Drugs acting on the heart: antiarrhythmics

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Abstract

Arrhythmias are abnormalities of cardiac rate or rhythm occurring for a variety of reasons. They are common in the perioperative period and in intensive care. Causes may reflect an underlying heritable predisposition, the presence of new pathology either of the heart or conducting system, or as a result of systemic illness. Targets for antiarrhythmics include myocardial ion channels, muscarinic or nicotinic acetylcholine receptors, adrenergic or adenosine receptors. Arrhythmias may cause cardiac arrest and haemodynamic compromise, requiring rapid identification and corrective treatment either of rate or rhythm. Even where stable, arrhythmias present an increased risk of thromboembolic events requiring the use of anticoagulation. Treatment may be directed at controlling heart rate or rhythm to restore the circulation and tissue perfusion. Strategies may include prevention or correction of precipitating factors (such as electrolyte abnormalities or sepsis) and sometimes non-pharmacological treatments (cardioversion, surgical ablation or pacing). Antiarrhythmic drugs are often required. The targets, mechanisms and clinical guidelines are reviewed for common antiarrhythmic agents.

Keywords Amiodarone; antiarrhythmia agents; arrhythmias; cardiac; digoxin; lidocaine; magnesium

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- draw the cardiac myocyte and pacemaker action potential, and note the effects of common antiarrhythmics on these
- list the major targets for antiarrhythmic actions
- identify at least five common causes of arrhythmias
- give named examples of the major classes of antiarrhythmic drugs, along with their site and mechanism of action
- describe the evidence in relation to the treatment of common arrhythmias

Introduction

The myocardium contracts as a result of coupling to organized initiation and conduction of electrical activity (Figure 1). Myocardial muscle has gap junctions to facilitate conduction of electrical currents. The heart contains specialized conducting tissues, the His-Purkinje system, and sino-atrial and atrioventricular nodes (SAN and AVN, respectively), which together enhance impulse initiation and transmission.

The depolarization of the myocardial cells is initiated via the SAN. This pacemaker generates a depolarizing impulse which passes via the atria to the AVN, the His-Purkinje system and finally to the ventricles. Arrhythmias are abnormal cardiac rhythms caused by abnormalities of impulse generation, impulse conduction or both. They may originate from any part of this system, and may be congenital or acquired in nature. Agents may increase or decrease rate, speed or force of conduction, and therefore be positively or negatively chronotropic, dromotropic, or inotropic respectively.

Some arrhythmias may cause little or no symptoms, but risk the formation of a malignant rhythm precipitating acute cardiovascular collapse. Patients who are otherwise well may tolerate some tachyarrhythmias that would otherwise cause symptoms of cardiovascular compromise in the critically ill, frail or those with impaired cardiac function. To understand arrhythmias and their treatment, it is helpful to review the normal electrophysiology of the cardiac myocyte and conducting system (Figure 1).

Pharmacological management of arrhythmias

Classification

Antiarrhythmic drugs have traditionally been classified by the Vaughan–Williams system according to drug class and mode of action. However, this classification has limitations: it does not include all drugs with antiarrhythmic properties, particularly newer agents, and some drugs have more than one action.

Table 1 gives a functional classification of antiarrhythmic agents, showing site and mode of action as well as the arrhythmias for which the drugs are indicated.

Mechanisms of drug action – cardiac electrophysiology

Myocyte depolarization causes calcium influx and cellular contraction. The mechanism of excitation–contraction coupling is beyond the scope of this article (see Eisener, 2017 in further reading below for a detailed review). Membrane potential is determined by the intracellular and extracellular ratios of potassium (K^+), sodium (Na^+) and calcium (Ca^{2+}). The resting membrane potential is maintained at −60 mV by the sodium–potassium ATPase pump. The voltage-gated ion channels in the myocyte and pacemaker cells cause distinct ion fluxes, which cause characteristic changes in membrane potential in response to a depolarizing stimulus (Figure 1).

In general, Na^+ or Ca^{2+} influx into myocytes and pacemaker cells causes the membrane potential to become less negative. Once this depolarization reaches a threshold, further voltage-gated ion channels promote more rapid depolarization and an action potential.

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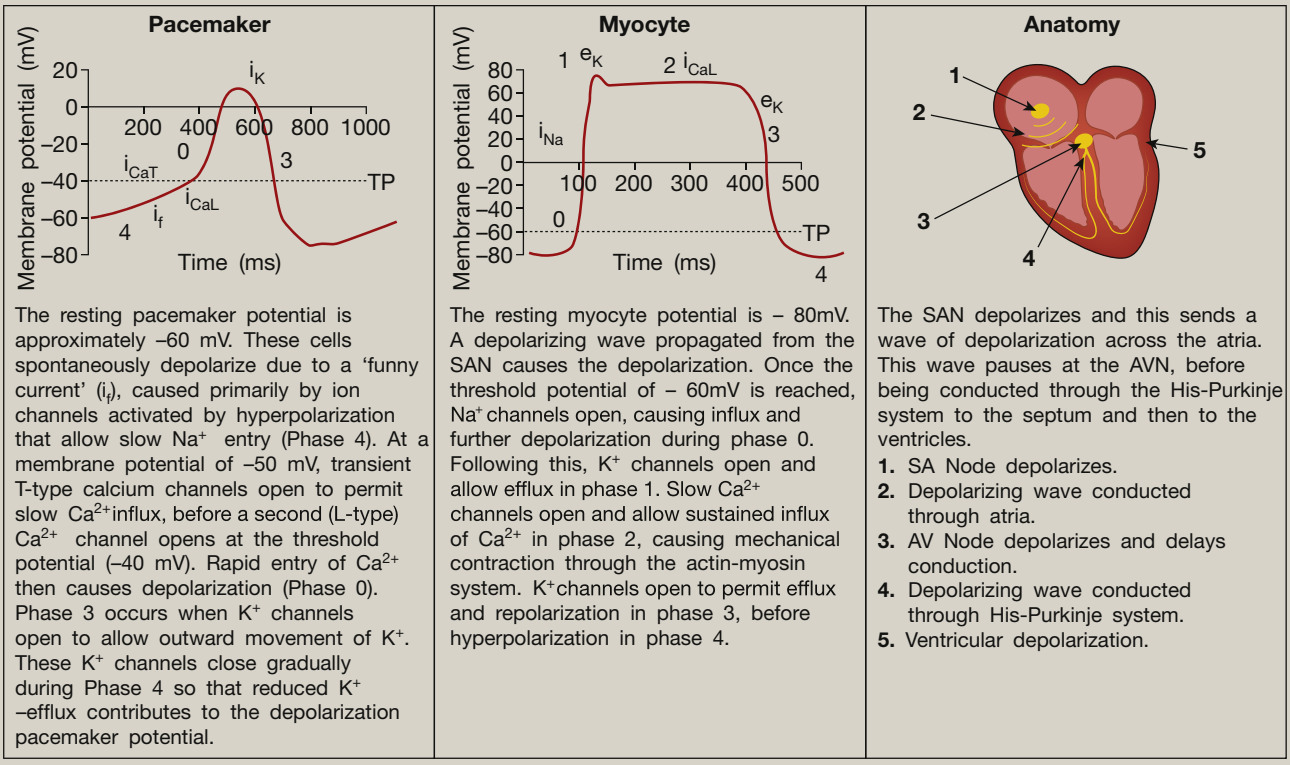
Link between myocardial contraction, electrical activity and contraction



The resting pacemaker potential is approximately –60 mV. These cells spontaneously depolarize due to a 'funny current' (i_f), caused primarily by ion channels activated by hyperpolarization that allow slow Na^+ entry (Phase 4). At a membrane potential of –50 mV, transient T-type calcium channels open to permit slow Ca^{2+}influx, before a second (L-type) Ca^{2+} channel opens at the threshold potential (–40 mV). Rapid entry of Ca^{2+} then causes depolarization (Phase 0). Phase 3 occurs when K^+ channels open to allow outward movement of K^+. These K^+ channels close gradually during Phase 4 so that reduced K^+ –efflux contributes to the depolarization pacemaker potential.

The resting myocyte potential is – 80mV. A depolarizing wave propagated from the SAN causes the depolarization. Once the threshold potential of – 60mV is reached, Na^+ channels open, causing influx and further depolarization during phase 0. Following this, K^+ channels open and allow efflux in phase 1. Slow Ca^{2+} channels open and allow sustained influx of Ca^{2+} in phase 2, causing mechanical contraction through the actin-myosin system. K^+channels open to permit efflux and repolarization in phase 3, before hyperpolarization in phase 4.

The SAN depolarizes and this sends a wave of depolarization across the atria. This wave pauses at the AVN, before being conducted through the His-Purkinje system to the septum and then to the ventricles.

1. SA Node depolarizes.
2. Depolarizing wave conducted through atria.
3. AV Node depolarizes and delays conduction.
4. Depolarizing wave conducted through His-Purkinje system.
5. Ventricular depolarization.

The overall membrane potential is determined by the balance of intracellular and extracellular ion concentrations. Na^+ and Ca^{2+} influx contribute to depolarization, whereas K^+ efflux contributes to hyperpolarisation and reduced excitability. Ca^{2+} and K^+ channels are influenced by autonomic nervous activity as well as hypoxia, temperature and drugs.
(ARP, absolute refractory period; RRP, relative refractory period; TP, threshold potential.)

Figure 1

K^+ efflux promotes hyperpolarization and membrane stability, reducing electrical activity. Most antiarrhythmics work directly or indirectly by blocking voltage-gated Na^+ or Ca^{2+} channels, ATPase pumps, or opening K^+ channels.

Antiarrhythmic targets within the myocardium

Hyperpolarization causes reduced membrane excitability, and thereby reduces the occurrence of tachyarrhythmias. Increasing K^+ efflux, or reducing the influx of Na^+ or Ca^{2+}, promotes myocardial stability through drug actions on voltage-gated K^+, Na^+ and Ca^{2+} channels on the myocardium, conducting system, and in the SAN and AVN. Ca^{2+} channel blockers (e.g. *verapamil*), K^+ channel openers (e.g. *nicorandil*), and local anaesthetics (e.g. *lidocaine*) target these channels and are used in the management of arrhythmias. Non-specific therapies (such as Magnesium) also modulate the activity of these channels. Na^+ and Ca^{2+} channel blockade opposes phase 0 of the pacemaker potential, whereas enhanced K^+ channel activity enhances Phase 3 (Figure 1).

The myocardium is innervated by sympathetic and parasympathetic nerve fibres, which act via G-protein coupled receptors. β_1-Adrenoceptors, coupled to G_S, promote increases in intracellular calcium via cyclic-AMP and protein kinase C acting on L-type Ca^{2+} channels, and the 'F' channels in pacemaker cells of the SAN. Blockade of β_1-adrenoceptors (e.g. by *metoprolol*) therefore reduces chronotropy, inotropy, dromotropy and automaticity for the control of rate compromising tachyarrhythmias. Stimulation (e.g. by *isoprenaline*) increases rate and is used in the treatment of bradyarrhythmias prior to pacing.

Muscarinic M_2 receptors, linked to G_i proteins, cause reduced cAMP and activity of the L-type calcium and 'F' channels, reducing heart rate. M_2 blockade (e.g. *atropine* or *glycopyrrolate*) is used in the treatment of bradyarrhythmias.

Adenosine receptors are expressed in cardiac myocytes and pacemaker cells (A_1) and coronary vascular smooth muscle (A_{2A}). A_1 receptor agonism by adenosine causes SAN and AVN blockade, and is used in the management of supraventricular tachycardias; however, the non-specific effects on A_{2A}, A_{2B} and A_3 receptors can cause flushing and chest discomfort.

Which drug to use?

Where compromised, tachyarrhythmia in the presence of syncope, instability, chest pain or cardiac failure, the priority is to restore a perfusing rhythm by synchronized electrical cardioversion. For emergency treatment of acute arrhythmias within

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