mechanisms of arrhythmia [created by Paul Young 02/10/07]

general

1. fast or slow?
2. ventricular or supraventricular?
3. compromised or not?
4. does arrhythmia need management?
5. what is underlying substrate predisposing?
6. what is trigger?
7. will arrhythmia recur?

bradycardia

- blocks and bradys are caused by impaired automaticity or conduction
- if one pacemaker fails another generally takes over at a lower rate
- factors that impair pacemaker automaticity or myocardial impulse conduction:
1. hypoxia
2. drugs (eg beta blockers)
3. electrolyte & pH disturbances
4. myocardial ischaemia
5. anything that enhances parasympathetic tone (eg carotid sinus hypersensitivity)

tachycardia

general mechanisms

1. reentrancy
2. increaed automaticity
3. triggered activity

Enhanced normal automaticity	Adrenergic stimulation
Abnormal automaticity	Ischaemia
Early after-depolarizations	Hypoxia
	Hypercapnia
	Catecholamines
	Class IA anti-arrhythmic drugs
	Class III anti-arrhythmic drugs
	Other drugs that prolong re-polarization
Delayed after-depolarizations	Digoxin toxicity
	Increased intracellular Na^+
	Decreased extracellular K^+
	Increased intracellular Ca^{2+}
	Intracellular Ca^{2+} overload
	Myocardial infarction
	Myocardial hypertrophy
	Reperfusion after ischaemia

reentrancy

- basic concept is that impulse reaches a point where it can go two ways (path A or path B). If path A is blocked, then impulse travels down path B only. However, when impulse reaches point where paths A & B re-join, impulse is retrogradely conducted up path A until it reaches then beginning and travels down path A creating a reentry loop
- the blocks that lead to rentry are often transient & timing dependent.
- sometimes they do not even occupy a fixed anatomical location (eg some forms of AF)

increased automaticity

- cardiac tissue has a normal tendency to spontaneous depolarisation
- a variety of insults can lead to 'ectopic activity' such as:
1. local ischaemia
2. hypokalaemia
3. drugs

triggered activity

- key concept is 'afterdepolarisation' where after a normal action potential, the cellular transmembrane potential suddenly swings positive again, & if the upswing is sufficient, a full depolarisation may occur again & again
- there are (at least) two different mechanisms of triggered activity and these result in:
(i) early afterdepolarisations (EADs)
(ii) delayed afterdepolarisations (DADs)
- EADs occur before repolarisation has finished - there is a sudden upswing in the transmembrane potential, which usually occurs in the context of a prolonged action potential - for example with partial blockade of Ik, the inwardly rectifying current that normally terminates the action potential
- DADs occur after membrane potential has returned to normal - here the upswing occurs due to raised intracellular calcium levels

Vaughan-Williams classification of anti-arrhythmics

class I - sodium channel blockade
class II - beta adrenergic blockade
class III - prolongation of repolarisation often due to potassium channel blockade
class IV - calcium channel blockade

	Mechanism of action	Effect on action potential	Indicative drugs
Class I	Sodium channel blockade	Depresses rate of rise of phase	
Class IA		Prolongs repolarization	Procainamide Disopyramide Quinidine
Class IB		Shortens repolarization	Lignocaine Mexiletine Phenytoin
Class IC		Minimal effect on repolarization	Flecainide Encainide Propafenone
Class II	β-adrenergic receptor blockers		Propranolol Atenolol Metoprolol Esmolol
Class III	Potassium channel blockers	Prolongs repolarization	Amiodarone Sotalol Ibutilide Bretylium
Class IV	Calcium channel blockers		Verapamil Diltiazem

factors contributing to arrhythmogenesis

Structural influences:
(i) myocardial infarction - acute, healed, aneurysm
(ii) hypertrophy
(iii) myopathic ventricle - dilation, fibrosis

Transient influences:
(i) transient ischaemia / reperfusion
(ii) systemic factors
- hypoxia
- acidosis
- electrolyte abnormalities
(iii) neurophysiological factors
- autonomic tone
- endogenous catecholamines
(iv) toxicity
- proarrythmic drugs
- exogenous catecholamines

factors facilitating anti-arrhythmic proarrythmia

Toxic blood levels due to excessive dose or reduced clearance from old age, heart failure, renal disease or hepatic disease
Severe left ventricular dysfunction. Ejection fraction less than 35%
Pre-existing arrhythmia or arrhythmia substrate
Digoxin therapy
Hypokalaemia or hypomagnesaemia
Bradycardia
Combinations of anti-arrhythmic drugs and concomitant drugs with similar toxicity