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Antiarrhythmic drugs

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Cardiac muscle is unique in that it has automated or pacemaker cells and non-automated (contractile) cells. Pacemaker cells are found in the sinoatrial (SA) node, atrioventricular (AV) node, and the conduction system of the heart, while contractile cells are found in the atria and ventricles. The cardiac action potential (AP) of both these cell groups differs and results from the sequential changes in membrane permeability to Na^+, K^+, and Ca^{2+} and the flow of these ions through ion channels.

Understanding the physiology of cardiac conduction enables the understanding of the pathophysiology of arrhythmogenesis and the targets of antiarrhythmic drugs (AADs). The Singh Vaughan-Williams framework is the simplest classification system for AADs and is based on the main mechanism of action of each drug. It has recently been expanded to include previously unclassified AADs and broaden the mechanisms of action. The pharmacology and clinical applications of commonly used AADs are discussed.

Keywords: antiarrhythmic, pharmacology, cardiac action potential, pacemaker potential, arrhythmogenesis, Singh Vaughan-Williams

Cardiac action potentials (APs)

The heart is different from other tissues as it consists of automated (pacemaker) and non-automated (contractile or cardiac) cells, each with a different morphology of the AP (Figure 1).[1-3] The cardiac AP results from the sequential changes in membrane permeability to Na^+, K^+, and Ca^{2+} and the flow of these ions through ion channels.[1-3]

Non-automated or contractile cells have a stable resting membrane potential (RMP) of -90 mV.[2,3] The AP is divided into five phases based on the sequential changes in the permeability of Na^+, K^+, and Ca^{2+} flow via their respective ion channels.[1,3] There are two types of Ca^{2+} channels in the heart involved in the cardiac AP: L-type (low-threshold) and T-type (transient).[3,5] Figure 2 illustrates the phases of the AP and the action of AADs at each phase.

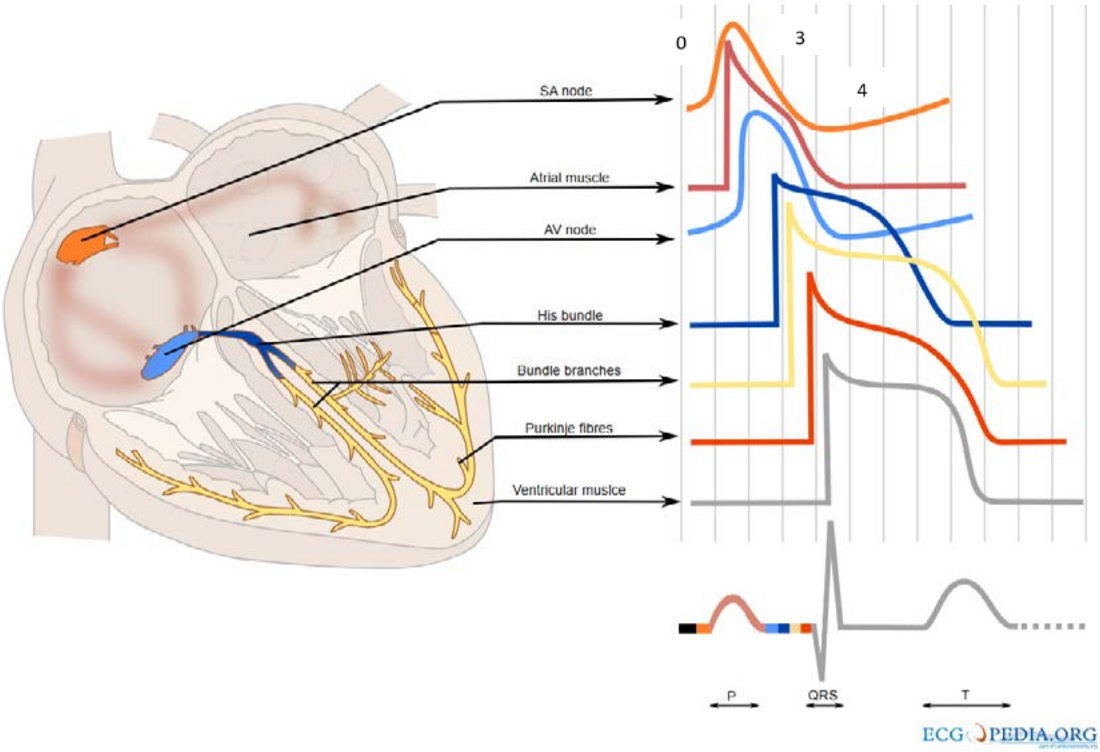

Figure 1: Cardiac APs in different parts of the heart; the phases of the pacemaker APs at the SA node are annotated[4]

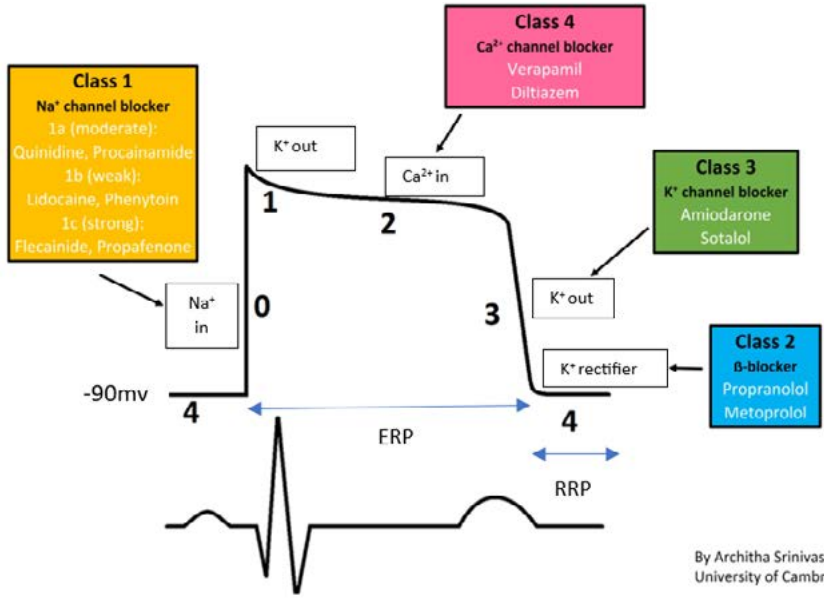

Figure 2: Cardiac AP of a contractile cell and AAD action[6]
ERP – effective refractory period, RRP – relative refractory period

Phase 0 represents rapid depolarisation due to a rapid increase in Na^+ conductance via fast voltage-gated Na^+ ion channels (I_{Na}), resulting in a membrane potential of +30 mV.[1,3,7] The conductance of K^+ decreases.[1] The rate of depolarisation depends on the conduction velocity of the AP.[8] It corresponds with the R wave on the electrocardiogram (ECG).[1,3]

Phase 1 is the "notch" on the AP and represents early transient repolarisation due to the rapid decrease in Na^+ permeability and increased permeability of K^+ ions out of the cell via voltage-gated K^+ channels (I_{to}).[1,3,7] The Na^+ ion channels are in an inactivated state at this time and only enter the active state after repolarisation.[8]

Phase 2 represents the plateau phase and corresponds with the ST segment on the ECG. Voltage-gated L-type Ca^{2+} ion channels (I_{CaL}) open and Ca^{2+} enters the cell during this phase, maintaining depolarisation.[1,3] The Ca^{2+} entering the cell is balanced by K^+ efflux (I_{Ks} and I_{Kr} – see below).[7] The conductance of Na^+ slowly declines.[3] In pathophysiological states, phase 2 of the AP can be prolonged due to continued Na^+ inflow via late Na^+ conductance channels (I_{NaL}).[8] Class Id agents specifically target this channel.[9]

Phase 3 represents the repolarisation phase due to K^+ efflux out of the cell and corresponds with the T wave on the ECG. K^+ efflux occurs via voltage-gated slow delayed rectifier currents (I_{Ks}) and hERG rapid delayed rectifier current K^+ channels (I_{Kr}).[10] Na^+ channels remain closed until a threshold of -65 mV is reached (phase 2). No impulses can be conducted during this time regardless of the strength (effective refractory period - ERP). Once the RMP falls below -65 mV, impulses may be conducted if sufficiently strong (relative refractory period - RRP).[1]

Phase 4 represents the RMP. Na^+ moves into the cell and K^+ moves out via ATPase-dependent ionic pumps to restore the RMP.[1]

Automated cells can be found in the SA node, as well as atrial conduction pathways, parts of the AV node, and the His-Purkinje system.[1] The SA node has the fastest spontaneous depolarisation rate of the automated cells and determines the heart rate.[2] The maximum negative RMP of the SA node is between -50 mV and -70 mV, which is lower than in contractile cells.[1,2] The phases of the AP in the SA node are shown in Figure 1 (phases 0, 3 and 4).

The SA node AP has an unstable RMP and there is no phase 1 or phase 2.[1] Depolarisation is initiated by the inward flow of Na^+ and K^+ (I_f or funny current) via hyperpolarisation-activated cyclic nucleotide-gated (HCN) ion channels, and this determines the automaticity of the SA node (phase 4).[8] Slow, spontaneous inward Ca^{2+} flow via voltage-gated T-type Ca^{2+} channels (I_{CaT}) determines the upstroke of the AP (phase 0).[2] Depolarisation occurs at a RMP of -60 mV (phase 0) and is produced by opening the voltage-gated L-type Ca^{2+} channels (I_{CaL}).[3] It is less rapid than in contractile cells and does not have a plateau phase.[1] Repolarisation occurs after depolarisation due to the inactivation of Ca^{2+} channels and conductance of K^+ via the inward rectifier current channel (I_{K1}) until the maximum negative RMP is achieved again (phase 3).[2,3,8,10] Na^+ conductance changes very little.[2,3]

Mechanisms of arrhythmogenesis

Arrhythmias can occur because of impulse generation or conduction problems, and may be classified as bradyarrhythmias or tachyarrhythmias.[8] Bradyarrhythmias arise from the lack of generation of APs from the SA node or impaired conduction from the atria to the ventricles via the AV node or bundle of His.[8] Tachyarrhythmias can occur due to enhanced automaticity, triggered automaticity, or the reentry phenomenon.[8] Transmural dispersion of repolarisation (TDR) can also predispose to arrhythmia development.[8]

Enhanced automaticity may be normal resulting from vagolytic medication, β-adrenergic stimulation, mechanical stretch, or hypokalaemia.[8] This causes an increase in the upslope of phase

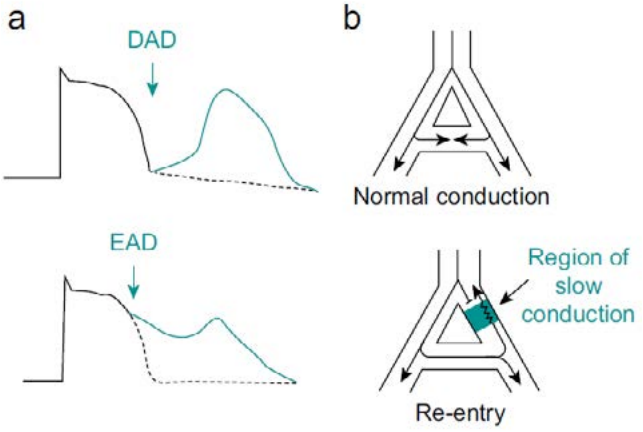

Figure 3: Triggered automaticity and the reentry phenomenon[8]

4 of the pacemaker potential in the SA node, stimulating a faster heart rate.[8] However, enhanced abnormal automaticity occurs when injured myocytes other than in the SA node partially depolarise to a RMP between -60 mV and -40 mV, causing spontaneous depolarisation and ectopic atrial or ventricular tachycardias.[8]

Triggered automaticity may be delayed afterdepolarisations (DAD) or early afterdepolarisations (EAD) resulting from the initiation of a premature AP before the previous beat is complete (Figure 3a).[8] DADs occur during phase 4 of the AP due to an intracellular Ca^{2+} ion overload, which upregulates the Na^+/Ca^{2+} exchanger, bringing the membrane to a threshold potential and triggering a premature contraction.[8] Ca^{2+} overload can be caused by adrenergic stimulation, digoxin toxicity, or myocardial ischaemia.[8]

EADs occur during phase 3, prolonging the AP.[8] This is caused by Na^+ and Ca^{2+} movement into cells and less K^+ efflux out of cells.[8] Drugs or pathologies that inhibit K^+ channels can result in prolonged APs that manifest as a prolonged QT interval.[8] An important clinical consequence of EADs is the development of *torsade de pointes* ventricular tachycardia (VT).[8]

The reentry phenomenon occurs in regions of the heart where there is a structural (accessory pathway) or functional (depolarised from ischaemia) unidirectional block to conduction (Figure 3b).[8] Diseased regions slow conduction velocity and cannot propagate conduction orthograde, but APs can be conducted in a retrograde fashion when Na^+ channels are depolarised outside the ERP.[11] This creates a circular pathway of high-frequency impulses that can be propagated throughout the heart.[11] Pharmacological management that treats the reentry phenomena alters either the timing of conduction or the length of the ERP.[11] AV nodal blocking agents, such as calcium-channel blockers, adenosine, and β-blockers are effective at terminating supraventricular tachycardias (SVTs) involving reentry circuits.[11]

Repolarisation times differ in different regions of the heart resulting in varying durations of APs.[8] These differences are due to intrinsic differences between cell types (e.g. epicardial, endocardial, and M cells) and different ion channel distributions.[8] Drugs that prolong the QT interval or the presence of abnormal tissue preferentially prolong APs in the M cells where the APs are already longer.[8] This increases TDR, predisposing to EADs or reentry circuits that can cause arrhythmias.[8] Increased TDR in patients with long QT syndrome predisposes the development of *torsade de pointes* VT.[8]

Drugs that prolong the QT interval are shown in Table I. Phenylephrine and metaraminol do not affect the QT interval and are safe adrenergic agents to use.[8] Ondansetron has been used safely, although other 5-HT3 antagonists should be avoided.[8]

Table I: Drugs that prolong the QT interval[1,8]

Class of drug	Examples
Adrenergic drugs	Adrenalin, noradrenalin, dopamine, dobutamine, salbutamol, ephedrine
Antiarrhythmic drugs	Quinidine, procainamide, sotalol, amiodarone, ibutilide, dofetilide, isradipine
Antibiotics	Azithromycin, clarithromycin, erythromycin, moxifloxacin, ofloxacin, trimethoprim, sulfamethoxazole
Antifungals	Ketoconazole, fluconazole, itraconazole
Antiemetics	Chlorpromazine, droperidol, domperidone, metoclopramide
Antihistamines	Terfenadine, astemizole
Antipsychotics	Haloperidol, risperidone, clozapine
Anticholinergic agents	Atropine, glycopyrrolate, neostigmine-glycopyrrolate combination
Intravenous anaesthetic agents	Ketamine
Neuromuscular blocking agents	Pancuronium, suxamethonium
Opioids	Methadone, sufentanil
Chemotherapeutics & immunosuppressants	Tamoxifen, tacrolimus
Oxytocic agents	Oxytocin

The mechanisms of arrhythmia generation in the cardiac myocyte cells and the pacemaker cells are summarised in Figure 4.

Ionic changes in arrhythmias

Autonomic nervous system effects alter the permeability of ion channels, resulting in physiological effects.[3] Sympathetic nervous system stimulation leads to the opening of HCN channels with the increased inwards Na^+ and K^+ inflow via the I_f current.[8] Phase 4 of the pacemaker AP is steepened and Ca^{2+} simultaneously enters into cells via I_{CaL}, predisposing to arrhythmias caused by triggered automaticity.[3,8] Conversely, parasympathetic stimulation results in hyperpolarisation of the cell membrane by increased permeability to K^+, inhibiting cardiac activity.[3]

The I_{CaL} channels are predominant in the heart and open when the membrane is depolarised to -10 mV (phase 0); they are also responsible for the maintenance of the plateau phase (phase 2) of the cardiac AP.[3,8] Ca^{2+} channel antagonists block I_{CaL} channels.[3] Verapamil and diltiazem block open and inactivated Ca^{2+} channels and cause a use-dependent block of conduction in pacemaker cells with Ca^{2+}-dependent APs.[5] Dihydropyridines (e.g. nifedipine or amlodipine) block open Ca^{2+} channels.

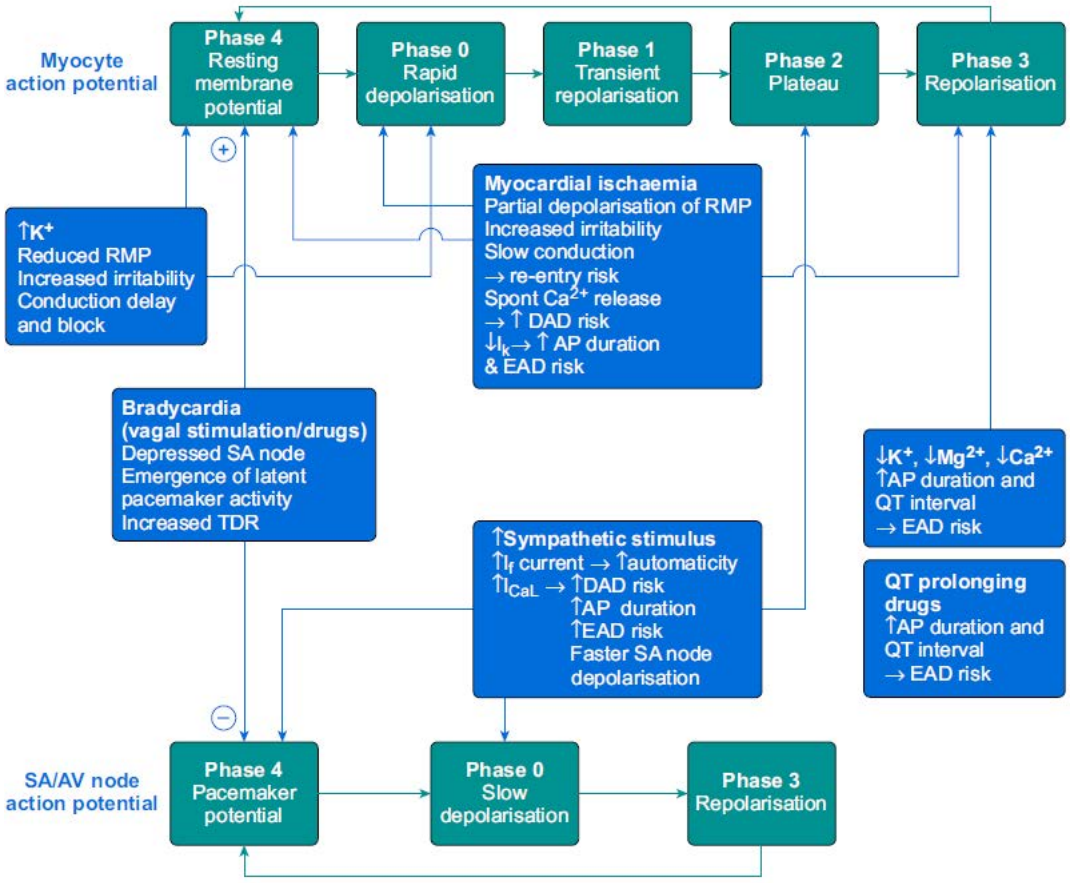

Figure 4: Mechanisms of arrhythmia generation (reproduced with permission)[8]

Catecholamines increase the activation of the I_{CaL} channels via β-stimulation of membrane adenylyl cyclase and increase intracellular cyclic adenosine monophosphate (AMP) production, thereby increasing cardiac activity.[3] The I_{CaT} channels are not affected by catecholamines as they open more briefly at a negative membrane potential (-40 to -70 mV).[3]

Electrolyte disturbances can cause numerous changes at the ionic level of the cell membrane and induce several arrhythmias. Hypokalaemia hyperpolarises the RMP, decreasing membrane excitability, depressing automaticity and causing AV block.[8] K^+ < 2.5 mmol/L inhibits delayed rectifier K^+ channels (I_{Kr}), resulting in a prolongation of the AP and delayed repolarisation.[12] The ERP is prolonged at a time when cardiac tissue is increasingly excitable with an increased risk of developing afterdepolarisations (both EADs and DADs).[8,12] Atrial fibrillation (AF) and atrial flutter are common arrhythmias associated with hypokalaemia.[8]

Hyperkalaemia results in increased membrane permeability to K^+ ions via I_{Kr} and I_{K1} channels, accelerating repolarisation and resulting in a shortening of the AP duration and the refractory period.[8,12] However, as K^+ levels continue to rise (K^+ > 7 mmol/L), the RMP becomes partly depolarised, decreasing excitability and inducing refractoriness, prolonging the ERP.[8] The conduction velocity slows and the slope of phase 0 decreases as the number of Na^+ channels available for depolarisation are reduced.[8] Severe hyperkalaemia is associated with conduction blocks, including atypical bundle branch blocks, intraventricular conduction delays, idioventricular rhythms, asystole, VT, and ventricular fibrillation (VF).[8,12]

Hypocalcaemia (ionised Ca^{2+} < 1.17 mmol/L) can exacerbate the arrhythmogenic effects of hypokalaemia.[8] Phase 2 is prolonged due to a slow increase in Ca^{2+} concentration, thus causing a prolonged AP duration and prolonged ERP.[12] EADs can develop that predispose to *torsade de pointes* VT.[8] Hypercalcaemia (ionised Ca^{2+} > 1.4 mmol/L) shortens phase 2, thus shortening the AP duration and ERP.[12] Elevated Ca^{2+} levels have a stabilising effect on the membrane with limited clinical effects.[8,12]

Hypomagnesaemia (< 0.74 mmol/L) depolarises the membrane due to a decrease in the Na^+/K^+-ATPase pump activity.[8] This slows depolarisation and decreases outward K^+ current flow, resulting in a prolonged QT interval, which increases the risk of ventricular ectopy and *torsade de pointes* VT.[8] Hypermagnesemia, if severe (> 4 mmol/L), can act as a calcium antagonist and depress AV and intraventricular conduction, which may cause bradycardia, hypotension, and conduction defects.[8,12] Administration of Mg^{2+} causes the following effects: prolongs SA node recovery time, prolongs ERP, prolongs QRS duration, suppresses triggered activity, and it is an effective treatment of *torsade de pointes* VT.[12]

Pharmacological principles of antiarrhythmic agents

Mechanisms of arrhythmia management (Table II) include the suppression of automaticity, prevention of triggered automaticity, and alterations to conduction velocity and refractoriness of tissue to prevent the reentry phenomena.[10]

Table II: Mechanisms of arrhythmia prevention and management[10]

Mechanism	Effect	Example
Suppression of enhanced automaticity		
Hyperpolarisation of RMP	Increase inward K^+ ion effect during phase 4 of AP	Adenosine
Decrease slope of spontaneous pacemaker cells	Reduce the inward flow of cations during phase 4 of the pacemaker potential	β-blockers (Class II)
Increase threshold potential	Na^+ or Ca^{2+} channel blockade	Class I agents Ca^{2+} channel blocker (Class IV)
Increase AP duration	Block flow of ions via K^+ rectifier channels	Class III agents
Inhibition of triggered automaticity		
DADs prevented by reducing the possibility of the membrane reaching threshold potential	Reduce activity of Ca^{2+} ion channels by reducing Na^+/Ca^{2+} exchanger	Directly: β-blockers (Class II) Indirectly: Ca^{2+} channel blocker (Class IV)
EADs prevented by shortening the AP duration	Effect on ionic channels during phase 3 of AP	β-blockers (Class II), Ca^{2+} channel blockers (Class IV), Na^+ channel blockers (Class Ib)
Inhibition of reentry phenomena		
Increase the ERP	Na^+ channel recovery slowed from an inactivated state Block K^+ rectifier channels	Class Ia & Ic agents Class III
Increase conduction velocity in affected regions	Bind inactivated Na^+ channels with very rapid dissociation causing Na^+ channels to recover rapidly, reducing AP duration	Lignocaine (Class Ib)

Most AADs work on channels that are active or inactive, not those in a resting state (termed user dependency).[10] Thus, agents are more effective during tachycardia or when the RMP is not at a normal level (such as in diseased tissue). With increasing doses, pro-arrhythmogenicity can result due to ion channels in normal tissue being affected.[10]

Classification of antiarrhythmic agents

The simplest classification of AADs is the Singh Vaughan-Williams classification, which divides agents into four classes based on the primary mechanism of action.[1,2] A fifth group is described in some texts.[7]

There are several limitations to this classification system. Some drugs have multiple mechanisms of action and do not fit into one class only.[13] Active drug metabolites may have different mechanisms to the parent drug.[1] Some AADs were not originally included and do not fit into this classification system.[13] AP duration prolongation can occur from multiple ion channel effects, which is not considered.[13] The mechanism of arrhythmogenesis is not taken into account.[13] Classification is based on electrophysiological effects on normal tissue and not diseased tissue or tissue chronically exposed to AADs.[13] The American Heart Association updated the Singh Vaughan-Williams classification in 2018, retaining the four core classes but expanding the classification based on newer and potential AADs and assigning previously unclassified AADs into these classes (Table III).[1,7,9,10,13] Changes to the original classification are italicised in Table III.

The Sicilian Gambit classification system was described in 1991, providing a more holistic approach to AADs from an electrophysiological, electrocardiographic, and clinical perspective.[13] The mechanism of arrhythmogenesis is considered rather than the mechanism of action of the AAD.[13] Novel approaches to the choice of AAD prescription consider the vulnerable electrophysiological parameters present and aim to address this directly.[13]

AADs can also be classified according to their site of action, as described below:[1,2]

- Supraventricular tachyarrhythmias: quinidine, procainamide, disopyramide, propafenone, β-blockers
- Ventricular tachyarrhythmias: lignocaine, mexiletine
- SA node: atropine, isoproterenol
- AV node: digoxin, verapamil, β-blockers, atropine, isoproterenol
- Accessory pathway: β-blockers, amiodarone, disopyramide

The mechanism of action of AADs on the phases of the cardiac and pacemaker APs is schematically shown in Figure 5.[10]

Clinical pharmacology

Most AADs have a pro-arrhythmogenic potential, predominantly from effects on the QT interval.[7] Prolongation of the QT interval can increase the risk of *torsade de pointes* VT.[7] AV block and bradycardia can occur from several AADs as a result of effects on automaticity and conduction velocity.[7]

Other side effects specific to certain AADs can occur. Procainamide can induce reversible systemic lupus erythematosus.[1] Disopyramide can cause anticholinergic effects, including mydriasis, urinary retention, dry skin, thirst, and agitation, limiting the tolerability of this drug.[7] Dronedarone can cause acute fulminant liver failure, requiring transplantation.[1]

Several AADs are commonly used for the management of acute arrhythmias. The clinical pharmacology of selected AADs is described below with doses shown in Table IV.

Table III: Updated Singh Vaughan-Williams classification of AADs[1,7,9,10,13]

Class	Pharmacological target	Electrophysiological effects	AP/ERP duration	ECG effects	Drugs	Clinical applications & mechanisms
HCN channel blockers						
0	*HCN channel modulators*	*Inhibition of I_f and cation inflow, reduced SA node phase 4 pacemaker depolarisation rate*	*0*	*↑ RR intervals*	*Ivabradine*	*HR control in angina and stable cardiac failure*
Voltage-gated Na^+ channel blockers (Ic > Ia > Ib)						
Ia	Block fast I_{Na} in open state, intermediate dissociation kinetics	↓ rate of depolarisation (phase 0), reduced excitability of non-nodal tissue	↑ AP ↑ ERP	↑ PR, ↑ QRS, ↑ QT	Quinidine, procainamide, disopyramide	SVT, AF, VT/VF ↓ reentrant tendency ↓ automaticity
Ib	Block I_{Na} in open state, fast dissociation kinetics	Little effect on phase 0, suppression of phase 4 in pacemaker cells	↓ AP ↓ ERP	↓ QT (slight)	Lignocaine, mexiletine, phenytoin	VT, particularly after MI ↓ reentrant tendency Reduced DADs
Ic	Block I_{Na} in inactivated state, slow dissociation kinetics	Marked ↓ phase 0, slows conduction velocity, reduces excitability	No effect on AP & ERP	↑ PR, ↑ QRS, no effect on QT	Propafenone, flecainide	AF and atrial flutter ↓ reentrant tendency Reduced DADs
Id	*Late Na^+ channel blocker (I_{NaL})*	*Decreased AP recovery time, ↑ refractoriness of Na^+ channels*	*↓ AP* *↓ ERP*	*↓ QT*	*Ranolazine*	*AF treatment & prevention* *Reduction in EADs*
Autonomic modulators						
IIa	Nonselective β-blockers (NS) and selective β1 blockade (S)	Slowed SA node pacemaker rate caused by reduced I_f & I_{CaL}, reduced automaticity (phase 4)	↓ AP ↑ ERP	↑ PR, ↓/0 QT	NS: carvedilol, propranolol S: atenolol, esmolol, bisoprolol, metoprolol	Prevention of SVT Rate control of atrial and ventricular tachyarrhythmias Reduced EADs & DADs
IIb	*Nonselective β-agonist*	*Activate Ca^{2+} entry and sarcoplasmic-mediated Ca^{2+} release*	*↓ AP*	*↓ PR, ↓ RR interval*	*Isoproterenol*	*Ventricular escape rhythm* *Complete AV block*
IIc	*Muscarinic M2 receptor inhibitors*	*Inhibition of M2 receptors at SA node, increased automaticity, ↑ AV conduction*	*↓ AP*	*↓ PR, ↓ RR interval*	*Atropine, glycopyrrolate*	*Symptomatic sinus bradycardia* *Conduction block*
IId	*Muscarinic M2 receptor activators*	*Hyperpolarised SA node & reduced automaticity, reduced conduction* *Digoxin: inhibits Na/K-ATPase pump, ↑ Na^+/$Ca2^+$ intracellularly, prolonging phase 4 & phase 0 of AP*	*↓ AP*	*↑ PR, ↑ RR interval*	*Pilocarpine, carbachol, methacholine* *Digoxin*	*SVT*
IIe	*Adenosine A1 receptor activators*	*Activate inward K rectifier channels, hyperpolarising the SA node & decreasing automaticity; ↓Ca influx via I_{CaL}*	*↓ AP*	*↑ PR, ↑ RR interval*	*Adenosine*	*SVT* *Reduced EADs & DADs*
K^+ channel blockers/openers						
IIIa	Voltage-dependent K^+ channel blockers: NS, rapid K^+ (R, hERG) or ultra-rapid K^+ (UR) current blockers	Block multiple K^+ channel targets resulting in prolonged AP recovery time, ↑ refractory period with ↓ reentrant tendency Amiodarone: sympatholytic, Na^+/Ca^{2+} channel blockade	↑ AP ↑ ERP	NS: ↑ PR, ↑ QRS, ↑ QT R: ↑ QT UR: ↑ QT	NS: amiodarone, dronedarone R: ibutilide, sotalol UR: vernakalant	NS: AF, VT, VF R: VT, WPW associated AF UR: cardioversion of AF
IIIb	*Metabolically dependent K^+ channel blockers*	*Open ATP-sensitive K^+ channels*	*↓ AP recovery time*	*↓ QT*	*Nicorandil, pinacidil*	*Stable angina* *Hypertension (investigational)*
Ca^{2+} handling modulators						
IVa	Surface membrane Ca^{2+} channel blockers: nonselective or I_{CaL}	Decrease the slope of phases 0 & 4 and prolong phase 2 of the cardiac AP, inhibits SA node pacing	↑ AP ↑ ERP	↑ PR	NS: bepridil, falipamil I_{CaL}: verapamil, diltiazem	SVT SVT, rate control AF & atrial flutter Reduced EAD & DAD triggered arrhythmias

IVb	*Intracellular Ca^{2+} channel blockers*	*Reduced sarcoplasmic Ca^{2+} release*	*0/↑ AP*	*↑ PR, ↑ QRS, ↑ QT*	*Propafenone, flecainide*	*Catecholaminergic Polymorphic VT Reduced EAD & DAD triggered arrhythmias*
V	*Mechanosensitive channel blockers*	*Intracellular Ca^{2+} signalling*			*Drugs under investigation*	*Reduced EAD & DAD triggered arrhythmias*
VI	*Gap junction channel blockers*	*Reduced cell-cell coupling and AP propagation*			*Drugs under investigation*	*Reduced conduction*
VII	*Upstream target modulators*	*Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodelling*			*ACEi, ARBs Statins, omega-3 fatty acids*	*Reduce AP conduction and ↑ reentry tendency*

AF – atrial fibrillation, AP – action potential, AV – atrioventricular, DAD – delayed afterdepolarisations, EAD – early afterdepolarisations, ERP – effective refractory period, SVT – supraventricular tachycardia, VT – ventricular tachycardia, VF – ventricular fibrillation, WPW – Wolff-Parkinson-White, 0 - no effect

Lignocaine[1,10]

Lignocaine is a Class Ib agent and blocks fast-conducting Na^+ channels in the AV node and conducting tissue. It is the first-line agent for the treatment of VT and VF and is ineffective for atrial arrhythmias.

Lignocaine undergoes hepatic metabolism and drug concentration can be affected by other drugs that affect hepatic cytochrome oxidase metabolism, by low cardiac output states, or hepatic dysfunction. Lignocaine has a rapid onset of action with a wide therapeutic index. In therapeutic doses, it has a minimal effect on cardiac contractility and vascular tone and does not affect the QRS duration, ERP, and QT interval. The main adverse effect is central nervous system excitation, which can occur in high doses or with prolonged infusions. This should be managed as local anaesthetic systemic toxicity and should be treated with Intralipid administration.

β-blockers[1,7,10,14]

β-blockers are Class IIa agents and can be selective or nonselective β-adrenergic antagonists. They can be used for the treatment of supraventricular tachyarrhythmias, ventricular arrhythmias (VT, polymorphic VT or VF), or for rate control in AF, atrial flutter, or orthodromic Wolff-Parkinson-White (WPW) syndrome.

β_1-receptor antagonism decreases automaticity in the heart and slows down conduction in the SA and AV nodes and ventricles. The decreased heart rate reduces myocardial oxygen demand, which could be beneficial in patients with coronary artery disease.

Side effects of β-blockers include myocardial depression, bronchospasm, AV block, bradycardia, and worsening of peripheral vascular symptoms. β_1-selective blockers (bisoprolol, esmolol, atenolol, metoprolol) may limit the adverse effects of bronchial reactivity and peripheral vasculature.

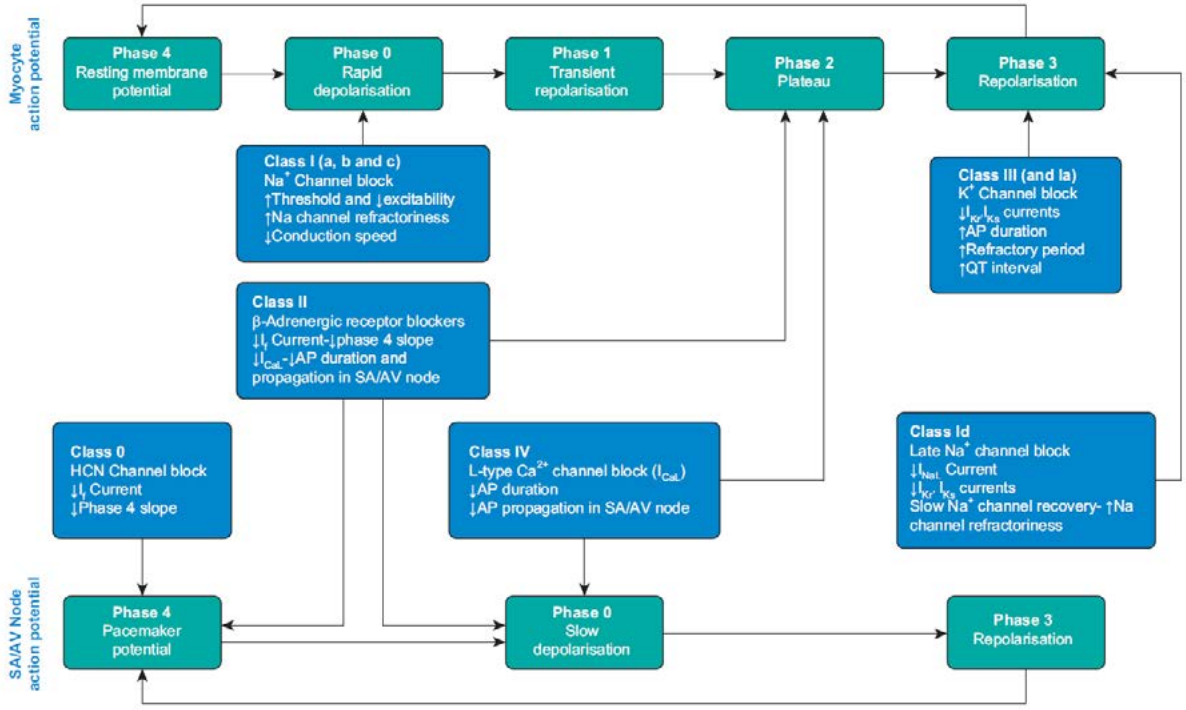

Figure 5: Schematic diagram of the mechanism of action of AADs (reproduced with permission)[10]

Esmolol is an ultra-short-acting β_1-selective blocker with negative chronotropic, dromotropic, and inotropic effects. It has a distribution half-life of two minutes and a clinical effect lasting 20 minutes. Metabolism occurs by hydrolysis by red cell esterase, its metabolites are inactive and are renally excreted. It is a water-soluble drug and does not cross the placenta or the blood-brain barrier. Propranolol is a long-acting nonselective β-blocker that is highly fat-soluble with central effects. It has a half-life of 3–4 hours and undergoes an extensive first pass effect (oral administration). It can be used during the management of thyroid storm, provided the patient does not exhibit features of cardiac failure. Sotalol is a unique nonselective β-blocker with Class III effects. It can prolong the QT interval and may be pro-arrhythmogenic.

Digoxin[1,7,10,15]

Digoxin inhibits the Na^+/K^+ -ATPase pump increasing the intracellular concentration of Na^+. This reduces the 3 Na^+/Ca^{2+} exchanger, increasing intracellular Ca^{2+} and causing positive inotropy. Digoxin also suppresses the SA node (decreased phase 4) and delays conduction via the AV node making it negatively chronotropic and dromotropic. The vagolytic effect is caused by AV node refractoriness decreased by Ca^{2+} flow and increased K^+ flow in the AV node and atria.

Digoxin can be used in patients with AF with impaired cardiac function, reentrant arrhythmias involving the AV node, and control of rapid ventricular response rate in AF. Digoxin is contraindicated in patients with heart block, hypertrophic obstructive cardiomyopathy, and preexcitation syndromes (e.g. WPW). Slow AV conduction can result in rapid conduction via an accessory pathway in WPW that can lead to cardiovascular collapse.

Digoxin has a long half-life of 36 hours and is renally excreted. It has a narrow therapeutic index and should be monitored in patients with renal dysfunction, low body mass index, or in elderly patients. Toxicity occurs at plasma levels > 2.5 ng/ml and can be precipitated by electrolyte abnormalities (hypercalcaemia, hypokalaemia, or hypomagnesaemia), hypoxia, hypoventilation, or in combination with other AADs. Toxicity can result in nausea, vomiting, visual abnormalities, delirium, and convulsions. Cardiac effects of toxicity may manifest early with bradycardia; however, ventricular bigeminy or trigeminy, VT, paroxysmal atrial tachycardia (with variable blocks), or VF can occur. Digoxin toxicity is treated with lignocaine (tachyarrhythmias), atropine (bradyarrhythmias), or a pacemaker can be temporarily used. Hypokalaemia must be urgently corrected. Immunotherapy with anti-digoxin antibody fragments can be considered.

Adenosine[1,7,10]

Adenosine acts on adenosine-sensitive K^+ channels, increasing conductance and shortening the AP. It also decreases Ca^{2+} conductance resulting in a hyperpolarised membrane at the SA and AV nodes, thus decreasing automaticity and slowing conduction via the AV node. It is negatively chronotropic and dromotropic. It is used in AV reentry tachycardias and orthodromic WPW syndrome. It can be used to diagnose or terminate SVTs and to unmask atrial flutter or AF. As there are no adenosine-sensitive K^+ channels in the ventricles, it is not effective for ventricular arrhythmias.

Adenosine has a short half-life of 10 seconds as it is rapidly taken up into red blood cells. It should be avoided in patients with a heart block. It can cause flushing, chest pain, AV block, and transient asystole. It may occasionally cause AF or bronchospasm.

Amiodarone[1,7,10]

Amiodarone is unique among the AADs as it has activity across all the classes. It predominantly inhibits nonselective K^+ channel conductance (I_{Kr} and I_{Ks}), but also inhibits fast Na^+ channels and Ca^{2+} channels, and blocks β-adrenergic blockers in the SA and AV nodes, accessory pathways and ventricular tissue. It can be used for both atrial (SVT, AF, flutter) and ventricular (monomorphic or polymorphic VT) arrhythmias, as well as arrhythmias caused by accessory pathways. It forms part of the cardiac arrest algorithm for VF or pulseless VT unresponsive to defibrillation.

An intravenous loading dose is needed to achieve a steady-state concentration. It is highly lipid soluble and protein bound with a long elimination half-life of 29 days. It is metabolised in the liver with an active metabolite as effective as the parent drug. Amiodarone can prolong the QT interval and should be used with caution in combination with other drugs that prolong the QT interval (Table I). Drugs that potentiate the hepatic cytochromes that metabolise amiodarone can affect its levels. Amiodarone can also inhibit cytochromes causing increased levels of warfarin and digoxin.

Amiodarone is a negative inotrope and vasodilator. It can result in bradycardia and hypotension that can be potentiated by coadministration with other AADs. Acute pulmonary toxicity is a life-threatening side effect resembling acute respiratory distress syndrome. Amiodarone can also be pro-arrhythmogenic causing VT, VF or *torsade de pointes* , although the potential for this is low. Chronic side effects include chronic pulmonary toxicity, hepatic dysfunction, ocular toxicity (corneal opacities, photosensitivity, optic neuritis, decreased visual acuity), hyper- or hypothyroidism, and peripheral neuropathy.

Vernakalant[10]

Although classified as a Class III AAD, vernakalant acts on Na^+ and delayed K^+ rectifier channels, prolonging the ERP and AP. The QT interval is marginally prolonged and it does not increase the risk of *torsade de pointes*. Vernakalant can be used as pharmacological cardioversion in acute AF as it is atrium-specific in action. Bradycardia and hypotension are side effects.

Sotalol[10]

Sotalol is a selective K^+ channel blocker acting at the hERG K^+ channel. It is used for the management of VT and the maintenance of sinus rhythm in AF. There is a risk of developing *torsade de pointes* due to its prolongation of the QT interval, and it can cause nonselective β-blockade.

Calcium-channel blockers[1,7,10]

Non-dihydropyridine Ca^{2+} channel blockers have antiarrhythmic effects. Verapamil is classified as a phenylalkylamine and diltiazem is a benzothiazepine. Their effects are exerted by blockade of the L-type Ca^{2+} channels in the SA and AV nodes, depressing automaticity and decreasing conduction speed. Verapamil has a limited effect on AV conduction at low heart rates.

Ca^{2+} channel blockers are effective at reducing the ventricular response rate in AF or atrial flutter and for the management of reentry tachycardias. Ca^{2+} channel blockers are contraindicated in preexcitation syndromes as they do not suppress conduction via accessory pathways; they should be used with caution in patients with heart failure as they can cause myocardial depression. They are not effective in managing ventricular arrhythmias.

Verapamil can cause side effects including AV block, bradycardia, oedema, and constipation, while diltiazem can cause oedema, headaches, and dizziness.

Magnesium[10,12]

The antiarrhythmic mechanism of magnesium may be related to the membrane stabilising properties due to Ca^{2+} and K^{+} channel blockade. It also suppresses triggered activity. It does not affect the QT interval. Magnesium is indicated for the prevention or treatment of *torsade de pointes*, control of ventricular rate response in AF, and the management of arrhythmias associated with digoxin toxicity.

The doses of commonly used AADs are shown in Table IV.

Table IV: Dosages of commonly used intravenous AADs in adults[1,10,14]

Drug	Dose
Adenosine	6 mg as a rapid bolus 6–12 mg; repeat if needed
Amiodarone	Cardiac arrest: first dose 300 mg bolus, second dose 150 mg bolus 300 mg loading dose followed by 900 mg as an infusion over 24 hours
Atropine	600 µg bolus, up to a maximum of 3 mg
Digoxin	0.25–0.5 mg bolus or 10–20 µg/kg Maximum 1 mg per 24 hours
Diltiazem	20 mg
Esmolol	250–500 µg/kg bolus Infusion: 50–200 µg/kg/min
Lignocaine	Cardiac arrest: first dose 1–1.5 mg/kg, second dose 0.5–0.75 mg/kg Bolus: 2 mg/kg followed by infusion of 1–4 mg/min
Magnesium	1–2 g magnesium sulphate
Propranolol	1 mg increments up to 5–10 mg
Vernakalant	3 mg/kg bolus, repeat dose of 2 mg/kg after 10 minutes
Verapamil	75–150 µg/kg over 1–3 minutes or 5–10 mg Infusion: 5 µg/kg/min

Management of perioperative arrhythmias

The precipitant of the arrhythmia must be determined, and the risk versus the benefit of therapy must be considered before initiation an AAD. Unstable tachyarrhythmias must be treated with synchronised cardioversion with concomitant amiodarone administration.[7] Amiodarone has a low pro-arrhythmogenic potential and it is effective in managing both atrial and ventricular tachyarrhythmias.[7]

AF is a common arrhythmia in the perioperative period with the majority of episodes being self-limiting. Cardioversion should be reserved for AF with haemodynamic instability. β-blockers are the first-line agent for haemodynamically stable patients.[7] Digoxin in combination with β-blockers or Ca^{2+} channel blockers can be considered if the patient has impaired ventricular function.[7] Amiodarone or vernakalant can be considered for pharmacological cardioversion of acute AF to restore sinus rhythm when electrical cardioversion is not indicated.[7]

Conclusion

AADs can be classified using the updated Singh Vaughan-Williams classification based on the mechanism of action of each drug. Potential uses and side effects can be determined from the electrophysiological effects of each drug. In the perioperative period, patients on chronic AADs may be encountered or commonly used AADs may be needed for the management of perioperative arrhythmias. An understanding of the physiology of cardiac conduction, the mechanisms of arrhythmogenesis, and the classification of AADs enables the rational use of therapy and recognition of adverse effects.

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References

1. Hosking CA, Dippenaar JM. Antiarrhythmic agents. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 398-419.
2. Peck TE, Hill SA, Williams M. Pharmacology for anaesthesia and intensive care. 3rd ed. United Kingdom: Cambridge University Press; 2008. https://doi.org/10.1017/CBO9780511722172.
3. Kam P, Power I. Principles of physiology for the anaesthetist. 2nd ed. New York: Oxford University Press; 2008.
4. ecgpedia.org [Internet]. Shapes of the cardiac action potential in the heart. Wikimedia Commons; 2011. Available from: https://commons.wikimedia.org/wiki/File:Shapes_of_the_cardiac_action_potential_in_the_heart.svg. Accessed 29 August 2023.
5. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185-94. https://doi.org/10.1161/CIRCEP.108.789081.
6. Srinivasan A. Drugs affecting the cardiac action potential [Internet]. In: commons.wikimedia.org. University of Cambridge; 2016. Available from: https://commons.wikimedia.org/wiki/File:Cardiac_action_potential.png. Accessed 28 August 2023.
7. King GS, Goyal A, Grigorova Y, Hashmi MF. Antiarrhythmic medications [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 February 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482322/. Accessed 29 August 2023.
8. Kim CJ, Lever N, Cooper JO. Antiarrhythmic drugs and anaesthesia: part 1. mechanisms of cardiac arrhythmias. BJA Educ. 2023;23(1):8-16. https://doi.org/10.1016/j.bjae.2022.11.001.
9. Lei M, Wu L, Terrar DA, Huang CL-H. Modernized classification of cardiac antiarrhythmic drugs. Circulation. 2018;138(17):1879-96. https://doi.org/10.1161/CIRCULATIONAHA.118.035455.
10. Kim CJ, Lever N, Cooper JO. Antiarrhythmic drugs and anaesthesia. Part 2: pharmacotherapy. BJA Educ. 2023;23(2):52-60. https://doi.org/10.1016/j.bjae.2022.11.005.

11. Klabunde RE. Cardiology physiology concepts: reentry [Internet]. 2022. Available from: https://cvphysiology.com/arrhythmias/a008c. Accessed 26 August 2023.
12. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Cardiol J. 2011;18(3):233-45.
13. Dan G-A, Martinez-Rubio A, Agewall S, et al. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). Europace. 2018;20(5):731-2an. https://doi.org/10.1093/europace/eux373.
14. Nienaber LN, Biccard BM. Autonomic nervous system. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 161-216.
15. Royse C, Radford HM, Milner A. Organ failure. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 217-46.