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Conduction abnormalities and ventricular arrhythmogenesis: The roles of sodium channels and gap junctions

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ABSTRACT

Ventricular arrhythmias arise from disruptions in the normal orderly sequence of electrical activation and recovery of the heart. They can be categorized into disorders affecting predominantly cellular depolarization or repolarization, or those involving action potential (AP) conduction. This article briefly discusses the factors causing conduction abnormalities in the form of unidirectional conduction block and reduced conduction velocity (CV). It then examines the roles that sodium channels and gap junctions play in AP conduction. Finally, it synthesizes experimental results to illustrate molecular mechanisms of how abnormalities in these proteins contribute to such conduction abnormalities and hence ventricular arrhythmogenesis, in acquired pathologies such as acute ischaemia and heart failure, as well as inherited arrhythmic syndromes.

1. Introduction

Cardiac arrhythmias arise from disruptions in the normal orderly sequence of electrical activation and recovery of the heart. On the one hand, ventricular arrhythmias can lead to sudden cardiac death (SCD), which accounts for around 400,000 deaths in the United States [1–3]. This represents a prevalence of 0.1% in the population. On the other hand, atrial arrhythmias are the most common arrhythmias observed in clinical practice [4], affecting around 2 million people in the U.S. [5]. It is a major contributor to cardiovascular morbidity. For example, up to 15% of all strokes in the U.S. can be attributed to atrial fibrillation [6].

Ventricular arrhythmias can be categorized into disorders affecting cellular depolarization or repolarization [7], but can also be caused by abnormalities in action potential conduction [8]. The commonest underlying mechanism is the formation of re-entry circuits [9]. Re-entry occurs when an action potential fails to extinguish itself and re-activates a region that has recovered from refractoriness [10,11]. It may occur in the presence of an obstacle, around which an action potential can travel (circus-type) [12], or without an obstacle (reflection or phase 2) [13,14]. For circus re-entry to occur, three criteria must be met. First, there must be an obstacle around which an action potential (AP) can circulate. This need not to be a structural abnormality, but can be a functional core of refractory tissue. Secondly, conduction velocity (CV) must be sufficiently reduced so that the myocardial tissue ahead of the excitation wavefront remains excitable. Finally, unidirectional conduction block must be present to prevent waves from self-extinguishing. These three conditions form part of the arrhythmogenic substrate, which upon a trigger, for example from premature generation of an AP, can serve to sustain re-entry. Recent review articles have focused on the mechanisms of cardiac conduction [15] and the factors governing myocardial CV [8,16]. This article briefly discusses the factors causing conduction abnormalities, as well as the roles that sodium channels and gap junctions play in AP conduction and how abnormalities in these proteins contribute to ventricular arrhythmogenesis.

2. Reduced conduction velocity and unidirectional conduction block

CV of the propagating APs depends on both active and passive properties of the cell membrane (Fig. 1). Active properties refers to voltage-dependent conductances, mainly mediated by I_{Na}, which determines the AP upstroke (phase 0) [18]. A faster CV can arise from two situations. Firstly, a higher maximum upstroke velocity, dV/dt_{max} brings the membrane to threshold much more quickly. Secondly, increased myocardial excitability given by 1/(threshold potential–resting membrane potential) means that smaller inward currents are required to reach threshold. The resting membrane potential also influences I_{Na} through regulation of the inactivation kinetics of sodium channels [19–23]. In contrast, passive properties depend on capacitive and resistive components of the cell membrane as well as the myocardial architecture [24]. Axial resistance (r_i) depends on the resistance of both the myoplasm [25] and the gap junctions between myocytes [26]. Decreased r_i would increase CV. Membrane capacitive load is

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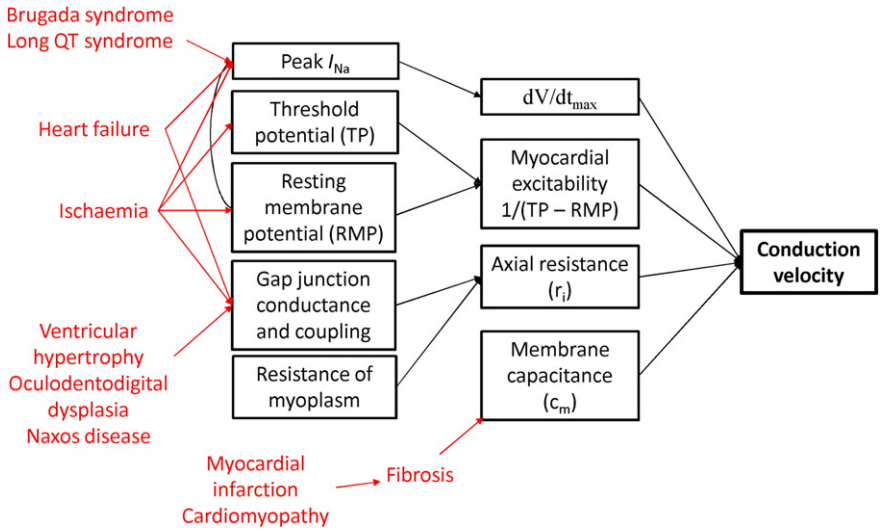

Fig. 1. Determinants of conduction velocity, and the effects of different pathological conditions on these.

determined by the surface area and volume ratio [24]. Increased membrane capacitance (C_m) prolongs the time needed to bring membrane to threshold, thereby reducing CV. These processes determining CV can be described mathematically by the cable theory [27]. However, recent experimental data have challenged the applicability of this theory to cardiac conduction [28], and have attracted ongoing debate [29,30]. Traditional cable theory does not explicitly consider junctional clefts in the extracellular space and is therefore incompatible with the notion of ephaptic coupling: interested readers should be directed to this article here [31]. As shown in Fig. 1, acquired and congenital heart diseases influence various determinants of CV, which will be discussed in turn.

Additional factors can modulate the CV of the AP wave. Firstly, gap junctions, high-resistance ion channels located between successive myocytes [32,33] cause conduction slowing and discontinuous propagation [34,35]. Secondly, the complex tissue architecture of the myocardium leads to anisotropic conduction, with greater velocity in the longitudinal compared to the transverse direction [36,37]. This is in part due to higher density of gap junctions at the ends of myocytes than in the lateral margins [38]. Finally, the source and sink are determined by the plasma membrane excitability and tissue-structure properties, respectively [8]. Interactions between these factors are recognized to cause reduced CV, conduction block and fractionation of the excitation wave [39]. Finally, it is also important to appreciate that conduction and repolarization are not independent processes, but one can affect the other. For example, I_{to} inhibition enhances conduction between cell pairs, suggesting that repolarization currents are able to influence CV [40,41]. The accepted view that voltage-gated sodium channels, gap junctions and desmosomes are separate entities with distinct functions has been challenged. Sodium channels were assumed to be separate from gap junctions but were later found in intercalated disks [42], co-localizing with gap junctions and playing an important role in cardiac conduction [43]. This co-localization may constitute a cardiac ephapse, thereby contributing to ephaptic coupling [44]. Its discussion is beyond the scope of the current paper and interested readers are referred to review articles here [45,46].

Unidirectional conduction block can occur in homogeneous cardiac tissues in the presence of functional asymmetries [8]. Firstly, it can arise from interaction between the activation wavefront and the refractory tail [47]. This can occur with premature initiation of an AP, e.g. from early or delayed afterdepolarization phenomena, or co-existence of interacting wavefronts during multiple wavelet re-entry [8]. Secondly, heterogeneities in membrane excitability increase the vulnerability to unidirectional block. This could occur in regional ischaemia in which there is local accumulation of potassium ions [48], causing both a positive shift in the resting membrane potential and inhomogeneities in sodium channel recovery [49]. Thirdly, increased spatial heterogeneities in refractoriness can arise from alterations in depolarizing or repolarizing currents; for example, this can occur with regional ischaemia where extracellular accumulation of potassium produces shortening of the AP [49].

3. Sodium channels

Voltage-gated sodium channels are responsible for the initiation and propagation of APs in excitable cells. Each channel consists of a pore-forming α-subunit, a modulatory β-subunit and other regulatory proteins. Of these, the $Na_V1.5$ α-subunit is encoded by the *SCN5A* gene [50] and is made of four domains (I to IV) with each domain containing six transmembrane segments (S1 to S6). Upon depolarization, the S4 segments, which are positively charged, undergo outward movement [51,52]. This opens the channel pore and allows the influx of sodium ions. The resulting transmembrane current, I_{Na}, therefore determines myocardial excitability and CV of the APs. Depolarization also initiates fast inactivation [53,54]. The mechanism involves the linker region between domains III and IV, which functions as a 'lid' to occlude the pore [55–58]. Slow inactivation involves the P-segment linker sequence between S5 and S6 bending back into the membrane and lining the outer pore [59,60]. Binding sites for Ca^{2+} and the Ca^{2+}-binding protein calmodulin are present at the carboxyl terminus [65,66], allowing modulation of channel function [67,68]. Ca^{2+}/calmodulin-dependent Kinase II phosphorylates the sodium channel, causing a negative shift in the voltage-dependence of steady-state inactivation without altering the voltage-dependence of steady-state activation or the peak I_{Na} [69].

I_{Na} consists mainly of a tetrodotoxin-insensitive component, attributable to the cardiac isoform $Na_V1.5$ [50,70,71]. It also contains a persistent, tetrodotoxin-sensitive component, as suggested initially by voltage clamp technique [61,62] and later confirmed by patch clamping [63,64]. This is mediated by neuronal isoforms $Na_V1.1$, $Na_V1.3$, and $Na_V1.6$ [72–74]. Recent immunohistochemical experiments have demonstrated neuronal isoforms in cardiac tissue of many species, in keeping with the electrophysiological findings [75]. They were found in pacemaker cells with whole cell current and voltage clamp experiments demonstrating a contributory role in pacemaker activity [76]. Furthermore, they were localized to the transverse tubular system of cardiomyocytes, and tetrodotoxin application resulted in desynchronization of excitation-contraction coupling and a decrease in cardiac contractility [77]. However, this is a contentious area as another study showed no significant effects of tetrodotoxin on shortening of rat ventricular myocytes [78].