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Mechanism of Cardiac Arrhythmias

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ABSTRACT

Blood circulation is the result of the beating of the heart, the heart has two basic properties, namely electrical property (impulse generation) and a mechanical property force to pump oxygenated blood to and deoxygenated blood away from the peripheral tissue. Disruption in the orderly pattern of this propagating cardiac excitation wave can lead to arrhythmias. Noteworthy for understanding their mechanism their generation and maintenance requires knowledge of ionic contributions to cardiac action potential which is discussed in the review. The purpose of this review is to highlight arrhythmogenesis, automaticity, triggered activity and reentry then followed by a detailed discussion for each mechanism in turn.

1. INTRODUCTION

The heart has two basic properties, namely an electrical property (impulse generation) and mechanical property force to pump oxygenated blood to, and deoxygenated blood away from peripheral tissue. Disruption in the orderly pattern of this propagating cardiac excitation wave can lead to arrhythmias. The mechanism that can lead to clinical arrhythmias and frequently due to abnormalities beyond the tissue level is also essential to understand what occurs at the cellular level. Since then intracardiac recordings and programmed cardiac stimulation have advanced our understandings of arrhythmia and micro-electrode, voltage-clamping and patch-clamping techniques have allowed considerable insight into the electrophysiologic actions and mechanisms of anti-arrhythmic drugs. The discovery of the genetic abnormalities in the ion channels that control electrical repolarizations.

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. Cardiac myocytes are highly specialized cells responsible for both conductions of electrical impulse and mechanical contraction. Some myocytes demonstrate automaticity, defined by the capability of cardiac cells to undergo spontaneous diastolic depolarization and to initiate an electrical impulse in the absence of external electrical stimulation.

Spontaneously originated action potential (AP's) are propagated through cardiac myocytes, which are excitable, referring to their ability to respond to a stimulus with a regenerative action potential (AP). The cardiac AP in humans has five different phases (from 0 to 4).In Phase 0 or Initial phase, there is a rapid depolarization of atrial and ventricular tissue, which is caused due to increased permeability of membrane for Na^+ influx. In Phase 1 or Initial depolarization, the Na^+ current is quickly inactivated, followed by subsequent outward K^+ current and beginning of Ca^{2+} influx (-60mv) causing slower depolarization. In Phase 2 or Plateau phase Ca^{2+} current or channels plays an important role, there will be a continuation of Ca^{2+} influx and is balanced by K^+ efflux. Phase 3 The Ca^{2+} channels or currents plays the main role for Ca^{2+} and triggers Ca^{2+} release from the sarcoplasmic reticulum, initiating contraction of the myocyte. Activation of delayed rectifier K^+ channels and inactivation of Ca^{2+} channels leads to termination of plateau and initiates late re-polarization or cellular re-polarization. Phase 4 Finally outward K^+ channel mediates the final or gradual depolarization. Following contraction, the cardiac

myocytes must enter a relaxation or refractory period or phase during which they cannot be depolarized. Refractory period is defined by the time interval following excitation during which the cell remains unexcitable.

Under normal conditions, the sinoatrial node is the primary pacemaker of the heart, with the resting membrane potential of approximately -60mv. The aggregate activity of, various currents results in the net inward flow of sodium (Na^+) and thus increase in the membrane potential. When it reaches -40mv calcium (Ca^{2+}) currents(T- type $C_{a,\,T-}$ and L-type $I_{Ca,\,L-}$) are activated and serve as predominant ion carriers during AP upstroke of pacemaker cells (Ca^{2+} dependent). Subsequently, outward potassium (K^+) currents are activated and Ca^{2+} currents are inactivated. The membrane potential decreases due to the outward flow of K^+, the major re-polarizing ion of the heart upon reaching the resting membrane potential, the cycle is ready to repeat itself.

3. Mechanism of arrhythmia's

The mechanism of cardiac arrhythmias may be divided into Non-Reentrant and Reentrant activity. An alternative scheme divided these into those occurring at cellular and tissues level.

3.1 Non-Reentrant activity

3.1.A Enhanced automaticity / Abnormality in impulse generation

Pacemaker cells are present in the SA node, atria, AV node and the His-Purkinje system. In human heart, the normal rate of discharge of SA node is between 60 and 100 beats per minute. Automatic pericardia depend upon spontaneous impulse generation in latent pacemaker and may be result of several different mechanisms. Enhanced automaticity of pacemaker cells can increase the rate of action potential discharge, this can result from three main mechanisms (i) A negative shift in the threshold potential (ii) A positive shift in the maximum diastolic potential. (iii)An increased rate of phase 4 depolarization.

When these occur in the SA node, it can lead to an increases in heart rate, termed sinus tachycardia. This can physiological due to increased sympathetic tone during exercise, pathophysiological due to hypovolemia, ischemia or electrolyte disturbance. Moreover, tachycardia-bradycardia syndrome is alternating bradycardia and tachycardia, seen in patients with atrial fibrillation and sick sinus node syndrome. Both sodium calcium exchanger (NCX)

and hyper-polarization activated cyclic nucleotide gated channels (HCN) are responsible for the "voltage clock" of pacemaker activity.

Enhanced automaticity can also occur in AV node, under conditions of acute Myocardial Infarction, digitalis toxicity, isoprenaline administration and recent cardiac surgery. When discharge rate of AV node is higher than the sinus rate, it can lead to abnormal rhythms called accelerated junctional rhythm. These rhythm can occur at the site close to atria, such as pulmonary veins, superior vena cava, crista terminalis, coronary sinus, atrial septum and the parahisian region that includes the tricuspid and mitral cannulae, leading to focal atrial tachycardia.

Factors which experimentally lead to abnormal automaticity are also known to be arrhythmogenic in clinical situation. Automatic tachycardias have the following characteristics (i) The onset of tachycardia is unrelated to an initiating event such as premature beat. (ii)The initiating beat is usually identical to subsequent beats of tachycardia. (iii) The tachycardia cannot be initiated by programmed cardiac stimulation. (iv) The onset of the tachycardia is usually preceded by a gradual deceleration in rate.

Ex. Sinus tachycardia and junctional tachycardia.

3.1.B Triggered activity

Triggered activity is defined by impulse initiation caused by after depolarization (membrane potential oscillations that occur during or immediately following a preceding action potential). Triggered activity is also a possible mechanism for abnormal impulse generation. Based on temporal relationship two types of after polarizations are described (i) Early afterdepolarizations (EAD_S) (ii) Delayed afterdepolarizations (DAD_S).

(i) Early After depolarizations (EAD_S)

EAD_S can develop before full repolarization, corresponding to phase 2 or phase 3 of the cardiac action potential in humans. They are usually but not exclusively associated with prolonged AP durations, which occur when the inward current is greater in amplitude than the outward current. Two mechanisms have been proposed for EAD_S that are associated with prolongations in AP durations and occur during phase 2 of the AP. Firstly depolarizing shifts in the membrane potential can reactive the L-type Ca^{2+} channels, resulting in increase $I_{Ca^{2+}-,L}$ that

further depolarizes the membrane. This setup a positive feedback loop triggering an AP. Secondly, at membrane potentials negative to the threshold of $I_{Ca^{2+}-,L}$ activation (but before full repolarization), spontaneous Ca^{2+} release from the sarcoplasmic reticulum can activate I_{NCX}, resulting in membrane depolarization. The intermittent nature of EAD_S has recently been examined demonstrating that it is due to slow changes in $[Na^+]$ and potentially explaining why arrhythmia do occur all the time. These late EAD_S are clinically relevant, as they can occur immediately after termination of other types of tachycardia such as Atrial flutters, Atrial tachycardia, ventricular tachycardia, VF. In such instances, repolarization time is shortened and a transient increase in sarcoplasmic calcium release can be induced when reverting to sinus rhythm. EAD_S and their resulting triggered activity are thought to underlie the arrhythmogenesis observed in heart failure and long QT syndromes.

(ii) Delayed afterdepolarizations (DAD_S)

DAD_S were first described as oscillatory after potentials. They can develop after full repolarization, corresponding to phase 4 of cardiac action potential in human. These oscillations are caused by a variety of conditions that raise the diastolic intracellular Ca^{2+} concentration which cause Ca^{2+} mediated oscillations that can trigger a new AP if they reach the stimulation threshold. As the cycle length decreases, the amplitude and the rate of the DAD_S increases and therefore is expected to initiate arrhythmia's triggered when DAD_S increases the heart rate (either spontaneously or during pacing).

Toxic concentration of digitalis was the first observed case of DAD_S via inhibition of Na^+/K^+ pump, which promotes the release of $Ca^{2+}$from the sarcoplasmic reticulum. Clinically, digoxin toxic bidirectional fascicular tachycardia is felt to be an example of TA. Catecholamines can cause DAD_S by causing intracellular Ca^{2+} overload via an increase in $I_{Ca^{2+}-L}$ and Na^+-Ca^{2+} exchange current, among other mechanisms. Ischemia induced DAD_S are thought to be mediated by the accumulation of lysophospoglycerides in the ischemic tissue, with subsequent elevation in Na^+ and Ca^{2+}. Abnormal sarcoplasmic reticulum function (Ex. Mutations in ryanodine receptor) can also lead to intracellular Ca^{2+} overload, facilitating clinical arrhythmias, such as catecholaminergic polymorphic VT.

Triggered arrhythmias induced by DAD_S may be terminated by single stimuli, therefore other electrophysiologic features are needed to distinguish them from the reentrant tachycardias. The rate dependency of the coupling interval may be useful because in most cases of DAD_S induced

arrhythmias the shorter the cycle of stimulation, the shorter the coupling interval to the induced arrhythmia. This is in contrast to the inverse relationship seen in reentrant arrhythmias. Adenosine has been used as a test for the diagnosis of DAD_S. Adenosine reduces the Ca^{2+} inward current indirectly by inhibiting effects on adenylate cyclase and cyclic adenosine monophosphate. Thus it may abolish DAD_S induced by catecholamines but does not alter DAS_S induced by Na^+/K^+ pump inhibition.

3.2 Reentrant Activity / Reentry

Reentry occurs when an AP fails to extinguish itself and reactivates a region that has recovered from refractoriness. It can be divided into two types (A) Reentry that occurs in the presence of obstacle, (B) Reentry that occurs without an obstacle.

3.2.A Reentry that occurs in the presence of obstacle

This occurs when an AP travels around an anatomical or functional obstacle and excites its site of origin.

(i) Anatomical obstacle

The anatomical reentry mechanism is based on an excitable anatomical obstacle surrounded by a circular pathway in which the wavefront can reenter, creating fixed and stable reentrant circuits. The anatomical obstacle determines the presence of two pathways, when wavefront encounters the obstacle, it will travel down one pathway (unidirectional block), propagating until the point of block, thus initiates a reentrant circuit.

Initiation and maintenance of reentry will depend on the conduction velocity and refractory period of each pathway, which determines the wavelength (wavelength= conduction velocity*refractory period). For reentry to occur, the wavelength must be shorter than the length of the pathway. The excitable gap is a key concept essential to understand the mechanism of reentry. The excitable gap refers to the excitable myocardium that exists between the head of the reentrant wavefront and the tail of the preceding wavefront. The presence of excitable gap also makes it possible to enter in the reentrant circuit using external pacing and explains the phenomenon of resulting entertainment, and termination of tachycardia with electrical stimulation.

(ii) Functional obstacle

In functional reentry the circuit is not determined by anatomic obstacles, it is defined by dynamic heterogeneities in the electrophysiologic properties of the involving tissues. The location and size of functional reentrant circuits can vary, but they are usually small and unstable. Subsequent experiment then obtained transmembrane potential recordings, which led to the leading circle model.

The CV of the propagating AP depends on the wave curvature. For a planar wave, each cell activates one cell downstream, for a wavefront curving inwards (concave), each cell will be activating less than one cell downstream. This source sink mismatch will increase the depolarizing current available for each downstream cell, resulting in a greater rate of voltage rise, and therefore a higher CV compared to that of a planar wave. If the curvature is sufficiently convex, conduction block can result. The point where the activation and repolarization wavefronts meet is called the wave singularity. This corresponds to a non-excited point because all phases of the wave meet here. A spiral wave is a 2-dimensional wave of excitation emitted by a self organizing source of functional reentrant activity termed a rotor. The 3 dimensional equivalent of a spiral wave were described earlier in the Belousov-Zhabotinsky chemical reaction in which cerium ion catalyze the oxidation of malonic acid by bromate. In this reaction the ratio of cerium (iv) to cerium (iii) undergoes repeated temporal oscillations, generating spiral waves with alternating colors. Spiral wave have been subsequently reproduced in a model of cardiac tissue and demonstrated in the slices of epicardial muscle using a potentiometric dye, which changes its spectral properties in response to voltage changes. Experiments have shown that the phase singularity is excitable but remains non-excited and therefore acts as functional obstacle around which the spiral wave can circulate.

3.2.B Reentry not involving obstacle

Reentry can also occur without circus movement. This can be divided into (i) Reflection (ii) Phase 2 reentry.

(i) Reflection

The concept of reflection was first suggested by studies of the propagation characteristics of slow AP responses in K^+ depolarized Purkinje fiber wit and coworkers demonstrated a phenomenon similar to that observed by Schmitt and enlarger in which slow anterograde conduction of the impulse was at times followed by a retrograde wavefront that produce a "return extra systole". They proposed that non stimulated impulse was caused by circuitous reentry at the level of the syncytial interconnections, made possible by longitudinal dissociation of the bundle, as the most likely explanation for the phenomenon but also suggested the possibility of reflection Direct evidence in support of reflection as mechanism of arrhythmogenesis was provided by Antzelevitch and colleagues in the early 1980_S. The first model of reflection involves use of ion-free isotonic sucrose solution to create a narrow (1.5 to 2mm) central inexcitable zone(gap) in unbranched Purkinje fibers mounted in a 3-chamber tissue bath. A second model of reflection involved the creation of an inexcitable zone permitting delayed conduction by superfusion of a central segment of a Purkinje bundle with a solution designed to mimic the extracellular milieu at a site of ischemia. The gap was shown to be largely composed of an inexcitable cable across which conduction of impulses was electronically mediated. Reflected reentry has been demonstrated in isolated atrial and ventricular myocardial tissues as well reflection has also been demonstrated in Purkinje fibers in which a functionally inexcitable zone is created by focal depolarization of the preparation with long duration constant current pulses. Reflection is observed in isolated canine Purkinje fibers homogeneously depressed with high K^+ solution as well as in branched preparations of normal Purkinje fibers.

(ii) Phase 2 reentry

Phase 2 reentry occurs when the dome of action potential, most commonly epicardial, propagates from sites at which it is maintained to sites at which it is abolished, causing local re-excitation of the epicardium and the generation of a closely coupled extra-systole. Severe spatial dispersion of re-polarization is needed for phase 2 reentry to occur. It has been proposed as a mechanism responsible for closely coupled extra-systole that precipitates ventricular tachycardia/ventricular fibrillation (VT/VF) associated with early re-polarization syndromes.

Spatial dispersion of re-polarization

The ventricular myocardium is electrically heterogeneous and composed of at least 3 electrophysiologically and functionally distinct cell types:-epicardial, Myocardial (M), and endocardial cells. The 3 principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics. Ventricular epicardial and M, but not the endocardial, cells generally display a prominent phase 1, because of a large 4-aminopyridine sensitive transient outward current giving the action potential a spike and dome or notched configuration. These regional differences in transient outward current first suggested on the basis of action potential data, have now been directly demonstrated in ventricular myocytes from a wide variety of species including canine, feline, guinea pig, swine, rabbit, and humans.

4. Future directions

The traditional approach to the treatment of atrial fibrillation or atrial flutters and be organized into several sequential goals.

1) To evaluate the need for acute treatment.

2) Contemplate methods to restore sinus rhythm taking into consideration the risks.

3) Consider ways to prevent the long term complications of AF/atrial flutters such as arrhythmia reoccurrences and thromboembolism.

Severe symptoms:- DCC (direct current cardioversion)

Mild or moderate symptoms:- slow ventricular rate (beta blockers, calcium channel blockers, digoxin).

In acute treatment, although the patients may present with signs and symptoms of hemodynamic instability (Ex. Severe hypotension, angina, pulmonary oedema), which qualifies a medical emergency. In these situations, DCC is indicated as a first line therapy in an attempt to restore sinus rhythm immediately.

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