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Purkinje Fibers and Arrhythmias

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Johannes Purkinje (1787–1869) was a prolific Czech anatomist and physiologist.¹ He established the first Department of Physiology in the world in 1839 in Prussia. He was the first to use a microtome to obtain thin tissue sections for microscopic examination and was the first to describe sweat glands. He introduced the terms “plasma” and “protoplasm.” He made major contributions to the study of vision, including discovery of the Purkinje effect, the Purkinje shift, and Purkinje images. He discovered two types of Purkinje cells: large neurons in the cerebellum and, of particular interest to cardiac electrophysiologists, large cardiac muscle fibers specialized for rapid conduction along the endocardium of the ventricles.¹

Purkinje fibers differ in numerous ways from working myocardial cells. The relative sizes of Purkinje and myocardial cells are species-dependent.^{2–5} In general, Purkinje cells are larger than myocardial cells and are distinguishable histologically.² Purkinje cells lack transverse tubules that are present in myocardial cells.⁶ Because of their primary role in rapid conduction of the electrical impulse, Purkinje cells have fewer myofibrils than myocardial cells. As a result, microscopically they appear lighter than myocardial cells. The amount of glycogen in Purkinje fiber is much higher than that in myocardial cells.⁷ The glycogen can be metabolized anaerobically which may make Purkinje cells more resistance to hypoxia than working myocardial cells,⁷ although some evidence suggests that the opposite is true.⁸

The conduction velocity of electrical impulses is much higher in Purkinje fibers (2–3 m/s) than in myocardial cells (0.3–0.4 m/s).⁹ The fast propagation is partially due to the different connexins in the gap junctions in these cells. The amount of Cx40, a connexin protein that causes high conductance channels, is at least three fold greater in Purkinje fibers than in myocardial cells.¹⁰ As part of the conduction system, the Purkinje cells have potential automaticity, which is normally suppressed by the faster pacemaker activity of the sinoatrial node.¹¹ Myocardial cells usually do not have automaticity. The transient outward potassium current (I_{to}) is more prominent in Purkinje fibers than in myocardial cells.¹¹ I_{to} is responsible for the rapid repolarization in the phase 1 repolarization, typical of Purkinje action potentials.¹² On the other hand, the density of the inward rectifier current (I_{K1}) and the L-type Ca^{2+} current ($I_{Ca,L}$) are significantly higher in myocardial cells than in Purkinje fibers.^{5,13} The density of calcium currents in these cells agrees with their respective contractive and conductive roles. These ionic differences are also responsible for the differences in the action potential waveforms of the two types of cells and may contribute to unidirectional block at the Purkinje-ventricular junctions (PVJs).¹⁴

Purkinje fibers have been implicated in both the maintenance and the initiation of tachyarrhythmias. Recent mapping studies in dogs and pigs suggest that Purkinje fibers help maintain ventricular fibrillation (VF) by giving rise to activation that propagates through the PVJs to stimulate the working myocardium.^{15–17} The Purkinje system may also play a role in post-infarction monomorphic VT.¹⁸ In one series of patients with polymorphic VT following myocardial infarction, Purkinje signals preceded every premature beat, and ablation of the sites of the Purkinje signals eliminated all premature beats and no arrhythmia occurred during a follow-up of 16 ± 5 months.¹⁹ Mapping studies have shown that Purkinje fibers can initiate VF in some patients with structurally normal hearts,²⁰ Brugada syndrome,²¹ Long QT syndrome,²¹ amyloidosis,²² myocardial infarction,²³ and ischemic cardiomyopathy.²⁴

The paper by Sinha et al. in this issue of PACE provides evidence that Purkinje fibers can also initiate VF in some patients with non-ischemic cardiomyopathy.²⁵ During an electrophysiology study of 5 patients with non-ischemic cardiomyopathy, an implantable cardioverter/defibrillator (ICD), and VF storm that did not respond to medical therapy, 4 patients had VF or premature ventricular contractions induced by isoproterenol. These 4 patients all had scar in the posterior-basal wall of the left ventricle identified by low voltage (<0.5 mV) surrounded by a border zone identified by intermediate voltage (0.5 mV to 1.5 mV). Within the border zone of all 4 patients, low-amplitude, high-frequency potentials were recorded that the authors called Purkinje-like potentials (PLPs). Ablation performed along the border zone eliminated these potentials. After a mean follow-up of 12 ± 5 months, the ICDs revealed that the 4 patients who had ablation targeting PLPs had no sustained arrhythmias. One patient without a scar detectable by mapping who did not undergo ablation had 4 VF episodes that required ICD shocks. The authors conclude that, in patients with non-ischemic cardiomyopathy and VF, the results suggest that left ventricular posterior wall scar near the mitral annulus is common and that ablating sites exhibiting PLPs along the scar border prevents VF recurrence.

One could quibble with these conclusions. VF storms can be episodic,²⁶ so that the absence of sustained arrhythmias in only 4 patients over a mean interval of 12 months may have occurred by chance and not because of ablation. Because ablation was apparently performed along the entire scar border in 3 of the patients and not just at the sites of the PLPs, it is not known if ablating PLP sites alone would have prevented arrhythmia recurrence. It also is not definitely known if the PLPs are in fact generated by Purkinje fibers rather than isolated strands of working myocardium within the scar border.

If we discount these criticisms and take the conclusions of the paper at face value, the results indicate that Purkinje fibers can trigger arrhythmias in yet another very important form of heart disease, non-ischemic cardiomyopathy. What causes Purkinje fibers to be arrhythmogenic in so many different types of heart disease? Ionic current remodeling of the Purkinje fibers may underlie their arrhythmogenicity in many of these disease conditions. In Purkinje fibers surviving myocardial infarction, I_{CaL} and I_{CaT} are significantly reduced.²⁷ The abnormal calcium microreleases in these postinfarction Purkinje cells have been shown to be arrhythmogenic.²⁸ A variety of K^+ currents are also reduced in the infarction border zone.²⁹ In several different animal models of congestive heart failure, I_{to} and I_{K1} are reduced and inactivation of I_{CaL} is slowed in Purkinje as well as myocardial cells.^{30–31} The down-regulation of K^+ currents in these disease conditions could prolong action potential duration and provide a substrate for reentry or triggered activity. Another possibility is that mechanoelectric feedback in heart failure activates stretch channels in Purkinje fibers that cause afterdepolarizations.³² The PVJs may also be involved in arrhythmias under pathological conditions because of their high resistance and low conduction safety factor.

Hyperkalemia, hypoxia, and acidosis that occur during ischemia may impair electrical coupling at PVJs, causing conduction block.³³

In summary, with the inclusion of non-ischemic cardiomyopathy by Sinha et al.,²⁵ there is now evidence that Purkinje fibers can be responsible for arrhythmias in most common forms of adult cardiac disease. This study raises the question as to how often Purkinje fibers are responsible for these arrhythmias. Is it only a few isolated cases or is it a sizeable percentage of cases? If it is responsible in a significant number of cases, then there is a pressing need to develop improved techniques for mapping this thin layer of specialized cells on the endocardium in the clinical cardiac electrophysiology laboratory.

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