CELL TO BEDSIDE

Cardiac Purkinje cells

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Purkinje cells are specialized for rapid propagation in the heart. Furthermore, Purkinje fibers as the source as well as the perpetuator of arrhythmias is a familiar finding. This is not surprising considering their location in the heart and their unique cell ultrastructure, cell electrophysiology, and mode of excitation–contraction coupling. This review touches on each of these points as we outline what is known today about Purkinje fibers/cells.

KEYWORDS Arrhythmia; Calcium; Ion channel; Pacemaker activity; Purkinje cell

ABBREVIATIONS **AP** = action potential; **APD_{90}** = action potential duration at 90% repolarization; **AV** = atrioventricular; **DAD** = delayed afterdepolarization; **EAD** = early afterdepolarization; **IZPC** = Purkinje cell from 48-hour infarcted heart; **RyR** = ryanodine receptor; **SR** = sarcoplasmic reticulum

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Introduction

Johannes (Jan) Purkinje was a Czech phenomenologist who in the 19th century carefully described the now famous subendocardial Purkinje fibers of the heart.[1] At that time, he was "inclined to regard this new tissue as cartilage." Sixty years later, Tawara,[2] in describing the connections of the atrioventricular (AV) node, showed that the connection between the AV bundle and Purkinje fibers was integral to electrical impulse propagation in the heart. The Purkinje fiber network is large, with free-running fibers (false tendons) as well as a subendocardial network. In all species, this highly specialized cell network provides a vital role in conduction from the AV downward to the endocardial ventricular muscle. *In situ* bipolar recordings of the His Bundle were first performed in 1959.[3] At that time, it was shown that the sharp rapid deflection of the His electrogram followed atrial activity by 20 to 30 ms and in normal sinus rhythm preceded ventricular activity (Figure 1A). Conduction through the His bundle (conduction velocity 1–3 m/s) and bundle branches occurs during the isoelectric interval between the end of the P wave and the beginning of the QRS complex. Conduction through His Purkinje cells is little affected by vagal stimulation, epinephrine, or removal of stellate ganglia.

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Many ventricular arrhythmias are initiated in the Purkinje fiber conduction system (Figure 2).[4–7] Both reentrant' triggered and enhanced automatic rhythms can arise from the Purkinje fiber network in the presence of acquired disease or gene-based ion channelopathies. For instance, in the presence of valvular disease, dilated cardiomyopathy, and severe left ventricular dysfunction, a macroreentrant circuit through bundle branches with slowed conduction has been described.[8] Bundle branch reentrant tachyarrhythmias (cycle length 300 ms) also can occur in patients with heart disease. Here the reentrant circuit is due to impulse propagation up one bundle and down the other, giving rise to a QRS configuration seen during sinus rhythm. For some intrafascicular verapamil-sensitive tachycardias, reentry in Purkinje fiber bundles is thought to be the mechanism. On the other hand, polymorphic ventricular tachycardias in patients with heart disease can be due to several mechanisms, but triggered beats preceding some of those reentrant tachycardias can arise from the Purkinje network. In the case of the initiating beats of catecholaminergic polymorphic ventricular tachycardia in patients, Purkinje cells with abnormal Ca^{2+} cycling most likely underlie the varying QRS morphologies, as shown in a mouse model of catecholaminergic polymorphic ventricular tachycardia.[9] The same may be true for initiating arrhythmic beats in patients with long QT syndrome.

In one study of post myocardial infarction patients with rapid polymorphic ventricular tachycardias, ablation of Purkinje regions eliminated premature depolarizations and the arrhythmias.[10] Even earlier mapping studies had implicated a role of Purkinje fibers in the initiation and maintenance of ventricular fibrillation in patients with long QT syndrome,[11] ischemia,[12] and Brugada syndrome.[11] Mapping experiments

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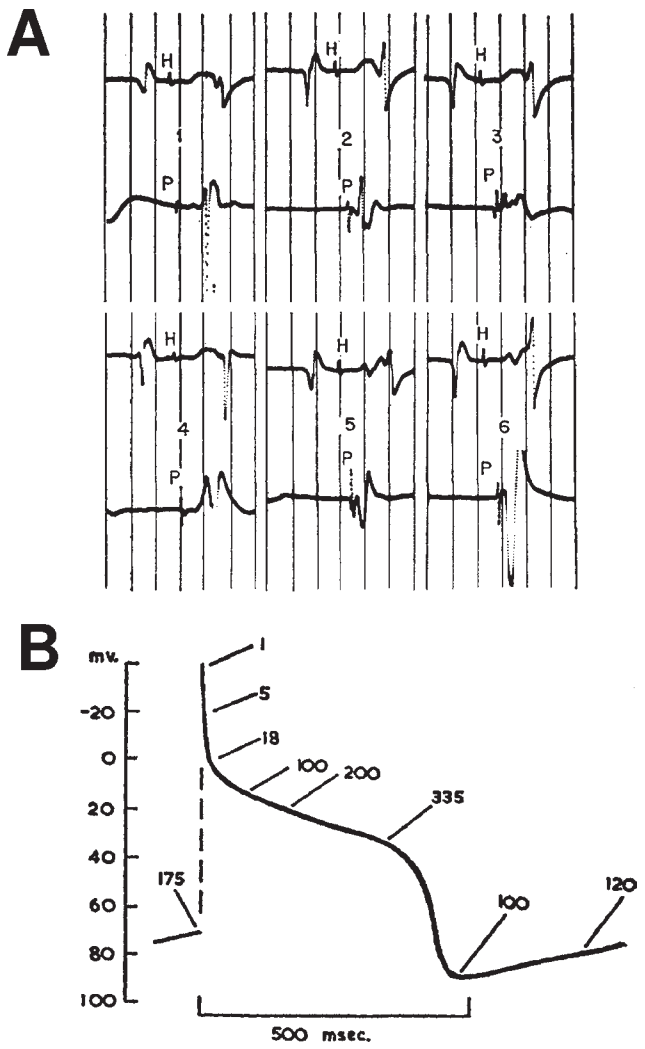

Figure 1 **A:** Bipolar recordings from a specialized conducting system at various locations (*1–6*) in the *in situ* canine heart. Upper electrode is fixed on the His-Purkinje bundle. Note H deflection is His activation. Lower electrode records at sites from right bundle branch (*1*) to left anterior false tendon (*6*). P indicates activation of Purkinje fibers. Time lines = 40 ms.[3] **B:** Transmembrane action potential of kid Purkinje fiber during spontaneous activity. Numbers indicate value of membrane resistance during electrical activity.[73]

using an animal model of nonischemic cardiomyopathy also have implicated a role for the Purkinje fiber network in ventricular tachycardias,[13] similar to that shown to occur in patients.[14] Thus, Purkinje fibers as the source as well as the perpetuator of arrhythmias is a familiar finding. This is not surprising considering their location in the heart and their unique cell ultrastructure, cell electrophysiology, and mode of excitation–contraction coupling. This review touches on each of these points as we outline what is known today about Purkinje fibers/cells.

Purkinje's definition of specific Purkinje cells in the heart led to a detailed analysis and a comparison with the working ventricular cell by Sommer and Johnson[15] in 1968. Subsequent qualitative and quantitative studies have only emphasized these early findings, that is, Purkinje cells are quite different from ventricular cells at both the histologic and ultrastructural levels. Histologically, Purkinje cells stain lightly, presumably due to the reduced, but still significant, myofibrillar content and enhanced glycogen. Electron microscopic studies show that Purkinje cells lack t-tubules and the all important core dyad.[16] Recent immunostaining studies have confirmed distinguishable Purkinje cell-to-cell junctions and the existence of the connexin40 (Cx40) protein as an important Purkinje connexin isoform.[17] All of these features help to dictate the Purkinje fiber's specialized function in the heart.

Cell electrophysiology

Action potentials

Purkinje cell action potentials (APs) are longer than their ventricular counterparts.[18] In rabbit and kid (Figure 1B), Purkinje cells exhibit a prominent phase 1 of repolarization, a more negative plateau, and a significantly longer action potential duration at 90% repolarization (APD_{90}) than do ventricular cells.[19] In canine Purkinje fibers, APD_{50} and APD_{90} are prolonged compared with their ventricular counterparts,[20,21] yet there is no difference in resting potential between the two cell types. However, the total amplitude of the AP and the maximal rate of rise of the AP upstroke (V_{max}) are larger in Purkinje fibers.

Women are susceptible to the development of torsades de pointes, a life-threatening polymorphic ventricular tachycardia that may originate in Purkinje fibers. Gender differences in APs have been observed in canine Purkinje fibers,[22] where APD_{40}, APD_{50}, APD_{70}, and APD_{90} of Purkinje fibers from female hearts have been found to be significantly longer compared with their male counterparts. However, no differences in resting potential, AP amplitude, and V_{max} between male and female Purkinje cells have been reported. Although human Purkinje cell APs are assumed to be longer than ventricular APs, this has not yet been shown by any systematic study.

Inward rectifier K^+ channels—I_{K1} (Kir2.1, Kir2.2, Kir2.3), I_{KATP} (Kir6.1, Kir6.2), and I_{KACh} (Kir3.1, Kir3.4)—conduct K^+ ions more in the inward direction than the outward direction and play an important role in setting the resting potential close to the equilibrium potential for K^+ in cardiac cells. Although it has long been known that Purkinje fibers display two levels of resting potential,[23] this situation is significantly different in myocytes. Purkinje cells have reasonably strong I_{K1},[24] but some characteristics (e.g., nature of the negative slope) differ from those of ventricular cells,[25] impacting not only the resting potential but also the slope of phase 3. A complete review of ion channel functions (I_{Na}, I_{CaL}, I_K, etc.) of both Purkinje and ventricular cells is given in Dun and Boyden.[26]

Pacemaker currents

The automaticity that occurs in the isolated normal multicellular Purkinje fiber strand is an example of normal au-