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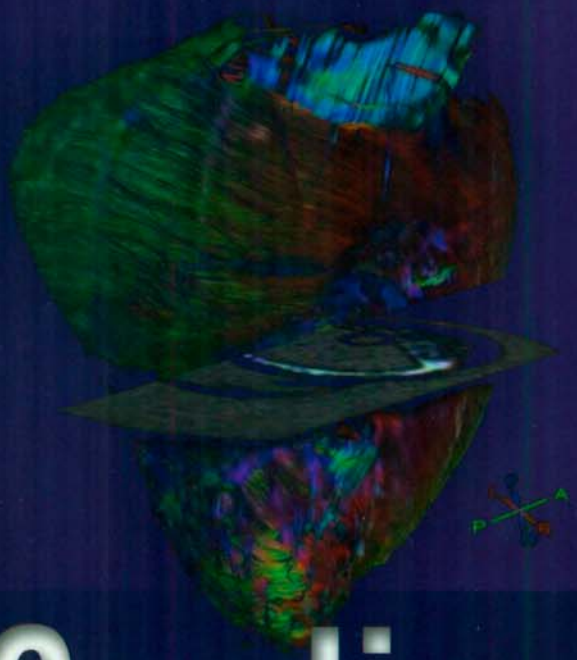
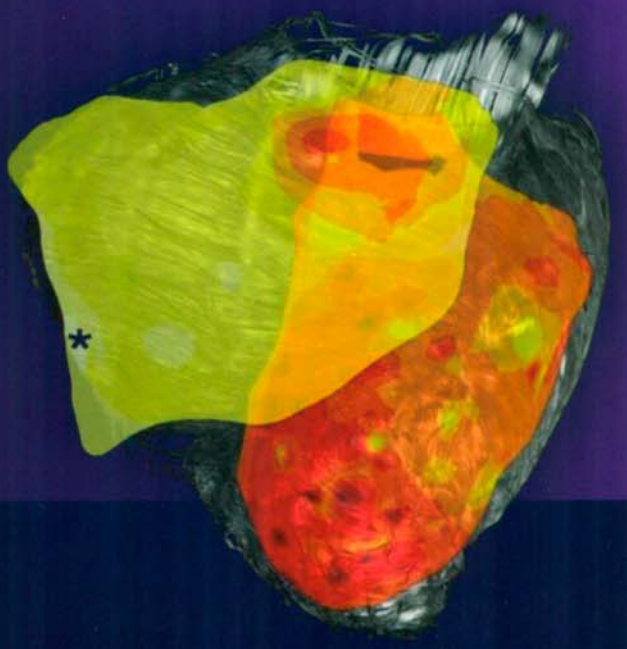
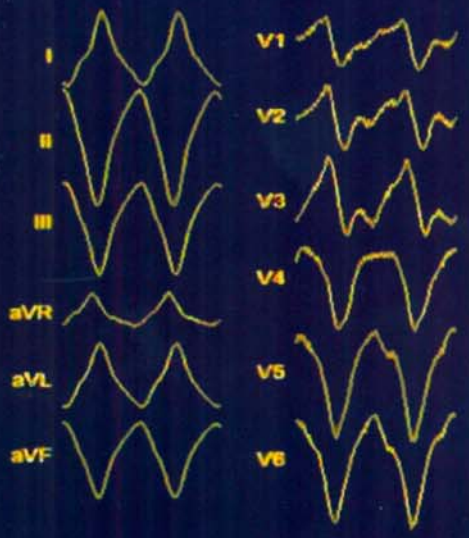
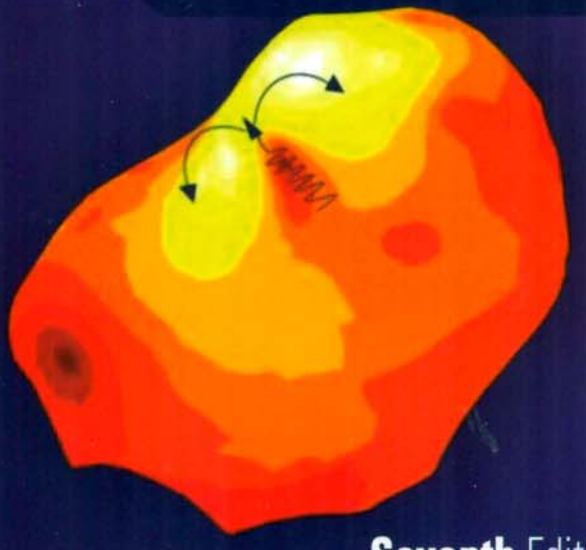




Cardiac Electrophysiology

From Cell to Bedside





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Seventh Edition

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The current understanding of the relationship between the sodium current (I_{Na}) and inward rectifier potassium current (I_{K1}), the two most important ionic currents that control ventricular excitability, began in 1955 with the seminal work by Dr. Weidmann.[1] It also derives from the basic and clinical studies on arrhythmogenesis in ion channel diseases and heart failure, which have demonstrated that the modification in the peak density of either I_{Na} or I_{K1} changes cell excitability and conduction velocity (CV). However, until recently, the pathophysiological consequences of a molecular interplay between the individual channels at the center of such diseases had not been investigated.[2] In the heart, I_{K1} is the major current responsible for the maintenance of the resting membrane potential (RMP), whereas I_{Na} provides the largest fraction of the inward depolarizing current that flows during an action potential (AP).[3] It is well known that by controlling RMP and AP duration (APD) at the end of repolarization, I_{K1} modifies the Na^+ channel availability and therefore cell excitability.[4] In addition, I_{K1}-I_{Na} interactions are important for stabilizing and controlling the frequency of the electrical rotors that are responsible for the most dangerous cardiac arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF).[5,6]

is much more complex than previously considered. It comprises model independent, reciprocal modulation of the expression of their respective channel proteins ($Na_V1.5$ and Kir2.1) within a macromolecular complex that involves the membrane-associated guanylate kinase (MAGUK)-type protein synapse-associated protein 97 (SAP97),[2] α1-syntrophin, and possibly additional scaffolding proteins. In adult transgenic mice overexpressing Kir2.1 (Kir2.1 OE), peak I_{Na} density is twice as large as that measured in cells from control hearts. In heterozygous Kir2.1 knockout (KO) mice ($Kir2.1^{-/+}$), $Na_V1.5$ protein and I_{Na} are significantly reduced. Similarly, in single ARVMs, I_{K1} increased significantly on the adenoviral transfer of $Na_V1.5$. In NRVM monolayers, the co-overexpression of $Na_V1.5$ with Kir2.1 increased CV, abbreviated APD, and increased rotor frequency beyond those produced by Kir2.1 OE alone.[2] Furthermore, recent data in the literature suggest that conditions that result in $Na_V1.5$ protein reduction, such as those occurring in dystrophin-deficient mdx^{5cv} mice, are accompanied by a concomitant reduction in Kir2.1 protein levels.[7] Importantly, the finding that coexpression of $Na_V1.5$ can reduce internalization of Kir2.1 is a central mechanistic observation.[2] The purpose of this chapter is to discuss those results in the context of cardiac excitability and the mechanisms of reentrant arrhythmias. It will be shown that sodium and potassium channel interactions depend on more than membrane voltage alone. Altogether, the evidence that will be discussed suggests that cardiac cells undergo model-independent coregulation that involves the posttranslational mechanisms of Kir2.1 and $Na_V1.5$, with important functional consequences for myocardial excitation, impulse velocity, and arrhythmogenesis. Moreover, the evidence suggests that similar interactions are applicable to other sarcolemmal ion channels, which could themselves have unique effects on myocardial function.