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Review

Mechanisms of cardiac arrhythmias

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ABSTRACT

Blood circulation is the result of the beating of the heart, which provides the mechanical force to pump oxygenated blood to, and deoxygenated blood away from, the peripheral tissues. This depends critically on the preceding electrical activation. Disruptions in the orderly pattern of this propagating cardiac excitation wave can lead to arrhythmias. Understanding of the mechanisms underlying their generation and maintenance requires knowledge of the ionic contributions to the cardiac action potential, which is discussed in the first part of this review. A brief outline of the different classification systems for arrhythmogenesis is then provided, followed by a detailed discussion for each mechanism in turn, highlighting recent advances in this area.

Contents

1. Introduction

The heart beat provides the mechanical force for the pumping of oxygenated blood to, and deoxygenated blood away from, the peripheral tissues [1]. This depends critically on the orderly activation and recovery of electrical excitation through the myocardium.

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Disruptions of this can lead to arrhythmias. Understanding of the mechanisms underlying their generation and maintenance requires knowledge of the ionic contributions to the cellular action potential, which is discussed in the first part of this review. A brief outline of the different classification systems of arrhythmogenesis is then provided, followed by a discussion of each mechanism in turn, highlighting recent advances in this area.

2. Cardiac action potential and its ionic contributions

The cardiac action potential results from the sequential opening and closing of ion channel proteins that span the plasma membrane of individual myocytes. Its conduction through the heart depends on electrical coupling between these cells, which is mediated by gap junctions [2]. Differences in the expression and properties of ion channels result in heterogeneities in action potential waveforms in different cardiac regions and cell types, and in the normal unidirectional spread of the action potentials through the heart [3]. The cardiac action potential in humans has five different phases (from 0 to 4). Depolarization from the SA node brings the membrane potential to the threshold, opening the voltage-activated sodium channels [4]. This allows the sodium ions to diffuse down their electrochemical gradient from the extracellular space, across the membrane and into the cell. The resulting sodium current, I_{Na}, produces a positive feedback loop that causes further sodium channels to open, and depolarization of the membrane proceeds until the sodium Nernst potential is reached or when the channels are inactivated. This is responsible for the rapid upstroke, termed phase 0, of the action potential.

Early rapid repolarization then results from the activation of the fast and slow transient outward potassium currents, $I_{to,f}$ and $I_{to,s}$, and is responsible for phase 1 of the action potential. This is followed by a prolonged plateau resulting from a balance between the inward currents mediated by the voltage-gated L-type calcium channel ($I_{Ca,L}$) and sodium–calcium exchanger (I_{NCX}), and the outward currents mediated by the voltage-gated delayed rectifier potassium channels (I_K) [5]. The rapid and slow currents (I_{Kr} and I_{Ks}, respectively) make up I_K. There is also contribution from the inward rectifying current (I_{K1}). This plateau is responsible for phase 2 of the action potential. The driving force for potassium efflux remains high during the plateau phase due to a large difference between the membrane potential and the potassium Nernst potential. As the calcium channels become inactivated, the outward potassium currents predominate, causing further repolarization and bringing the membrane potential towards the potassium equilibrium potential. This is responsible for phase 3 of the action potential.

The membrane potential returns to its resting value after full repolarization, which corresponds to phase 4 of the action potential, and is normally polarized at values between −80 and −64 mV relative to the extracellular space [6]. This resting state is maintained mainly by the inward rectifier current, I_{K1}. The weak inward rectifying ATP-dependent potassium channels ($I_{K,ATP}$), activated by nucleotide diphosphates and inhibited by adenosine triphosphate, are also active during this phase. They are thought to provide a link between cellular metabolism and the membrane potential.

Pacemaker cells are distinct from other cell types in showing automaticity, a property resulting from both voltage- and calcium-dependent mechanisms [7]. The former involves the funny current (I_f) carried by hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [8], which have several unusual characteristics, such as activation on hyperpolarization, permeability to both sodium and potassium ions, modulation by intracellular cyclic AMP, and a small single channel conductance. The latter involves spontaneous calcium release from the sarcoplasmic reticulum [9], which activates I_{NCX}. Its crucial role was demonstrated in mice with complete atrial-specific knockout of NCX, which showed no pacemaker activity [10]. Both mechanisms result in spontaneous depolarization that is responsible for the rising slope of the membrane potential.

3. Mechanisms of arrhythmias

Several schemes have been used to classify the mechanisms of cardiac arrhythmias. Traditionally, these have been divided into nonreentrant and reentrant activity [11]. An alternative scheme divided them into those occurring at the cellular and tissue levels [12]. A dynamics-based classification, focusing on the trigger-tissue substrate interactions, divided arrhythmogenic mechanisms into unstable calcium cycling, reduced repolarization reserve, and excess repolarization reserve [13].

4. Focal activity

Focal activity can arise from enhanced automaticity or triggered activity (Fig. 1).

4.1. Enhanced automaticity

Pacemaker cells are present in the SA node, atria, AV node, and the His-Purkinje system. In the human heart, the normal rate of discharge of the SA node is between 60 and 100 beats per min (bpm). Subsidiary pacemakers discharge at slower rates. They are usually latent and reset by the dominant pacemaker with the highest intrinsic rate of discharge (i.e., the SA node). For example, the AV node discharges at 40–60 bpm and the Purkinje system discharges at 20–40 bpm. Enhanced automaticity of pacemaker cells can increase the rate of action potential discharge (Fig. 1). This can result from three main mechanisms: a negative shift in the threshold potential (TP, *top broken arrow*), a positive shift in the maximum diastolic potential (MDP, *bottom broken arrow*), and an increased rate of phase 4 depolarization [14]. When this occurs in the SA node, it can lead to an increase in heart rate, termed sinus tachycardia. This can be physiological, due to increased sympathetic tone during exercise, or pathophysiological, due to hypovolemia, ischemia, or electrolyte disturbances. Moreover, tachycardia–bradycardia syndrome is alternating bradycardia and tachycardia, seen in patients with atrial fibrillation and sick sinus node syndrome [15]. Its underlying molecular mechanisms have not been fully elucidated. Recent evidence suggests a possible role of HCN channel downregulation in the SA node with a consequent

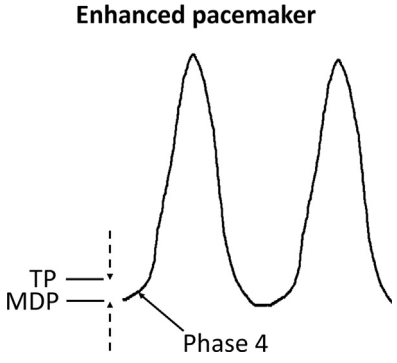

Fig. 1. Enhanced pacemaker can occur via three mechanisms: a negative shift in the threshold potential (TP), a positive shift in the maximum diastolic potential (MDP), and an increased rate of phase 4 depolarization.