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STATE-OF-THE-ART REVIEW

Cellular Physiology and Clinical Manifestations of Fascicular Arrhythmias in Normal Hearts

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ABSTRACT

Fascicular ventricular arrhythmias represent a spectrum of ventricular tachycardias dependent on the specialized conduction system. Although they are more common in structurally abnormal hearts, there is an increasing body of literature describing their role in normal hearts. In this review, the authors present data from both basic and clinical research that explore the current understanding of idiopathic fascicular ventricular arrhythmias. Evaluation of the cellular electrophysiology of the Purkinje cells shows clear evidence of enhanced automaticity and triggered activity as potential mechanisms of arrhythmias. Perhaps more importantly, heterogeneity in conduction system velocity and refractoriness of the left ventricular conduction system in animal models are in line with clinical descriptions of re-entrant fascicular arrhythmias in humans. Further advances in our understanding of the conduction system will help bridge the current gap between basic science and clinical fascicular arrhythmias. (J Am Coll Cardiol EP 2017;■:■–■)

Fascicular arrhythmias encompass a wide spectrum of ventricular arrhythmias that are dependent on the specialized conduction system including the His, right and left bundles, left-sided fascicular bundles, and the extensive subendocardial Purkinje network of fibers extending out from the fascicular bundles. Purkinje-dependent arrhythmias occur in both structurally normal as well as cardiomyopathic hearts, particularly when advanced conduction system disease is present. For this review, we focus on idiopathic left fascicular ventricular tachycardia (LFVT) limited to structurally normal hearts.

ANATOMY OF HIS-PURKINJE SYSTEM

The key to understanding the spectrum of fascicular arrhythmias and their mechanisms comes from a thorough understanding of the His-Purkinje system (HPS) anatomy. The conduction system and its postulated function were originally described by Dr. Sunao Tawara in 1906, demonstrating trifascicular branching off of the main left bundle before extending into a complex Purkinje network (1). The **Central Illustration**, Part A depicts the original description from Tawara, with 3 distinct fascicular bundles (left anterior fascicle [LAF], left septal fascicle [LSF], and left posterior fascicle [LPF]) arising from the main left bundle before extending into a web-like network of Purkinje fibers.

On the basis of histological evaluation of 20 healthy human hearts, Demoulin and Kulbertus (2) revealed the significant anatomic variations in the morphology of fascicular branches, with 4 major patterns of LSF organization observed (**Figure 1**): 1) extension of the LSF from the main left bundle between the angle

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ABBREVIATIONS AND ACRONYMS

LV = left ventricle/ventricular

PVC = premature ventricular complex

RBB = right bundle branch

RBBB = right bundle branch block

VT = ventricular tachycardia

formed by the LAF and LPF; 2) extension directly from the LAF; 3) extension directly from the LPF; and 4) contribution of fibers from both LAF and LPF to form either a septal branch or a septal fiber network (2).

Further evidence for a functional trifascicular nature comes from activation mapping confirming presence of 3 early endocardial activation sites during sinus rhythm (3,4), as well as newer recognition of the electrocardiographic (ECG) pattern of LSF block represented by prominent R waves V_1/V_2, a mild increase in QRS duration, and loss of septal forces (Online Figure 1) (5,6).

EARLY DEVELOPMENT OF THE HIS PURKINJE NETWORK

Current research suggests that the HPS is of subendocardial origin. Following looping of the embryonic heart tube, certain gene programs begin to activate expression of genes encoding connexin (Cx) proteins in developing Purkinje cells (PCs), specifically Cx40 and Cx43 (gap junction proteins), as well as Nav1.5, the cardiac sodium channel. This promotes cell-to-cell conduction of PCs at a high rate and allows for nondriven electrical activity, such as triggered or spontaneous activity. These changes isolate the HPS from working myocardium, allowing its further development (7,8). Studies in birds and mammals have shown that bundle branches and subendocardial layer of PCs are formed from the subendocardial trabeculae of the embryonic hearts (9,10).

To serve their function during cardiac excitation, PCs need to align and become encapsulated to form 3-dimensional networks in the subendocardium as well as free running bundles (which eventually combine to form fascicles). Single PC morphology is altered depending on the nature of this connective tissue sheath. Most single-canine PCs form a columnar shape: they are longer and wider than ventricular myocytes, running parallel to each other, with finger-like gap junctions mostly at terminal ends with few side-to-side junctions (**Figure 2A**). However, our laboratory (Boyden) has observed that in any PC preparation from normal canine left ventricular (LV) subendocardium, 10% of PCs are pancake-shaped with gap junctions surrounding the individual cell (**Figure 2B**). The arrangement of gap junctions in the different cellular forms is well suited for various functions. The columnar, laterally connected PCs keep the conducting wave front spatially uniform within the strand, whereas side-to-side junctions of the pancake cell provide transverse interconnections, allowing quick dispersion of the wave front in multiple directions. To our knowledge, there are no reports of anisotropic conduction in Purkinje bundles from normal hearts.

Later in development, free running strands extend from the bundle branches toward the trabeculated myocardium but remain insulated from underlying myocardium by connective sheaths. Thus, electrical activation cannot escape into myocardium (11). Eventually, PCs form electrical junctions with ventricular myocytes through Purkinje-muscle junctions. Ventricular activation occurs at these specific sites. Because the Purkinje network must excite a large ventricular mass, a transitional layer of cells serve as a high resistance barrier between myocardium and PCs (12).

Importantly, a propagated premature impulse, occurring close in time to the functional refractory period of the preparation, will travel through tissue in various stages of repolarization. If the impulse travels antegrade from the bundle branch to free-wall muscle, it will propagate through tissues, where action potentials progressively lengthen proximal to the "gate" and progressively shorten distal to the "gate" (13). This "gate" is a property of LV tissues and protects retrograde conduction from ventricular myocardium up the Purkinje fiber bundles.

PURKINJE CELLULAR ELECTROPHYSIOLOGY AND REQUIREMENTS FOR RE-ENTRY

Animal models have shown that conduction is not uniform throughout the specialized conduction system. Mapping of conduction velocity (CV) along the conduction system in normal murine hearts revealed heterogeneity of CV at various parts of the heart, specifically with reduced CV in the midseptum (14). Careful histological examination showed that although there are regional differences in expression pattern and distribution of gap junction proteins, the most likely cause of significant CV reduction in the midseptum is due to *local* changes in bundle branch architecture. In this region, there is intense branching of bundle branch fibers, resulting in load mismatch or increased path length (14). In canine hearts, CV is faster in proximal bundle branch areas than in the distal network areas. Some have suggested a similar architecture exists in human hearts (1,15). These variations in delay and CV may serve as the physiological substrate for fascicular mediated tachycardias.

Even in normal hearts, unidirectional block, slowed conduction, and differences in refractoriness may lead to re-entry within the Purkinje network.