ANTI - ARRHYTHMIC DRUGS
CARDIAC ACTION POTENTIAL

**Na in**
**K Out**

Balance Ca in/K out

Phase 0
Phase 1
Phase 2
Phase 3
Phase 4

+20 mV

-90 mV
GENERATION OF ARRHYTHMIAS

Four mechanisms of arrhythmia generation:

- Increased normal automaticity
- Abnormal automaticity
- Triggered activity
- Re-entry
CLASSIFICATION

- Vaughan Williams Classification
- According to arrhythmia/clinical indication
- Molecular targets
VAUGHAN-WILLIAMS CLASSIFICATION

- Classifies drugs according to their mode of action on the cardiac action potential
- Developed when fewer agents available
- Problems;
  - Drugs with more than one mechanism of action do not fit into one category
  - Some drugs not classified eg digoxin
<table>
<thead>
<tr>
<th>CLASS</th>
<th>MODE OF ACTION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Na (fast) Channel Blockade</td>
<td></td>
</tr>
<tr>
<td>(a)</td>
<td>Prolongs action potential</td>
<td>Quinidine, Procainamide, Disopyramide</td>
</tr>
<tr>
<td>(b)</td>
<td>Shortens action potential</td>
<td>Lignocaine</td>
</tr>
<tr>
<td>(c)</td>
<td>No effect on action potential</td>
<td>Flecainide</td>
</tr>
<tr>
<td>II</td>
<td>Beta Blockade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antagonize catecholamines</td>
<td>B blockers</td>
</tr>
<tr>
<td>III</td>
<td>K+ Channel Blockade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolongs action potential</td>
<td>Amiodarone, Sotalol</td>
</tr>
<tr>
<td>IV</td>
<td>Ca Channel Blockade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verapamil, Diltiazem</td>
</tr>
<tr>
<td>V</td>
<td>Other/Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenosine, Digoxin, Magnesium</td>
</tr>
</tbody>
</table>
Drugs Affecting the Cardiac Action Potential

Class 1
- Na⁺ channel blocker
  - 1a (moderate): Quinidine, Procainamide
  - 1b (weak): Lidocaine, Phenytoin
  - 1c (strong): Flecaïnide, Propafenone

Class 2
- β-blocker
  - Propranolol, Metoprolol

Class 3
- K⁺ channel blocker
  - Amiodarone, Sotalol

Class 4
- Ca²⁺ channel blocker
  - Verapamil, Diltiazem

By Architha Srinivasan
University of Cambridge
CLASS 1

- ‘Membrane stabilisers’
- Inhibit fast Na influx during phase 0
  - Class 1a: reduce conduction velocity through AV node + prolong the duration of the AP and refractory period
  - Class 1b: shorten the effective refractory period
  - Class 1c: Mainly effect conduction
CLASS II

- Beta blockers
  - Depress automaticity in the SA and AV nodes
  - Competitively block the effects of circulating catecholamines on $\beta_1$ adrenergic receptors
    - Reduce sympathetic activity at the heart
    - Reduce HR and contractility
  - Effects result in lengthening of Phase 4
CLASS III

- Block the K+ channel
- Prolongs repolarisation and slows AV node conduction
- Also has the effect of prolonging the QT interval
- Can precipitate Torsades
CLASS IV

- Calcium channel blockers
  - Decrease conduction through the AV node
  - Shortens phase 2 + 3 of the action potential
- Also reduce cardiac contractility
  - Adverse effect in heart failure
CLASS V

- Includes drug which do not fit into the above categories

- Sotalol: Class II and III actions
- Adenosine: alpha 1 receptors
- Digoxin: Na/K ATPase pump
- Magnesium: Ca antagonist
### CLASSIFICATION BASED ON INDICATION

<table>
<thead>
<tr>
<th>TYPE OF ARRHYTHMIA</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVT</td>
<td>Digoxin, Verapamil, Adenosine, B-Blocker</td>
</tr>
<tr>
<td>VT</td>
<td>Lidocaine, Phenytoin</td>
</tr>
<tr>
<td>SVT and VT</td>
<td>Amiodarone, B-Blockers, Flecainide</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Atropine, Glycopyrrolate, Adrenaline</td>
</tr>
<tr>
<td>ARRHYTHMIA</td>
<td>MECHANISM</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Sinus Tachycardia</td>
<td>Increased normal automaticity</td>
</tr>
<tr>
<td>Ectopic Atrial Tachycardia</td>
<td>Abnormal automaticity</td>
</tr>
<tr>
<td>Torsades</td>
<td>Triggered activity</td>
</tr>
<tr>
<td>WPW</td>
<td>Re-entry</td>
</tr>
<tr>
<td>VF</td>
<td>Re-entry</td>
</tr>
</tbody>
</table>
MOLECULAR TARGETS

- Anti-arrhythmics interact with cellular structures that alter the electrophysiology of cardiac cells
  - Drugs can be classified according to their site of action
  - Known as the ‘Sicilian Gambit’
- Cellular structures include:
  - Ion channels
  - Pumps/Carriers
  - Receptors
  - Cytoplasmic regulators of 2nd messengers
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Vaughan-Williams classification</th>
<th>Channels</th>
<th>Receptors</th>
<th>Pump</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Na⁺</td>
<td>Ca²⁺</td>
<td>K⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fast</td>
<td>Medium</td>
<td>Slow</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>I B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>I B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>I A</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>I A</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>I A</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>I C</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>I C</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>IV</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>IV</td>
<td></td>
<td>✧</td>
<td></td>
</tr>
<tr>
<td>Bretyllium</td>
<td>III</td>
<td></td>
<td></td>
<td>✧</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td></td>
<td></td>
<td>✧</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td></td>
<td>✧</td>
<td>✧</td>
</tr>
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<td>Propranolol</td>
<td>II</td>
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<td>Atropine</td>
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<td>Adenosine</td>
<td></td>
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<td></td>
<td>✧</td>
</tr>
<tr>
<td>Digoxin</td>
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<td></td>
<td></td>
<td>✧</td>
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</table>

**Legend:**
- Blockers: ● Low potency, ✧ Medium potency, ✧✧ High potency
- Agonists: • Full agonist, ◯ Partial agonist
- Pump: Na⁺/K⁺ ATPase
SUMMARY

- No ‘perfect’ classification system
- Traditional system Vaughan-Williams classification
- More useful splitting into clinical indication
DRUGS TO PRODUCE INTRA-OPERATIVE HYPOTENSION
INTRA-OPERATIVE HYPOTENSION

- Reduce bleeding: Improves the surgical field
- Considered ‘safe’ to reduce a patients MAP by 30% in young, healthy patients
  - MAP up to 50-60mmHg can be tolerated
- Extreme care required especially in high risk patients
AUTO REGULATION

![Graph showing CBF (mL/100 g/min) vs. MAP (mm Hg) for Normotension and Chronic Hypertension.]
CLASSIFICATION

- Agents used are based on their site of action
  - Direct vasodilators
  - alpha-adrenergic blockers
  - B blockers
  - Opioids
  - Calcium antagonists
  - alpha2 adrenoceptor agonists
  - Anaesthetic agents
DIRECT VASODILATORS

- Examples
  - Sodium nitroprusside
  - GTN
  - Hydralazine
  - Magnesium
SODIUM NITROPRUSSIDE

- Venous vasodilation > Arterial vasodilation
- Nitroprusside reacts with oxyhaemoglobin releasing NO and cyanide
- Infusion bag must be covered as the solution is unstable in light

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Rapid onset</td>
<td>Reflex tachycardia</td>
</tr>
<tr>
<td>Easily titrated to effect</td>
<td>Tachyphylaxis</td>
</tr>
<tr>
<td>Cardiac output is usually well maintained, even in heart failure</td>
<td>Rebound hypertension due to increased plasma renin activity</td>
</tr>
<tr>
<td></td>
<td>Cyanide toxicity</td>
</tr>
</tbody>
</table>
GTN

- Primarily dilates capacitance vessels (venules) although can cause arterial vasodilation at high doses

- GTN is converted to NO in the mitochondria via mADH2

- GTN is adsorbed onto plastic bags —> infuse from glass bottle or polyethylene syringes/infusion lines

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</tr>
<tr>
<td>Improves coronary blood flow</td>
<td>Rebound hypertension, less pronounced than with SNP</td>
</tr>
<tr>
<td></td>
<td>Very high dose and prolonged administration may cause methaemoglobinemia</td>
</tr>
</tbody>
</table>
HYDRAZINE

- Primarily arteriodilator
- Used mainly in pre-eclampsia
- Oral or IV form
  - Given in repeated boluses due to long duration of action
- No toxic metabolites or rebound hypertension on cessation
- Mechanism of action unknown
MAGNESIUM

- Arteriolar vasodilator with minimal effect on venous circulation
- Especially useful in surgery for pheochromocytoma
- Antagonist of calcium at presynaptic adrenergic terminal and vascular smooth muscle cells
- Augments neuromuscular block
- Stabilises cardiac rhythm by impairing AV conduction
**ALPHA ADRENERGIC BLOCKERS**

**PHENTOLAMINE**

- Non selective $\alpha$-adrenergic antagonist
  - Clinical effect is mainly due to $\alpha_1$ post synaptic antagonism
  - Given as boluses 0.5-1mg/Infusion 0.1-0.2mg/min
  - Effect within 2 minutes
  - Lasts 15-20 minutes
  - No toxic metabolite
  - Side effect: nasal congestion
BETA BLOCKERS

- Class 2 anti-arrhythmic
- Several actions which may contribute to hypotension
  - Negative inotropic and chronotropic effects: reduce cardiac output via blockade of $\beta_1$ receptors
  - Alteration in baroreceptor reflex sensitivity
  - Inhibition of renin release
### IV B BLOCKERS

- **Esmolol**
  - Relatively selective for $\beta_1$ receptors although $\beta_2$ antagonism can be seen in large doses
  - Short duration of action
  - No toxic or active metabolites (may cause metabolic acidosis with prolonged infusions)
- **Labetolol**
  - Primarily $\beta_1$ antagonist
  - Slower onset (5-10 minutes) and offset than esmolol (half life 4-6 hours)
THE OTHERS....

- **Opioids: Remifentanil**
  - Reduces peripheral vascular tone directly

- **Volatile**
  - Mixture of negative inotropy and peripheral vascular dilatation depending on agent used

- **Propofol**
  - Crude hypotension agent
  - Reduces SVR, depresses the baroreceptor reflex, small depressant effect on myocardium
ANY QUESTIONS?