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Role of the His-Purkinje system in the genesis of cardiac arrhythmia

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Although a plethora of earlier studies focused on the histology and action potential characteristics of Purkinje fibers, only recently has the His-Purkinje system been found to play a major role in the genesis of cardiac arrhythmias. The anatomic complexity of the left ventricular conduction system appears to favor reentrant arrhythmias in both diseased and healthy hearts. Macroreentrant circuits between the right and left bundles as well as between the left ventricular fascicles are amenable to cure by ablative techniques. Similarly, fascicular tachycardias occurring in individuals without structural cardiac disease appear to involve macroreentrant circuits between fascicles and associated strands (false tendons?). Exciting newer discoveries strongly implicate the Purkinje system as the cause of ventricular arrhythmias in patients with short-coupled premature ventricular complexes and in those with catecholaminergic polymorphous ventricular tachycardia. The role of the His-Purkinje system in the genesis and maintenance of ventricular fibrillation is yet another frontier for fertile investigation. A rich variety of cardiac arrhythmias appears to involve the ventricular specialized conduction system and may be amenable to ablative therapy.

KEYWORDS His-Purkinje system; Fascicular tachycardia; Idiopathic ventricular fibrillation; Interfascicular reentry; Polymorphous ventricular tachycardia

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History

The peripheral components of the Purkinje system were first described by Purkinje in 1839.[1] The Purkinje cell is a spindly, vacuolated (glycogen) cell with no T-tubular system and fewer myofibrils than the myocytes. The cellular architecture of the Purkinje cells compared with ventricular myocytes is shown in Figure 1. Although Purkinje was the first to describe the fibers, it was Tawara who first described their true function. The central compartment of the His-Purkinje system (HPS) was first described by Wilhelm His Jr. in 1893 as "specialized muscle fibers" that were the only direct connection between the atria and ventricles.[2] He was the first to show that severing the "His bundle" could result in atrioventricular dissociation.[3] In 1906 Tawara discovered the right and left bundle branches and correctly addressed the role of the ventricular specialized conduction system.[4]

Embryologic development of the HPS

Current concepts of the developmental anatomy of the cardiac conduction system suggest that the specialized ventricular conduction system arises from a primary ring of conduction tissue that covers the primitive intraventricular foramen. The His bundle and bundle branches are believed to arise from the posteromedial aspect of this ring.[5] Additional important insights relative to the developmental anatomy come from genetic cell labeling and immunohistochemical techniques. The Purkinje fibers are derived from closely related cardiac myocytes (rather than neural tissue) invariably in close association with coronary vessels.[6] It was subsequently found that the conversion of myocytes into Purkinje fibers can be induced by endothelin, an endothelial paracrine factor.[7,8] The HPS in mice was studied using a targeted reporter gene (enhanced green fluorescent protein [EGFP]) to define the specialized conduction system expressed under the control of connexin40 (Cx40), which is highly identified with the HPS. The investigators identified a single strand on the right and approximately 20 strands on the left. This is compatible with the more complex arrangement of the left-sided conduction system described in humans. The complex of genetic and epigenetic factors involved in the development of the cardiac conduction system is listed in Table 1.[9]

Cellular electrophysiology of Purkinje cells

The ionic currents that characterize Purkinje cells and serve to differentiate them from muscle cells have been exhaustively summarized in a recent report.[10] The transient outward current I_{to} is more prominent in Purkinje cells than in myocytes, and the converse is true for the inward rectification current I_{K1} and the L-type Ca^{2+} current. Normal Purkinje cells ordinarily do not show automaticity and are

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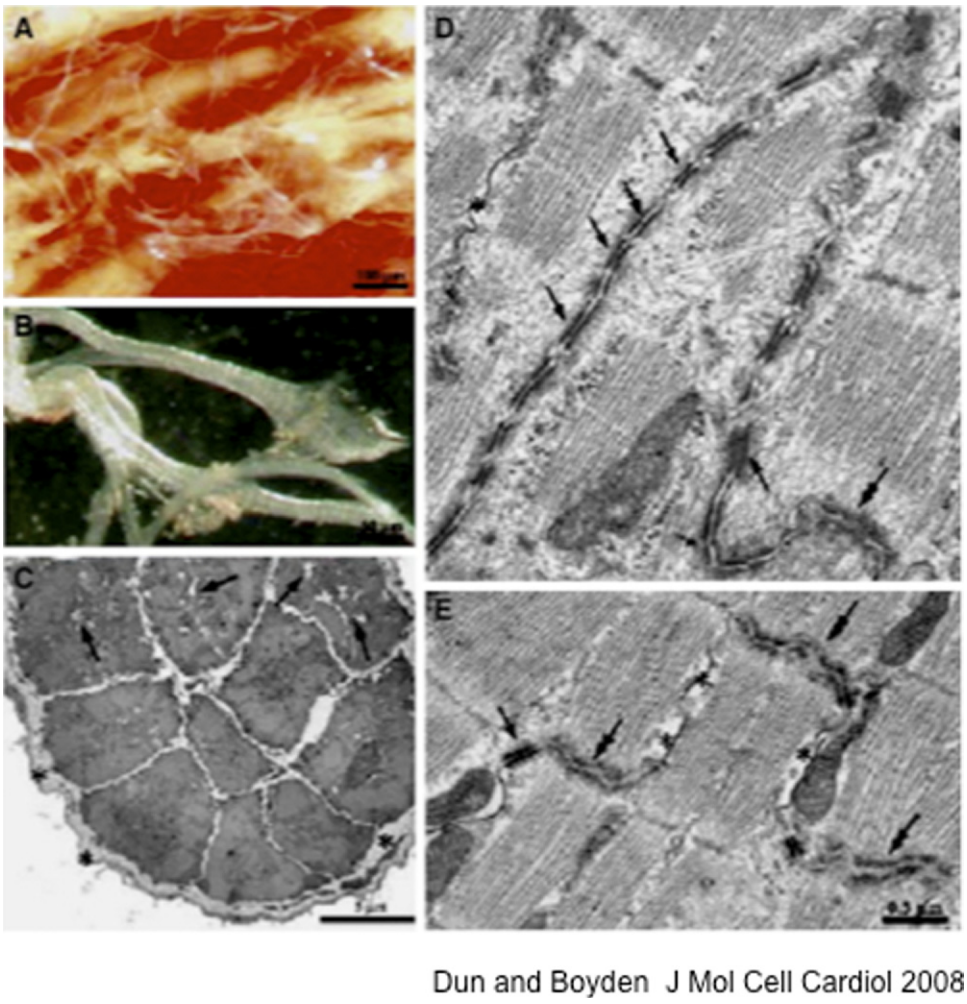

Figure 1 Examples of Purkinje fiber strands from rat ventricle at low power **(A)** and high power **(B)**. Strands can be isolated from ventricular tissue and are generally surrounded by a thick layer of collagen. **C:** Purkinje fiber strand cut in cross-section. Note collagen *(asterisks)* and empty cell areas filled with glycogen *(arrows)*. **D:** Intercalated disk region between connecting Purkinje cells. Note the long finger-like projections forming this connection. This differs substantially from the well-known staircase appearance of the disk region between two ventricular cells **(E)**. (Reproduced with permission from Dun W, Boyden PA. The Purkinje Cell; 2008 style. J Mol Cell Cardiol 2008;45:617–624. Di Maio A, Ter Keurs HE, Franzini-Armstrong C. T-tubule profiles in Purkinje fibres of mammalian myocardium. J Muscle Res Cell Motil 2007;28:115–121).

overdrive suppressed by sinus node activity. Purkinje fiber automaticity is enhanced by digitalis preparations, presumably by the action of digitalis in inhibiting Na^+/K^+ ATPase activity resulting in cytosolic Ca^{2+} overload.[11] Ca^{2+} waves have been shown to occur in normal Purkinje cells even without electrical stimulation.[12] Ca^{2+} waves originate at cell borders and can propagate through the full extent of a Purkinje cell aggregate. These studies show that Purkinje cells are capable of generating both automatic and triggered rhythms. The role of Purkinje cells in abnormal states is discussed later. Purkinje cells show distinctive expression of Cx. His bundle and Purkinje fibers express both Cx40 and Cx43, as opposed to ventricular myocardium, which predominantly expresses Cx43.[10] The cellular architecture of Purkinje fibers (Figure 1) is thought to explain the rapid conduction in the HPS (2–3 m/s) compared with cardiac muscle (0.2–0.4 m/s).

Gross histology of the HPS

The history of the concepts of a bifascicular versus a trifascicular conduction system is extensively reviewed by Riera et al.[13] Evidence from a number of histologic studies[14,15] proved the presence of a trifascicular system (Figure 2).[12] The pioneering work of Kulbertus and Demoulin[14,15] firmly established the concept of a trifascicular system. Among 34 dissections of normal hearts, they found evidence of a thin left anterior fascicle, which connects the left bundle branch to region of the anterolateral papillary muscle, a broader left posterior fascicle, which inserts midway between the base and apex near the base of the posterior papillary muscle, and a separate septal fascicle in 20 of the 34 hearts. In nine cases, the septal fascicle formed from branches of the left anterior and left posterior fascicles and in five from branches of the left posterior fascicle. The functional significance of these fascicles was amplified by the anatomic

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