulated by collagen, which is thick and fibrous in the proximal portions (Fig. 1), and gradually diminishes such that a delicate insulating layer is seen to surround individual Purkinje fibers (Fig. 2) [14, 15]. The His-Purkinje system is specialized for rapid conduction, with conduction velocities of 2.3 m/s as compared to 0.75 m/s in ventricular muscle, which facilitates rapid activation and synchronous contraction of the ventricles [16]. Disease of this system can manifest as various degrees of slowed conduction between atria and ventricles. The system is also fundamentally associated with and responsible for several ventricular arrhythmias, both in normal and diseased hearts [17, 18]. On account of the system's rapid conduction, the QRS duration of any rhythm which utilizes it for a significant proportion of its conduction tends to be shorter, including when of ventricular origin [9, 19].

2.1 Proximal infrasisian conduction system

The penetrating bundle of His is a cord-like structure measuring approximately 20 mm in length and up to 4 mm in diameter [20], identifiable by its encasement in the central fibrous body, being cytologically similar to the atrioventricular node from which it arises and undergoing a transition such that its emerging fibers are indistinguishable from those of the bundle branches [21]. In the majority of individuals, the His bundle lies towards the left of the septum and divides at the junction of the membranous septum and crest of the muscular interventricular septum into the left and right bundle branches (Fig. 3), although in approximately 30 % of individuals it can either run for several millimeters down the muscular septum or actually be to the right of the interventricular septal crest [22].

The right bundle emerges at an obtuse angle to the His in the majority or otherwise as a continuation of a rightward His [22]. It is a cord-like structure [23] which runs superficially in the right ventricular endocardium in its upper third up to the level of the muscle of Lancisi (septal papillary muscle of the tricuspid valve) where it courses deeper in the interventricular septum, becoming superficial in its distal third to course within the ventricular trabeculations. The distal right bundle travels to the right ventricular wall in the moderator band (Fig. 3), which is reported to be present in over 90 % of postmortem hearts, though the size, thickness, and location on the ventricular septum varies [24].

Occasionally the right bundle is intramyocardial in its first two-thirds or subendocardial throughout its extent [25].

The left bundle is a broad sheet-like structure [23] that emerges beneath the non-coronary cusp of the aortic valve (Fig. 3), although it can be a narrow structure in those with a rightward His during its course back to the left [22]. The left bundle branch has traditionally

been described as giving rise to a thin anterior fascicle, a broader posterior fascicle which is the main continuation of the bundle, and in approximately 60 % of individuals a third fascicle termed the left median fascicle [26, 27]. Considerable variation in proximal left bundle anatomy and interconnections between its fascicles exists (Fig. 4) [28]. The anterior fascicle crosses the left ventricular outflow tract to the anterolateral wall and the region of the anterolateral papillary muscle, the posterior fascicle extends inferoposteriorly to insert near the base of the posterior papillary muscle and the free wall, and the median fascicle runs in the interventricular septum.

The pattern of activation of the ventricles follows this anatomical configuration, with earliest activation of the left ventricle occurring simultaneously in three endocardial regions: high on the anterior paraseptal wall just below the attachment of the mitral valve, central on the left surface of the interventricular septum, and posterior paraseptal about one third of the distance from apex to base; right ventricular activation occurs 5–10 ms later near the insertion of its anterior papillary muscle, with a subsequent endocardial–epicardial depolarization vector (Fig. 5) [29].

2.2 Distal infrahisian conduction system

The bundle branches progressively divide to form the mesh-like Purkinje network (Fig. 6), which constitutes the distal infrahisian conduction system. The distribution is not uniform, for example with a predilection for the papillary muscles and sparse distribution over the base of the ventricles [20]. Purkinje fibers drape the ventricular cavity as free running fibers and penetrating the subendocardium to a degree which varies between species and in humans is reported to be approximately for a third of the myocardial thickness [14, 15, 30, 31]. There is also considerable variation between mammalian species in insulation (individual versus groups of cells), branching pattern, association with endocavitary structures, and cellular ultrastructure of Purkinje fibers [15]. In humans, Purkinje organization and fine structure varies between the left and right ventricles and respective bundles [15, 22, 23]. In human left ventricles, 4 to 8 Purkinje cells constitute each of the muscular trabeculations that form a network within the left ventricular cavity and are continuous with fine intricate Purkinje networks lying on the endocardium (Fig. 7) [15].

Functional studies in animals have identified Purkinje–ventricular myocyte junctions, thought to be related to specialized transitional cells, which localize and control the transmission of electrical signals from Purkinje to ventricular myocardium [32]. The Purkinje–cardiomyocyte junction has been proposed as the site of origin of triggered activity that leads on to Purkinje-based ventricular arrhythmias, based on *in vitro* experiments on animal tissue preparations and computer simulation [33–35]. However, the mechanism by which the small amount of depolarizing current (“source”) provided by a thin bundle of Purkinje fibers can activate a much larger mass of ventricular muscle (“sink”) remains unclear [36]. In animals, a unicellular or bicellular layer of transitional cells has been demonstrated between the Purkinje layer and ventricular mass, providing a high resistance circuit between the Purkinje tissue and cardiomyocytes [37]. Such a layer may provide the mechanism for current amplification required to excite the myocardium from a Purkinje source [18]. However, we were unable to identify any study demonstrating similar structural

relationships in human hearts. In contrast, the work of Ono et al. appears to demonstrate a direct connection between Purkinje tissue and ventricular cardiomyocytes in humans (Fig. 7c) [15].

2.3 Endocavitary structures

In a review of 190 patients undergoing VT ablation at our institution over a 15-year period, 15 (8 %) required specific ablation of an endocavitary structure to eliminate the arrhythmia (papillary muscle in 5 of 15, moderator band in 7 of 15, and false tendon in 3 of 15), with both focal and re-entrant mechanisms implicated [10]. The infrahisian conduction tissue is found in close association with these endocavitary structures (Fig. 8). A case report of idiopathic VF originating from the moderator band has recently been published [38]. More commonly, ventricular arrhythmia have been localized to and successfully ablated at papillary muscles, both left ventricular [39, 40] and right ventricular [41]. Furthermore, the papillary muscles have also been implicated in the genesis of malignant ventricular arrhythmia in patients with bileaflet mitral valve prolapse [42].

There is significant structural variation between individuals in the normal anterolateral and posteromedial papillary muscles of the left ventricle [43] and anterior, septal and posterior papillary muscles of the right ventricle [44]. The papillary muscles can become fibrosed in conditions such as mitral valve prolapse [45]. Normal activation of the papillary muscle has been studied in the canine heart, where the base of the papillary muscles is activated first, despite the presence of Purkinje fibers draping both apical and basal parts, as Purkinje tissue appears to activate the underlying ventricular layer only at specific junctional sites located at the base [32, 46, 47]. The converse is not true, as propagation from the ventricular myocardium to the Purkinje can occur at regions other than these specific sites [47].

Purkinje tissue has also been demonstrated within false tendons [48–50], structures normally found in 55 % of left ventricles [51] and 35 % of right ventricles [50] in postmortem studies. In the left ventricle, they are mostly (in just under 90 %) found in the proximity of one or both papillary muscles and in the remaining majority (10 %) between the septum and free wall [51]. On the right, they are again located near papillary muscles in the majority (approximately 85 %); otherwise, they are found running between the anterior tricuspid leaflet and free wall [50]. A thin overlying sheet of myocardium can sometimes be seen (Fig. 8a). False tendons have been associated with PVCs [52–54] and are over-represented in patients with idiopathic left ventricular VT (15/15 vs 34/ 671), the tendon being located from the posteroinferior left ventricle to the septum in these patients [55].

2.3.1 Points of clinical relevance

Purkinje redundancy and re-entry: Impulses propagate in pathways that join back together [19, 56], a redundancy which allows the theoretical advantage for a part to fail without comprising overall conduction, yet with conduction tissue disease and conduction slowing, re-entry within the bundle branches and fascicles can result in bundle branch re-entry and inter-fascicular re-entry VT. This can occur on a smaller scale in structurally normal hearts in the context of verapamil sensitive left fascicular VT, with the re-entry circuit comprising a mid-septal Purkinje fiber and the anterior/posterior fascicles, or with

Purkinje fibers surviving in and around myocardial scars, in the case of Purkinje fiber-mediated post infarction VT [19, 57, 58].

Purkinje automaticity: Purkinje cells are prone to early and delayed after depolarizations and demonstrate both normal and abnormal automaticity [59]. Given that on average each myocyte is coupled to an average 11 other myocytes [60], Purkinje tissue is required to overcome a high source sink-mismatch to trigger ventricular arrhythmia. Both its flat structure (thereby minimizing sink) [61] and the transition zone between the Purkinje–cardiomyocyte interface [18] have been proposed as potential mechanisms. Abnormal automaticity underlies focal Purkinje VT, which is seen more commonly in patients with ischemic heart disease, but may also occur in those with normal hearts and can be treated with catheter ablation [19]. Purkinje fibers are relatively resistant to ischemia and may be responsible for automatic ventricular tachycardia following myocardial infarction [62]. Purkinje tissue have been demonstrated to be involved in the maintenance of ventricular fibrillation in dog heart preparations, with abnormal automaticity or triggered activity from the Purkinje fibers in addition to re-entry [63]. In a pig model, Purkinje signals were consistently recorded in postshock ventricular reactivation cycles, indicating that the Purkinje system is active during the early period following defibrillation and may be responsible for shock refractory ventricular fibrillation [64].

Signal amplification: A depolarization within Purkinje tissue has the potential for amplification as a result of both the interconnections within the network (Fig. 6) and the multiple junctions between each Purkinje cell and cardiomyocytes (Fig. 7c). The connexins that constitute the major intercellular connections differ between Purkinje (Connexin 40 and 45) and ventricular myocytes (Connexin 43) [16]. The Purkinje–ventricular myocyte junction has been poorly characterized but putative difference in conduction at this level may be important in generation of ventricular fibrillation. In ischemic dog models, ectopic automatic or triggered ventricular impulses were found to initiate both ventricular tachycardia and fibrillation in the very early phase of myocardial ischemia, originating from the subendocardium in areas of Purkinje [65]. In the dog model, chemical ablation of the subendocardium using an agent such as phenol abolished ectopic activity during either ischemia or reperfusion [66] and markedly increased the ventricular fibrillation threshold [67]. In subsets of patients with idiopathic VF and long QT syndrome, ventricular arrhythmia arises from triggered beats within Purkinje tissue and ablation of these foci results in cure [8, 9, 68]. During the initiating beats of catecholaminergic polymorphic ventricular tachycardia, Purkinje cells with abnormal calcium ion cycling most likely underlie the varying QRS morphologies, as shown in a mouse model of catecholaminergic polymorphic ventricular tachycardia [69].

Purkinje plasticity: Mouse Purkinje tissue undergoes molecular and structural adaptation when faced with increased ventricular afterload (Fig. 6a) [70]. Fine structure cytological architecture of Purkinje cells in dog false tendons can be seen to undergo specific age-related histological changes [71]. The clinical relevance of these adaptations is unknown. Purkinje conduction is putatively linked to myocardial extracellular matrix ionic composition and myocardial fiber folding [72], which may also be dynamic, again with

unknown clinical consequences. Autonomic influences [30, 73, 74] and antiarrhythmic drugs confer further functional Purkinje plasticity. Purkinje tissue is relatively resistant to ischemic damage and surviving Purkinje fibers in regions of scar have been implicated in ventricular arrhythmia [57, 75].

Anatomical anchors and tissue heterogeneity: In the case of papillary muscle-related ventricular arrhythmia, several mechanisms have been postulated, and may be differentially involved depending on underlying substrate. Data from animal *in vivo* [76, 77] and *in vitro* [78] studies suggest that the papillary muscles serve, by virtue of either anisotropy or increased muscle mass, as anatomical anchors for re-entrant wave fronts. Ablating the posterior papillary muscle markedly reduces inducibility of VF in these animal studies [76, 77]. The associated Purkinje network has also been implicated through clinical studies which frequently identify Purkinje pre-potentials at sites of successful papillary muscle ablation for ventricular arrhythmia [40–42, 79–81], with evidence for both automatic and re-entrant mechanisms. Such prepotentials suggest either a zone of slow conduction between the arrhythmogenic site and the exit, or the presence of insulated conduction tissue (fascicle) present at the targeted site, with a subsequent exit to the ventricular myocardium [12]. In this regard, studies in canine hearts have identified that when a bundle branch or false tendon directly activates the distal (or upper) papillary muscle, there is a significant delay to activation compared to the usual basal papillary activation (50–150 ms versus 2–4 ms) [46]. The clinical significance of this potentially important observation is currently unclear. Finally, there is sometimes slowed conduction around the papillary muscles in cases of papillary muscle VT which may further contribute to re-entry [10, 42].

Considerations for ablation therapy: The infrahisian conduction tissue, given its location and insulation, is amenable to electrophysiologic interrogation and catheter ablation using standard endocardial access. In the case of bundle branch reentry tachycardia, the right bundle is more readily ablated on account of its structure, while the sheet-like left bundle is more difficult to ablate. Detailed reviews of ablating Purkinje-related monomorphic re-entry arrhythmias and ventricular fibrillation are available elsewhere [17, 19]. A key consideration in mapping these arrhythmias is that the morphology from any single automatic focus within a Purkinje network may vary, on account of its redundancy and variable exits, and a strategy based on identifying the earliest site of ventricular activation for targeting ablation has limited success [82]. A potential clue to a tachycardia originating in the Purkinje fascicles is an activation map showing simultaneous early ventricular activation at multiple disparate sites, and identifying discrete Purkinje potentials between these areas may allow successful targeting of the true arrhythmia origin [83].

With respect to endocavitary structures, these have been implicated in creating difficulty with some aspect of ventricular tachycardia ablation in approximately quarter of cases, including catheter manipulation or interpretation of mapping data [10]. Origin from an endocavitary structure should be suspected when no specific early site is noted [83]. The use of intraprocedural intracardiac echocardiography has resulted in an increased appreciation of the true importance of these structures with respect to mapping and ablation of ventricular arrhythmia [12], which were previously difficult to identify fluoroscopically. With this has

come the recognition that there is significant overlap between papillary muscle and fascicular ventricular tachycardia, and often fascicular tachycardia has been mapped to the vicinity of a papillary muscle [12, 80, 84].

When ablating papillary muscle ventricular tachycardia, similar considerations to fascicular or Purkinje ventricular tachycardia exist. For instance, multiple exits resulting in multiple QRS morphologies can exist (Fig. 8b) [40], depending on the relative timing dependent on fiber orientation, relative conduction delay, and exact origin of the tachycardia in the papillary muscle [83]. Targeting the exit site in these circumstances will be unsuccessful and either the primary substrate should be ablated or the anatomic structure housing the substrate needs to be electrically isolated [12]. Pace mapping correlates poorly with sites of successful ablation [40]. Proposed reasons for this include the site of origin of arrhythmia (which may be anywhere along the muscle) being different to the exit site (usually at the base), the geometry of the papillary muscle making it difficult to pace the papillary muscle in isolation whilst avoiding capture of the adjacent myocardium, differentiating papillary muscle capture from fascicular capture, and a reentrant as opposed to a focal mechanism [12].

The above considerations also apply to moderator bands and false tendons, which contain conduction tissue. Tachycardia origin within a false tendon may give rise to simultaneous early exit on the left ventricular free wall, left ventricular septum, and/or the papillary muscles [83].

3 Summary

The anatomy of the infrahisian conduction tissue and endocavitary structures is complex but necessary to appreciate. The invasive electrophysiology must be thoroughly cognizant of the regional anatomy and relationships between these structures when performing common diagnostic maneuvers and delivering radiofrequency energy to treat ventricular tachycardia or ventricular fibrillation. Similarly, the electrophysiology researcher needs to appreciate the large lacunae in our knowledge in terms of detailed anatomy of the conduction system in the human heart and the functional significance of these structures in arrhythmogenesis.

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Relevance for the Invasive Electrophysiologist

- Parahisian pacing leverages the fact that fibrous insulation coats the proximal conduction system
- High output pacing penetrates this insulation and directly captures the His bundle or proximal right bundle branch along with the overlying myocardium
- Lower output pacing captures only the local ventricular myocardium
- Direct His bundle pacing is difficult to implement because of the structure's insulation and location on the relatively thin membranous portion of the interventricular septum
- Mapping the earliest ventricular activation site is of little value when ablating fascicular arrhythmia
- The exit site can vary greatly with the arrhythmogenic fascicular tissue being located at significant distance from the exit site
- Commonly employed maneuvers such as pacemapping or approximating the pacing stimulus to ventricular exit site timing interval are difficult to do with fascicular arrhythmia because of the admixture of tissues in these regions (fascicular tissue, papillary muscle, false tendons, and overlying ventricular myocardium)

Fig 1.

a Diagrammatic depiction of the atrioventricular junction in anatomical orientation, demonstrating the relationship of the penetrating bundle of His (PB) to the atrioventricular node (AVN), and its bifurcation into the left and right bundle branches (LBB and RBB, respectively) at the junction of the membranous and muscular ventricular septum. Reprinted with permission from Ho SY, Ernst S. *Anatomy for cardiac electrophysiologists: A practical handbook*. Minneapolis, USA: Cardiotext Publishing, 2012. **b** Illustration demonstrating the fibrous tissue (purple) that invests the specialized conduction tissue (orange) as it emerges from the atrioventricular node (AVN). Note the thickness of the insulating sheath that surrounds the penetrating bundle of His (PB) and proximal bundle branches (LBB and RBB) as they emerge from the central fibrous body. From Tawara, Sunao [85]. *Provided courtesy of Mayo Clinic Libraries History of Medicine Collection*

Fig 2.
Individual human Purkinje fibre surrounded by insulating sheath. Light micrograph of ventricular endocardium impregnated with silver. From Ono et al. [15]

Fig 3.

The bundle branches. **a** Gross anatomical section demonstrating the origin of the left and right bundle branches (LBB and RBB, respectively) at the junction of the membranous septum and the crest of the muscular ventricular septum, and their superficial course in the subendocardium. Note the fibrous sheath that surrounds the bundle branches and the leftward attitude in the septum proximally. Reprinted with permission from Ho SY, Ernst S. *Anatomy for cardiac electrophysiologists: A practical handbook*. Minneapolis, USA: Cardiotext Publishing, 2012. **b, c** Diagrammatic representation (in red) of the cord-like right bundle branch (**b**) and broad left bundle branch (**c**) superimposed on respective anatomical specimens. The right bundle penetrates the muscular septum to emerge at the base of the medial papillary muscle of the tricuspid valve. The *arrow points* to the moderator band connecting the septum to the right ventricular free wall. Modified from Tawara, Sunao [85]. *Provided courtesy of Mayo Clinic Libraries History of Medicine Collection.* **d** Anatomical specimen demonstrating the relationship of the left bundle branch to the endocardial aspect of the left ventricular outflow tract. The membranous septum is transilluminated from behind and is the site of the penetrating bundle of His, and the course of the left bundle branch (LBB) on the endocardium as it emerges below the right and noncoronary cusps of the aortic valve is shown in red. R, N, and L are the right, non, and left coronary cusps of the aortic valve. Reprinted with permission from Ho SY, Ernst S. *Anatomy for cardiac electrophysiologists: A practical handbook*. Minneapolis, USA: Cardiotext Publishing, 2012

Fig 4.
Diagrammatic depiction of the proximal left-sided conduction system as observed in 20 normal human hearts demonstrating the origin of the anterior, posterior, and median fascicles, as well as their interconnections. Reprinted with permission Demoulin and Kulbertus [28]

Fig 5. Isochronic representation of ventricular activation of the isolated human heart. *Scale* represents milliseconds from the beginning of the left ventricular cavity potential. Reprinted with permission Durrer et al. [29]

Fig 6.

Techniques demonstrating fine structure of the distal infrahisian conduction system in various mammalian species **a** Mouse Purkinje system demonstrated using connexin 40 knockout/enhanced green fluorescent protein knockin transgenic mouse model. *Right-sided panels* demonstrate Purkinje remodeling upon aortic obstruction to increase afterload; *left-sided panels* demonstrate control animals. Reprinted with permission from Harris et al. [70]. **b** Mouse Purkinje system demonstrated using green fluorescence protein expression using Contactin-2 immunolabeling. SAN sinoatrial node, AVN atrioventricular node, His/Br His and bundle branches, lPFs left ventricle Purkinje fibers, rPFs right ventricle Purkinje fibers. Reprinted with permission from Pallante et al. [86]. **c** Rabbit Purkinje system stained using immunohistochemistry for middle neurofilament (NF-M), a neuronal cytoskeletal protein which is also exclusively expressed in rabbit cardiac conduction system. Reprinted with permission from Atkinson et al. [87]. **d** Calf Purkinje system stained with India ink, with overlapping red highlighting proximal and blue highlighting distal infrahisian system, with *insets* demonstrating high-power views with Goldner trichome (*upper left*) and India ink (*lower left*). Reprinted with permission from Sebastian et al. [88]. **e** Rabbit conduction system imaged with micro-CT scanning after treatment with an iodine based contrast agent (I2KI) *ex vivo*. Reprinted with permission from Stephenson et al. [89]

Fig 7. Distal infrahisian conduction system in man. **a** Muscular trabeculae (T) present on the left ventricular luminal surface ($\times 20$ magnification). These were reported to contain Purkinje (P) fibers by the authors and were continuous with fine intricate Purkinje networks lying on the endocardium (**b**, $\times 120$ magnification). In **c**, the junctional region (*arrows*) between a Purkinje cell (P) and cardiomyocyte (M) is demonstrated ($\times 300$ magnification). From Ono et al. [15]

Fig 8.

Endocavitary structures associated with ventricular arrhythmias. **a** Anatomic dissection demonstrating false tendons traversing the left ventricular cavity and between papillary muscle and the intraventricular septum (*narrow arrows*). Myocardium (*bold arrow*) on these false tendons, which may also carry conduction tissues, may be the focus or part of a circuit for ventricular tachycardia. Reprinted with permission from Abouezzeddine et al. [10]. **b** Anterior and posterior papillary muscles (APM and PPM) of the left ventricle and corresponding surface ECG complexes of ventricular tachycardia. Note the variation in ECG morphology depending on the exit site. Reprinted with permission from Yamada et al. [24]. **c** Normal variation in anatomy and relation to papillary muscle of the moderator band (MB) in human adults. Reprinted with permission from Loukas et al. [24]. **d** Pig moderator band histology demonstrating conduction tissue in progressively greater magnifications (hematoxylin and eosin stain). Reprinted with permission from Gulyaeva et al. [90]