Arrhythmias
Normal sinus rhythm is a right sinus rhythm with rate from 60 to (90) 100 beaten per minute. **ECG:** sinus rhythm is characterized by a P wave (upright in II, III and avF; inverted in AVR), followed by QRS complex. Normal range of PQ-interval is 0.12-0.2 s.
Definition

Arrhythmia is abnormal frequency, regularity or consistency of excitation and contractions of heart.

Block is a deceleration or discontinuation of impulse movement on conducting heart system.
Epidemiology

Arrhythmias and blocks are widespread and can be met in practice of each doctor. They can not only appreciably impair main disease but to determine its prediction. Arrhythmias are the most frequent complication of Myocardial Infarction, and even can be the cause of death.
Etiology

**Cardiac causes** are myocardial infarction, coronary artery disease, LV aneurism, mitral valve disease, cardiomyopathy, pericarditis, myocarditis, aberrant conduction pathways.

**Non-cardiac causes** are caffeine, smoking, alcohol, pneumonia, drugs (β2-agonists, digoxin, L-dopa, tricyclics, adriamycin, doxorubicin), metabolic imbalance (K+, Ca2+, Mg2+, hypoxia, hypercapnia, metabolic acidosis, thyroid disease, phaeochromocytoma).
Cardiac conduction system consists of sinoatrial node, atrioventricular node, HIS Bundle, left and right branch and Purkinje fibers.
Pathogenesis

Two general factors have the undoubted role in the base of arrhythmias:

- Change of functional parameters of naturals (normal) automatism’s centers (intensification, weakness) or appearing in myocardium new (pathologic) centers of impulses.
- Re-entry phenomenon (return enter) – single or numerous return of excitement’s wave at the same zone of myocardium.

Heart’s blockades develop as a consequence of structural (permanent) or functional (temporary) disturbances in heart’s conduction system that prevent normal spreading of excitement’s wave.
Rude morphological changes (necrosis, dystrophia, fibrosis, calcinosis) can be revealed besides signs of main disease at those patients who died as a result of heart’s rhythm disturbances and blocks. This changes can be situated in different zones of myocardium and heart’s conduction system. When the syndrome of early excitement of ventriculars has a place anatomical substrates of supplementary conduction ways can be revealed (tails of Kent, James and Mocheim).
Classification
There are several classifications of arrhythmias and blocks.

By location:
- ventricular,
- supraventricular.

The last one can be:
- sinus,
- atrial,
- atrioventricular.

By clinical course:
- acute,
- chronic,
- paroxysmal (repeating)

By influence on hemodynamic:
- safe (without dangerous),
- potential dangerous,
- dangerous,
- fatal.

By heart rate:
- tachiarhythmies (>100 beats per minute),
- bradiarhythmies (<60 beats per minute).
Diagnostic of arrhythmias and blocks consist of

- Clinical features,
- ECG,
- Holter’s method of ECG registration,
- Electrophysiologically research of heart,
- Reflection (vagal) and drug tests,
- Other laboratory and instrumental tests.
Treatment

Treatment of arrhythmias and blocks includes elimination of causes and special methods.

Special treating methods are:
• antiarrhythmic drugs;
• electrical methods of treatment;
• surgical treatment;
• reflection and mechanical influence;
• psychotherapy.
Arrhythmias
Sinus tachycardia

**Clinical features:** Patients complaint on palpitations.

**ECG:** Sinus rhythm with frequency 100 per minute and more is registered.

**Treatment:** You have to identify and treat the cause. Sometimes you can use β-blockers (propranolol, atenolol) or calcium antagonists (verapamil, diltiazem). If the cause of sinus tachycardia is systolic heart failure you can use digoxin.
Sinus bradycardia

Clinical features: it can be asymptomatic or cause haemodynamical changes: systemic (low BP, heart failure) regional (syncope, angina).

ECG: Sinus rhythm with frequency less than 60 per minute is registered.

Treatment of acute cases: If sinus bradycardia is asymptomatic and rate $>40$ bpm, no treatment is required. If rate $<40$ bpm or patient is symptomatic, give atropine. If no response, insert a temporary cardiac pacing.

In chronic cases if the patient is symptomatic you can use permanent pacing.
Premature Beats (Extrasystoles)

- **Premature Beat** – is extra (premature) excitation and contraction of the heart.
- **Clinical features:** It may be asymptomatic or cause palpitations. Sometimes it can cause hemodynamic disturbances.
- **ECG:** Atrial premature beat looks like normal complex QRS.

![ECG Image](image1.png)

Ventricular premature beat has a wide QRS complex without a preceding P wave.
- **Treatment:** Extrasystoles don’t required treatment in most cases. β-blockers can be used in symptomatic arrhythmia.
Atrial Fibrillation

Atrial Fibrillation is a rapid, irregular atrial rhythm.

Clinical features: AF is often asymptomatic, but many patients have palpitations, chest discomfort, or symptoms of heart failure.

ECG: Findings include absence of P waves, f (fibrillatory) waves between QRS complexes and irregular R-R intervals.

Treatment: electrical and medicamental cardioversion are used for AF conversion to normal sinus rhythm. For medicamental cardioversion propafenon, amiodarone and procainamide are used. For rate control beta-blockers, calcium antagonist and digoxin are used. For prophylaxis of thromboembolism warfarin is used.
Atrial Flutter

- It differs from atrial fibrillation by ECG.
- On ECG there are continuous and regular atrial activation with rate 300 beats per minute and ventricular rate 150 beats per minute a saw tooth pattern, most obvious in leads II, III, and aVF.
- Treatment: overdrive pacing and radiofrequency ablation are used for atrial flutter treatment besides of methods used for treatment of atrial fibrillation.
Atrioventricular tachycardia

- It is caused by re-entry wave in AV node. It has paroxysmal clinical course.
- ECG: tachycardia with normal QRS complex is registered.
- Treatment: This tachycardia is converted to normal sinus rhythm by vagal reflex, adenosine, verapamile, cardioversion, cardiac pacing and radiofrequency ablation.
Ventricular Tachycardia

It is caused by re-entry wave in myocardium of ventricle, observed at patient with severe injury of the heart, always leads to hemodynamic disturbances like a shock, circulatory arrest, often transformes into ventricular fibrillation.

**ECG:** Any wide QRS complex tachycardia (QRS ≥ 0.12 s) should be considered VT until proved otherwise.

**Treatment:** Hypotensive VT requires synchronized direct-current cardioversion with ≥ 100 joules. VT with stable blood pressure can be treated with drugs (lidocaine, procainamide or amiodarone).
Ventricular Fibrillation

- Ventricular fibrillation is caused by chaotic re-entry waves in myocardium of ventricles. Clinical feature is suddenly syncope.
- **ECG:** chaotic irregular oscillations of isoline with frequency more than 250 bpm, QRS and T-waves do not establish.
- **Treatment** is with cardiopulmonary resuscitation, including defibrillation.
Blocks
- **Sinoatrial block** is characterized by intermittence of heart rate
- **ECG:** Sinus pause is temporary cessation of sinus node activity, seen on ECG as disappearance of P and QRST waves.
Atrioventricular block

• **First-degree AV block:** on ECG interval P-R(Q) is more than 0.20 s. Clinical features are absent.
Second-degree AV block:

Some normal P waves are followed by QRS complexes, but some are not. Three types exist:

• **In Mobitz type I of 2nd-degree AV block**, the PR interval progressively lengthens with each beat until the atrial impulse is not conducted and the QRS complex is dropped (Wenckebach phenomenon)
• In Mobitz type II of 2nd-degree AV block, the PR interval remains constant. Beats are intermittently nonconducted and QRS complexes dropped. These types of AV block clinically showed up by intermissions of

![ECG Graph](image1)

• In high-grade 2nd-degree AV block, every 2nd (or more) P wave is blocked and it results in ventricular bradycardia and hemodynamic disturbances.

![ECG Graph](image2)
Third-degree AV block:

Heart block is complete. There is no electrical communication between the atria and ventricles and no relationship between P waves and QRS complexes that result in ventricular bradycardia and hemodynamic disturbances.
Right bundle branch block

- Prolongation of intrinsicoid (1-2) more than 0.05 s in V1, V2 leads. Complete right bundle branch block is showed up by wide QRS complex (1-3) more than 0.11 s. Clinical features are absent.
Left bundle branch block

- Prolongation of intrinsicoid (1-2) more than 0.05 s in V5, V6 leads. Complete left bundle branch block is showed up by wide QRS complex (1-3) more than 0.11 s. Clinical features are absent.
Treatment of blocks

• Main disease should be treated in acute conditions.
• Sometimes atropine could be effective.
• If there are the hemodinamic disturbances pacing is used.
On this picture you can see dual-chamber electrical pacing
Antiarrhythmic Drugs
Action Potentials

SA Node

- Threshold
- $i_{Ca(L)}$
- $i_{Ca(T)}$
- $i_f$
- $i_K$

Ventricular Myocyte Action Potential

- $i_{Kto}$
- $i_{Ca(L)}$
- $i_{Na}$
- $i_K$
The normal cardiac action potential in non-conducting tissues (e.g., ventricles)
Normal

Reentry
Antiarrhythmic drugs

**Types**

- I  sodium channel blocker
- II β blocker
- III prolonged repolarization
- IV calcium channel blocker

**miscellaneous**

- cardiac glycoside
- adenosine
- Na\(^+\)-K\(^+\) ATPase inhibitor
- K\(^+\) channel activator
Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.

Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.

Class IC drugs markedly slow Phase 0 depolarization.

Quinidine, procainamide, and disopyramide block open or inactivated sodium channels. These drugs have an intermediate rate of association with sodium channels.

Lidocaine, mexiletine, and tocainide block open or inactivated sodium channels. These drugs have a rapid rate of association with sodium channels.

Flecainide and propafenone block open or inactivated sodium channels. These drugs have a slow rate of association with sodium channels.
Ventricular Action Potential

- **Class IA:** *e.g.*, quinidine
  - Moderate $\text{Na}^+$-channel blockade
  - $\uparrow$ ERP
- **Class IB:** *e.g.*, lidocaine
  - Weak $\text{Na}^+$-channel blockade
  - $\downarrow$ ERP
- **Class IC:** *e.g.*, flecaïnide
  - Strong $\text{Na}^+$-channel blockade
  - $\rightarrow$ ERP
• **Amiodarone is used for treatment of:**
  • refractory life-threatening ventricular arrhythmias in preference to lidocaine
  • treatment of atrial and/or ventricular arrhythmias

• **Adverse effects**
  – Pulmonary fibrosis
  – Skin pigmentation
  – Corneal deposits
  – Interferes with the thyroid function
Class III drugs prolong Phase 3 repolarization, without altering Phase 0.

Amiodarone, dofetilide, and sotalol block potassium channels.
Treatment of bradyarrhythmias

1. Atropine
   • Atropine **blocks the effects of acetylcholine.**
   • It elevates sinus rate and AV nodal and sinoatrial (SA) conduction velocity, and it decreases refractory period.

   • Atropine is used to treat **bradyarrhythmias** that accompany MI.

   • Atropine produces **adverse effects** that include dry mouth, mydriasis, and cycloplegia; it may induce arrhythmias.
2. **Isoproterenol**

- Isoproterenol *stimulates* \( \beta \)-adrenoceptors and increases heart rate and contractility.

- Isoproterenol is used to maintain adequate heart rate and cardiac output in patients with AV block.

- Isoproterenol may cause tachycardia, anginal attacks, headaches, dizziness, flushing, and tremors.
This common arrhythmia involves multiple ectopic foci of atrial cells, creating a chaotic movement of impulses through the atria. The ventricular response is rapid (100–150 beats per minute) and irregular. Cardiac output is decreased and exercise intolerance is common.

\[\text{\textbf{Type of Arrhythmia}}\]

\[\text{\textbf{Antiarrhythmic Drugs}}\]

\[\begin{array}{cccccc}
\text{Class I} & \text{Class II} & \text{Class III} & \text{Class IV} & \text{Other} \\
\text{Atrial Arrhythmias} & & & & \\
\text{Atrial Flutter} & \text{Dofetilide} & \text{Propranolol} & & \\
\text{Atrial Fibrillation} & & \text{Propranolol} & \text{Amiodarone} & \\
& & & & \text{Verapamil} & \text{Digoxin} & \text{Anticoagulant therapy} \\
\end{array}\]

\[\text{\textbf{Key:}} \]

- \text{Drug name}
- Commonly used drugs
- \text{Drug name}
- Alternative drugs

\[\beta\]-Blockers are the drugs of choice in atrial fibrillation, because they decrease heart rate and promote conversion to sinus rhythm. Long-term, low-dose anticoagulant therapy reduces the risk of stroke that is associated with atrial fibrillation.
Conduction is slowed through the AV node with propranolol, verapamil, or digoxin.
This arrhythmia is a common cause of death in patients who have had a myocardial infarction. Cardiac output is impaired, and tachycardia may deteriorate into ventricular fibrillation. Therefore, ventricular tachycardia requires prompt management.
ANTI-ARRHYTHMIC DRUGS
CONTENT

• Physiology of normal cardiac rhythm
• Definition and mechanisms of arrhythmias
• Classification of drugs to treat arrhythmias
• Important anti-arrhythmic drugs (mechanism and pharmacological characteristics)
• Arrhythmias in clinical practice
PHYSIOLOGY OF CARDIAC RATE AND RHYTHM

- Cardiac myocytes are electrically excitable
- Resting intracellular voltage of myocardial cells is negative -90mV (SA node is -40mV)
- Resting state - K⁺ inside and Na⁺ outside cell (Na⁺/K⁺ pump)
- Action potential occurs when Na⁺ enters the cell and sets up a depolarising current
- Stimulation of a single muscle fibre causes electrical activity to spread across the myocardium
PHASES OF ACTION POTENTIAL OF CARDIAC CELLS

- Phase 0 rapid depolarisation (inflow of Na$^+$)
- Phase 1 partial repolarisation (inward Na$^+$ current deactivated, outflow of K$^+$)
- Phase 2 plateau (slow inward calcium current)
- Phase 3 repolarisation (calcium current inactivates, K$^+$ outflow)
- Phase 4 pacemaker potential (Slow Na$^+$ inflow, slowing of K$^+$ outflow) ‘autorhythmicity’
- Refractory period (phases 1-3)
SINUS RHYTHM

• Sinoatrial node is cardiac pacemaker
• Normal sinus rhythm 60-100 beats/min
• Depolarisation triggers depolarisation of atrial myocardium (‘forest fire’)
• Conducts more slowly through AV node
• Conducts rapidly through His bundles and Purkinje fibres
SINUS RHYTHM

• Sinoatrial rate controlled by autonomic nervous system
• Parasympathetic system predominates (M2 muscarinic receptors)
• Sympathetic system (β1 receptors)
  – Increased heart rate (positive chronotropic effect)
  – Increased automaticity
  – Facilitation of conduction of AV node
ECG

• Recording of electrical activity of the heart
• Net sum of depolarisation and repolarisation potentials of all myocardial cells
• P-QRS-T pattern
• P - atrial depolarisation
• QRS - ventricular depolarisation
• T - ventricular repolarisation
ECG

- Recording of electrical activity of the heart
- Net sum of depolarisation and repolarisation potentials of all myocardial cells
- P-QRS-T pattern
  - P - atrial depolarisation
  - QRS - ventricular depolarisation
  - T - ventricular repolarisation
DEFINITION OF ARRHYTHMIA

• Cardiac arrhythmia is an abnormality of the heart rhythm
• Bradycardia – heart rate slow (<55-60 beats/min)
• Tachycardia – heart rate fast (>100 beats/min)
CLINICAL CLASSIFICATION OF ARRHYTHMIAS

- Heart rate (increased/decreased)
- Heart rhythm (regular/irregular)
- Site of origin (supraventricular/ventricular)
- Complexes on ECG (narrow/broad)
MECHANISMS OF ARRHYTHMIA PRODUCTION

• Re-entry (refractory tissue reactivated due to conduction block, causes abnormal continuous circuit; eg accessory pathways linking atria and ventricles in Wolff-Parkinson-White syndrome)

• Abnormal pacemaker activity in non-conducting/conducting tissue (eg ischemia)

• Delayed after-depolarisation (automatic depolarisation of cardiac cell triggers ectopic beats, can be caused by drugs; eg digoxin)
VAUGHAN WILLIAMS
CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

- **Class I**: block sodium channels
  - Ia (quinidine, procainamide, disopyramide) $\uparrow$AP
  - Ib (lidocaine, mexiletine, phenytoin) $\downarrow$AP
  - Ic (flecainide, propafenone) $\leftrightarrow$AP
- **Class II**: $\beta$-adrenoceptor antagonists (atenolol, sotalol)
- **Class III**: prolong action potential and prolong refractory period (suppress re-entrant rhythms) (amiodarone, dronedarone, sotalol)
- **Class IV**: Calcium channel antagonists. Impair impulse propagation in nodal and damaged areas (verapamil)
MANAGEMENT OF ARRHYTHMIAS

- Acute management (clinical assessment of patient and diagnosis)
- Prophylaxis
- Non-pharmacological
- Pharmacological (some antiarrhythmics are also proarrhythmic)
NON-PHARMACOLOGICAL TREATMENT

• Acute
  – Vagal manoeuvres (Valsalva, carotid sinus massage)
  – DC cardioversion

• Prophylaxis
  – Radiofrequency ablation
  – Implantable defibrillator

• Pacing (external, temporary, permanent)
LIDOCAINE

- Class Ib (blocks Na\(^+\) channels, reduces AP duration)
- Ventricular arrhythmias (acute Rx)
- IV infusion only (2 hour half life, high first pass metabolism)
- Hepatic metabolism (inhibited by cimetidine, propranolol)
- SE mainly CNS - drowsiness, disorientation, convulsions, hypotension
PROPafenone

- Besides Na blocking effects, without affecting AP (class Ic), has weak Ca-blocker (class IV) and weak β-blocker effects (class II)
- It is metabolized to active metabolites, but slow metabolizers may have even 2x higher Cmax and 3x longer T1/2
- Indicated for SV tachyarrhythmias (WPW, AV node re-entry tachycardia, paroxysmal atrial fibrillation) and some ventricular arrhythmias
- Adverse effects
  - Cardiac – AV or bundle branch blockades, ventricular tachyarrhythmias -> avoid in CAD or depressed LVEF
  - GIT, CNS
BETA-BLOCKERS

- Decrease resting membrane potential (it is more negative; class II) – negative bathmotropic effects
- Pacemakers: decrease the rate of the spontaneous firing
- Prolong AV conduction
- Clinical correlates: ↓ TF, ↓ impulse conduction to ventricles, ↑ threshold for ventricular fibrillation, improved prognosis of patient after M.I. (sudden death prevention – antiarrhythmic effects)
- PK differences – t1/2!
- Esmolol < Propranolol < Atenolol < Metoprolol
AMIODARONE

- **Class III** - increases refractory period and AP
- Major effect acutely is depression of AV node
- Acute Rx/prophylaxis
- Atrial and ventricular arrhythmias
- Oral or IV (central line)
- Loading and maintenance doses
- T1/2 roughly 54 days
- Large volume of distribution
- Accumulates
- Hepatic metabolism- biliary and intestinal excretion
AMIODARONE – ADVERSE EFFECTS

• Photosensitive rashes
• Grey/blue discolouration of skin
• Thyroid abnormalities 2%
• Pulmonary fibrosis
• Corneal deposits
• CNS/GI disturbance
• Pro-arrhythmic effects (torsade de pointe)
• Heart block
• Nightmares 25%
• Abnormal LFT 20%
• Interacts with digoxin, warfarin ->
  (reduces clearance)
SOTALOL

- L-isomer (non selective b-blocker without ISA),
- PROLONG AP: block rapid outward K current ⇒ repolarization phase is slowed – i.e., prolonged, ⇒ longer is also effective refractory period (EPR)
- IND: i.v. - serious ventricular and SV arrhythmias; p.o. - effective in prophylaxis of recurrent SV arrhythmias; to keep the sinus rhythm after cardioversion of AF
- PK: relatively simple and predictable (p.o. i i.v.) – limited risk of drug interactions
- Adverse reaction: generally relatively tolerable drug;
  - If induction of the long QT due to the possibility of TdP occurrence (the risk in approx. in 3-4 % patients)
  - Bradycardia, HF precipitation, hypotension, bronchoconstriction, sleep disturbances (CI: severe HF, asthma..)
CA CHANNEL BLOCKERS

- The effects on slow response structures (SA and AV nodes; class IV)
  - conduction is based on Ca++
  - depresses spontaneous depolarization of SA node
  - decreases AV node conduction
    - decreases ventricular response in AF and flutter
    - suppresses AV nodal re-entry tachyarrhythmia
  - no major impact on ventricular tachyarrhythmias

- Rapid response structures (the rest of the myocardium)
  ⇒ Ca2+ channel block (L-type) in 2nd AP phase
  ⇒ less Ca for contraction - negative inotropic response
VERAPAMIL

- **Class IV** (calcium channel blocker)
- Prolongs conduction and refractoriness in AV node, slows rate of conduction of SA node
- Acute Rx /prophylaxis
- Used IV/oral
- SUPRAVENTRICULAR NOT VENTRICULAR ARRHYTHMIAS (cardiovascular collapse)
- Do not use IV verapamil with β- blocker (heart block)
- T1/2 6-8 hours
VERAPAMIL- ADVERSE EFFECTS

- Heart failure
- Constipation
- Bradycardia
- Nausea
ADENOSINE

• Not in Vaughan Williams class
• Purine nucleotide (activates adenosine receptors)
• Slows AV nodal conduction
• Acute Rx
• Termination of SVT/ diagnosis of VT
• Given IV only (rapid bolus)
• T1/2 < 2 seconds
ADENOSINE- ADVERSE EFFECTS

• Feeling of impending doom!
• Flushing, dyspnoea, chest pain, transient arrhythmias
• Contraindicated in asthma, heart block
DIGOXIN

- Not in Vaughan Williams class
- Cardiac glycoside (digitalis, foxglove)
- Act on Na/K-ATPase of cell membrane (inhibits Na⁺/K⁺ pump, increases intracellular Na⁺ and calcium)/ increases vagal activity
- Increase cardiac contraction and slows AV conduction by increasing AV node refractory period
DIGOXIN

- Atrial fibrillation or flutter (controls ventricular rate)
- Acute Rx/prophylaxis
- Oral/IV
- Loading and maintenance doses
- T1/2 36 hours
- Excreted by kidneys
- Narrow therapeutic index
- Therapeutic drug monitoring
- Reduce dose in elderly/renal impairment
DIGOXIN – ADVERSE EFFECTS

- Arrhythmias, heart block, anorexia, nausea, diarrhoea, xanthopsia, gynaecomastia, confusion, agitation
- AE potentiated by hypokalaemia and hypomagnesaemia
- Overdose – Digibind (digoxin binding antibody fragments), phenytoin for ventricular arrhythmias, pacing, atropine
SOME TYPICAL DOSAGES

- **Amiodarone** (150 mg vials): VT/VF refractory to DC shock -> 300 mg bolus in 20 ml D5%; continuous IV infusion 600-900 mg in 500 mL D5% @ 21 mL/h

- **Digoxin** (0.5 mg vials): 10-15 mcg/kg 50% stat, 25% in 6 h, and 25% afterwards; continuous IV infusion @ 0.0625-0.5 mg/d (eg 1/8 to 1 vial in 500 mL @ 21 mL/h)

- **Diltiazem** (50 mg vials): 0.25 mg/kg in 2 min, then 0.35 mg/kg in 5-10 min; continuous IV infusion @ 5-15 mg/h (eg 3 vials in 500 mL @ 17 mL/h)

- **Lidocaine**: IV infusion: 1-4 mg/min; IV bolus: 50-100 mg initially, can be repeated up to 3 mg/kg in 1 h (reduce bolus dose to 50% if elderly/CHF/hepatic disease)

- **Metoprolol** (5 mg vials): 5 mg every 2 min, max 3 doses

- **Propranolol** (5 mg vials): 1 mg in slow bolus, every 10 min, max total dose of 0.15 mg/kg

- **Verapamil** (5 or 125 mg vials): 2.5-10 mg in 2 min, then 10 mg in 30 min, max 20 mg; continuous IV infusion @ 5-10 mg/h (eg 125-mg vial in 500 mL @ 20 mL/h)
CLINICAL CASES
A COMMON APPROACH

- What is the average heart rate?
- Is the rhythm regular or irregular?
- Is the QRS narrow or large?
- Is there any evidence of sinus rhythm? Otherwise, what is the source of rhythm?
- How is AV conduction?
- Is there any evidence of ongoing ischemia or prior infarction?
- Is there any evidence of strain pattern or electrolyte disturbance?
WITH ASTHMA HAS ‘THUMPING IN CHEST’
WITH ASTHMA HAS 'THUMPING IN CHEST'

NORMAL EKG
69 YEAR OLD MAN WITH PALPITATIONS
69 YEAR OLD MAN WITH PALPITATIONS

WPW
81 YEAR WOMAN WITH DIZZINESS
81 YEAR WOMAN WITH DIZZINESS

2:1 ATRIAL TACHYCARDIA
72 YEAR MAN WITH FATIGUE
72 YEAR MAN WITH FATIGUE

2:1 ATRIAL FLUTTER
76 YEAR OLD MAN WITH RECENT STROKE
76 YEAR OLD MAN WITH RECENT STROKE

ATRIAL FIBRILLATION
COLLAPSES 24 HOURS POST MI

Hewlett Packard 4745A

RHYTHM STRIP: 11
25 mm/sec; 1 cm/mV

LOC 00000-0000
COLLAPSES 24 HOURS POST MI

VENTRICULAR TACHYCARDIA
94 YEAR WOMAN AWAITING ELECTIVE HIP SURGERY
94 YEAR WOMAN AWAITING ELECTIVE HIP SURGERY

2:1 ATRIAL FLUTTER WITH PRE-EXISTENT LBBB
71 YEAR OLD PULSELESS MAN
71 YEAR OLD PULSELESS MAN

VENTRICULAR FIBRILLATION
71 YEAR OLD PULSELESS MAN

VENTRICULAR FIBRILLATION AND DC SHOCK
SUMMARY

• Anti-arrhythmic drugs are classified by their effect on the cardiac action potential
• Not all drugs fit this classification
• In clinical practice treatment of arrhythmias is determined by the type of arrhythmia (SVT, VT), clinical condition of the patient, and therapeutic window of each specific treatment means
• Anti-arrhythmic drugs are efficacious but may have serious adverse effects
• Not all arrhythmias are treated with drug therapy alone
The pathways of Conduction

- Sinus node
- AV node
- Bundle of His
- Right bundle
- Left bundle
- Purkinje system
Normal ECG

[ECG waveform diagram with standard leads and annotations]

- Leads: I, aVR, aVL, V1, V2, V3, V4, V5, V6
- Speed: 25 mm/sec
- Limb: 10 mV
- Chest: 10 mm/mV
- 50% 0.15-150 Hz

Legend: LOC 0000-0000
Classification of arrhythmia:

- **Rapid, regular.** Sinus tachycardia, supraventricular tachycardia, atrial flutter, ventricular tachycardia.

- **Rapid, irregular.** Sinus arrhythmia, multiple ectopic beats whether atrial or ventricular, atrial fibrillation.

- **Slow, regular.** Sinus bradycardia, nodal rhythm, complete heart block.

- **Slow, irregular.** Slow atrial fibrillation.
**Sinus tachycardia**

Cardiac impulses arise in the sinus node at a rate more than 100/min. 4

**Etiology:**
A- Physiological: Infancy, childhood, exercise and excitement.
B- Pharmacological: Sympathomimetic drugs such as epinephrine and isoproterenol. Parasympatholytic drugs such as atropine. Thyroid hormones, nicotine, caffeine, alcohol.
C- Pathological: Fever, hypotension, heart failure, pulmonary embolism, hyperkinetic circulatory states as anemia.
A 34 year old woman with asthma
Sinus Bradycardia
Cardiac impulses arise in the sinus node at a rate less than 60/min.

Etiology:
A- Physiologic: Athletes, sleep, and carotid sinus compression.
B- Pharmacologic: Digitalis, propranolol, verapamil and diltiazem.
C- Pathologic: Convalescence from infections, hypothyroidism, obstructive jaundice, rapid rise of the intracranial tension, hypothermia and myocardial infarction (particularly inferior wall infarction)
SUPRAVENTRICULAR TACHYARRHYTHMIAS

SVTs may be separated into three groups based on duration: brief paroxysms, persistent, and chronic (permanent). Arrhythmias that are paroxysmal in onset and offset (e.g. paroxysmal SVT due to AV nodal reentry or WPW syndrome, paroxysmal atrial fibrillation, paroxysmal atrial flutter) tend to be recurrent and of short duration.
Supraventricular tachyarrhythmias include: atrial tachycardia, atrial flutter, atrial fibrillation and AV tachycardias.
PSVT

PREVIOUS ECG: 12 MAY 2000  3:20:31PM, CONFIRMED BY WB - AB
DENVER HEALTH MEDICAL CENTER - EAST SIDE CLINIC

FREDERICK MASOUEDI - 26 MAR 2001  4:36:18PM

PSVT

--AXES--
F
QRS  193
T   44

Requested by
BLUM
Tech BM
Edited  C-HP708

PR
QRS  100
QT   266
QTc  447

I    aVR    V1    V4
II   aVL    V2    V5
III  aVF    V3    V6
II

Loc 10038
25 mm/sec  10.0 mm/mV  F ~ W 0.50-40
Management of PSVT Due to AV Nodal Reentry

The acute attack: Vagal maneuvers serve as the first line of therapy. Simple procedures to terminate paroxysmal SVT
- Carotid sinus massage: If effective the rhythm is abruptly stopped; occasionally only moderate slowing occurs
- Cold water splash on face.
- Performance of Valsalva's maneuver (often effective).
Management of PSVT Due to AV Nodal Reentry

Intravenous adenosine, Ca channel blockers (verapamil), digoxin or B-blockers are the choices for managing the acute episodes. Adenosine, 6 mg given intravenously, followed by one or two 6-mg boluses if necessary, is effective and safe for acute treatment. A 5-mg bolus of verapamil (isoptin), followed by one or two additional 5-mg boluses 10 min apart if the initial dose does not convert the arrhythmia.
SVT
A 53 year old man with Ischaemic Heart Disease.
Wolf-Parkinson-White syndrome

- short PR interval, less than 3 small squares (120 ms)
- slurred upstroke to the QRS indicating pre-excitation (delta wave)
- broad QRS
- secondary ST and T wave changes

Localising the accessory pathway

An accessory pathway, bundle of Kent, exists between atria and ventricles and causes early depolarisation of the ventricle. The location of the pathway may be deduced as follows:

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>V1</th>
<th>V2</th>
<th>QRS axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>left posteroseptal (type A)</td>
<td>+ve</td>
<td>+ve</td>
<td>left</td>
</tr>
<tr>
<td>right lateral (type B)</td>
<td>-ve</td>
<td>-ve</td>
<td>left</td>
</tr>
<tr>
<td>left lateral (type C)</td>
<td>+ve</td>
<td>+ve</td>
<td>inferior (90 degrees)</td>
</tr>
<tr>
<td>right posteroseptal</td>
<td>-ve</td>
<td>-ve</td>
<td>left</td>
</tr>
<tr>
<td>anteroseptal</td>
<td>-ve</td>
<td>-ve</td>
<td>normal</td>
</tr>
</tbody>
</table>

Wolf-Parkinson-White syndrome
PSVT Due to Accessory Pathways (The Wolff-Parkinson-White Syndrome)
atrial fibrillation:

Duration

- Paroxysmal Minutes/hours
- Short-lasting Seconds -- <1 hour
- Long-lasting >1 hour; -- < 48 hours
- Persistent Two days -- weeks
- Permanent (Chronic) Months / years
Causes of atrial fibrillation

With structural heart disease
- Rheumatic mitral valve disease
- Ischemic heart disease
- Hypertension
- Cardiomyopathy: Dilated, Hypertrophic
- Atrial septal defect
- Constrictive pericarditis
- Myocarditis

Without structural heart disease
- Alcohol. Thyrotoxicosis
- Acute pericarditis. Pulmonary embolism
- Sick sinus syndrome, Lone atrial fibrillation
A woman with loud first heart sound and mid-diastolic murmur.
Treatment of Atrial Fibrillation

Pharmacologic Management of Patients with Recurrent Persistent or Permanent AF:

- **Recurrent Persistent AF:**
  A) Minimal or no symptoms: Anticoagulation and rate control as needed.
  B) Disabling symptoms in AF:
     1- Anticoagulation and rate control
     2- Antiarrhythmic drug therapy
     3- Electrical cardioversion as needed, continue anticoagulation as needed and therapy to maintain sinus rhythm

- **Permanent AF:** Anticoagulation and rate control as needed.
Recent-onset AF

Yes

Haemodynamic instability

Electrical

Patient/physician choice

Pharmacological

Structural heart disease

Severe

Intravenous ibutilide

Vernakalant

Moderate

Intravenous amiodarone

None

Pill-in-the-pocket (high dose oral)

Elective

Emergency

Intravenous amiodarone

Intravenous flecainide

Intravenous propafenone

Intravenous flecainide

Propafenone


\[a\] Ibutilide should not be given when significant left ventricular hypertrophy (\(\geq 1.4\) cm) is present.

\[b\] Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
Choice of antiarrhythmic drug according to underlying pathology.

- Minimal or no structural heart disease
  - HHD
    - No LVH: dronedarone/flecainide/propafenone/sotalol → amiodarone
    - LVH: dronedarone → amiodarone
- Significant structural heart disease
  - Treatment of underlying condition and prevention of remodelling – ACEI/ARB/statin
    - CHD
      - LVH: sotalol → amiodarone
    - HF: amiodarone

AF management
Anticoagulation of Patients with Atrial Fibrillation: Indications

Rheumatic mitral valve disease with recurrent or chronic atrial fibrillation.

Dilated cardiomyopathy with recurrent persistent or chronic atrial fibrillation.

Prosthetic valves.

Prior to (>3 weeks) elective cardioversion of persistent or chronic atrial fibrillation, and also for 3 weeks after cardioversion (because of atrial stunning).

Coronary heart disease or hypertensive heart disease with recurrent persistent or chronic atrial fibrillation.
Atrial Flutter
Treatment of Cardiac Arrhythmias with Catheter Ablative Techniques

Radiofrequency ablation destroys tissue by controlled heat production. Catheter ablation is used to treat patients with four major tachyarrhythmias: atrial flutter/fibrillation, AV nodal reentry, accessory pathways and ventricular tachycardia.
A 76 year old man with SOB
A 60 year old woman with HTN
A 68 year old women on Digoxin complaining of fatigue
A 57 year old woman with palpitations
QTc

Normal QTc

- **Men < 0.43**
  - borderline 0.43-0.45
  - prolonged >0.45
- **Women < 0.43**
  - borderline 0.43-0.47
  - prolonged >0.47

\[
QTc = \frac{QT}{\sqrt{RR}} = \frac{0.71}{\sqrt{1.11}} = 0.67 \text{ seconds}
\]
A 50 year old man with chest pain for 2-4 hours
VENTRICULAR TACHYCARDIA
A 45 year old women with palpitation and a history of CRF (Chronic Renal Failure)
A 69 year old man
2 weeks post IW MI
A 60 year old man with IHD
A 25 year old man with bouts of tachycardia
A 23 year old male with palpitations
AV HEART BLOCK
Mobitz type I (Wenckebach) block

Mobitz Type II second degree heart block
COMPLETE AV BLOCK
A 73 year old woman with dizziness.
A 70 year old man with exercise intolerance.
An 82 year old lady with dizzy spells
Drugs used in the Treatment of Cardiac Arrhythmias
Commonly Encountered Arrhythmias:

- Supraventricular arrhythmias
- Ventricular arrhythmias
- Arrhythmias caused by Digitalis
Supraventricular Arrhythmias:
Arise in atria, SA or AV node

• Supraventricular Tachycardia (SVT)
  – Caused by rapidly firing ectopic focus in atria or AV node
    • Heart Rate 150-250/min
    • Best treated by increasing vagal tone
      – Carotid sinus massage
      – Valsalva maneuver

• Drug therapy
  – Verapamil
  – Adenosine
Supraventricular Arrhythmias:
  Arise in atria, SA or AV node

• Atrial Flutter
  – Ectopic atrial focus
    • Fires at rate 250-350/minute
    • Slower ventricular response
    • A-V node unable to conduct
    • 1:3
  – Cardioversion is procedure of choice

• Atrial fibrillation
  – Primarily treated with cardioversion
Ventricular Arrhythmias:

• Premature Ventricular Contractions (PVC)
• Ventricular Tachycardia
• Ventricular Fibrillation
• Objective of treatment is abolition of arrhythmia
• Arrhythmia considered malignant
Cardiac Excitability:

• Refers to the ease with which cardiac cells undergo a series of events characterized by:
  – Sequential depolarization and repolarization
  – Communication with adjacent cells
  – Propagation of electrical activity in a normal or abnormal manner
Fast vs. Slow Response Tissues:

• Fast response tissues
  – Location
    • Atria, specialized infranodal conducting system, ventricle, AV bypass tracts
  – Normal resting potential
    • -80 to –95 mV
  – Active Cellular properties
    • Phase 0 current and channel kinetics
      – Sodium/fast
  – Automaticity
    • yes
Fast vs. Slow Response Tissues:

- **Slow Response Tissues**
  - **Location**
    - Sinoatrial and atrioventricular nodes, depolarized fast response tissues in which phase 0 depends upon calcium current
  - **Normal resting potential**
    - -40 to -65 mV
  - **Active cellular properties**
    - Phase 0 current and channel kinetics
      - Primarily calcium/slow activation
      - Inactivation depends upon voltage and cell calcium concentration
  - **Automaticity**
    - Yes
Action potential in fast response tissues:

- **Phase 0 (Rapid depolarization)**
  - Mediated by Na entry into cells
  - Secondary to marked increase in number of open Na channels in cell membrane

- **Phase 1 and 3 (Repolarization)**
  - Results from K exit from cells as Na channels are closed and K channels open

- **Phase 2 (Plateau)**
  - Reflects slow entry of Ca into cells
  - Counteracts effect of K exit

- **Phase 4 (Recovery)**
  - Exit of Na and reentry of K
  - Via Na-K-ATPase
Etiology of Arrhythmias:

- Abnormalities in impulse generation
- Abnormalities in impulse conduction

Etiologic factors include:
  - Drugs
  - Ischemia
  - Congenital
Etiology of Arrhythmias: Abnormalities in Impulse Generation

• Enhanced Normal Automaticity
  – SA node, AV node, His-Purkinje system
  □ β-stimulation, hypokalemia

• Abnormal Automaticity
  – Delayed afterdepolarization (DAD)
  – Early afterdepolarization (EAD)
Etiology of Arrhythmias: Abnormalities in Impulse Generation

• Drug effects on arrhythmia
  – Decreases slope of phase 4 depolarization
    \( \beta \)-blockade
  – Raising threshold of discharge
    • Na/Ca block
  – Prolongation of action potential
    • K channel block
  – Increases maximum diastolic potential
    • adenosine
Etiology of Arrhythmias: Abnormalities in Impulse Conduction

- **Reentry**
  - Unidirectional block
  - Heterogeneity for refractoriness

- **Drug effects**
  - Improvement of conduction in abnormal pathway
    - Reconverts unidirectional block to normal forward conduction
  - Slows conduction/increases refractory period
    - Converts unidirectional block into **bidirectional** block
Classification of Antiarrhythmic Drugs

- Drugs often have several effects on action potential generation and propagation and may also affect autonomic nervous system.
- Drugs that act on ion channels may preferentially influence the activated (open) or inactivated state.
Antiarrhythmic Drugs:

- Potent compounds
- Many with active metabolites
- Relatively narrow therapeutic index
- Drugs within a class cannot be considered interchangeable with other members of its class
- Large number of agents available
  - Each with unique pharmacologic profile
Antiarrhythmic Drugs:

• Many agents have proarrhythmic effects
• “Failures” of treatment can occur
  – Incorrect dosage of correct drug
  – Incorrect drug
• Pharmacodynamics determines actions in specific arrhythmias
  – Chronotropic effects
  – Inotropic effects
  – Toxic effects
• Not all “arrhythmias” need to be treated
Classification of Antiarrhythmic Drugs

- Vaughan-Williams (1970)
  - Electrophysiological
  - Assumes individual drugs have a predominant mechanism of action
  - Many useful drugs do not fit classification
    - Introduced after classification proposed and modified
    - Represents oversimplification of electrophysiologic events that occur
Classification of Antiarrhythmic Drugs

• Sicilian Gambit (1994)
  – Sacrifices popular simplicity of Vaughan-Williams classification
  – Identification of vulnerable parameters of target arrhythmia
  – Determine specific tissue and electrophysiologic actions to be manipulated to affect vulnerable parameter
  – Choose appropriate intervention resulting in needed activity with greatest safety
    • Drug therapy
    • Ablation
Ion fluxes during cardiac action potential: Effects of antiarrhythmic drugs

A. Fast potential of the His-Purkinje system and atrial and ventricular myocardium. Blockade of sodium influx by Class I drugs slows conduction in the His-Purkinje system. Blockade of calcium influx by beta blockers and calcium channel blockers decreases contractility. Blockade of potassium efflux by Class III drugs delays repolarization and thereby prolongs the effective refractory period.

B. Slow potential of the sinoauricular (S-A) node and atrioventricular (A-V) node. Blockade of calcium influx by beta blockers and calcium channel blockers slows A-V conduction. These same drugs decrease S-A nodal automaticity (phase 4 depolarization); the ionic basis of this effect is not known.
Vaughan-Williams Classification:

• Class I
  – Act by modulating or closing Na channels
  – Inhibit phase 0 depolarization
  – Produce blockade of voltage sensitive Na channels
  – Positively charged
    • Presumably interact with specific amino acid residues in Na channel
  – Related to local anesthetics
    • Membrane stabilizing
Vaughan-Williams Classification:

- **Class I**
  - Subdivided into three subgroups
  - Subdivision based on rates of drug binding to and dissociation from the Na channel receptor
  - **Class IC**
    - Slowest binding and dissociation from receptor
    - Marked phase O slowing
    - Promotes greatest Na current depression
Vaughan-Williams Classification:

• Class I
  – Class IB
    • Most rapid binding and dissociation
    • Shorten phase 3 repolarization
    • Shortens or no effect on action potential
  – Class IA
    • Intermediate effects on binding/dissociation
    • Lengthens action potential
Class I agents:

• Class IA
  – Quinidine
  – Procainamide
  – Disopyramide

• Class IB
  – Lidocaine
  – Tocainide
  – Mexilitene

• Class IC
  – Flecanide
  – Propafenone
  – Moricizine
Vaughan-Williams Classification:

- **Class II**
  - β–adrenergic blockers
    - Valuable because of their ability to reduce impulse conduction from atria to ventricles

- **Class III**
  - Block outward K channels
    - Prolong repolarization
    - Prolong action potential
    - Prolong duration of refractory period

- **Class IV**
  - Ca channel blockers, primarily verapamil
    - Primarily used to decrease A-V nodal conduction
Class IA agents:

• Depress phase O depolarization, thereby slow conduction
• Also have moderate K channel blocking activity
  – Tends to slow rate of repolarization
• Some agents have anticholinergic activity and depress contractility
Class IA agents:

- Quinidine
- Procainamide
- Disopyramide
Quinidine

- D-isomer of **quinine**
- **Direct effects**
  - Suppression of **automaticity** (ectopic foci)
  - Suppression of **impulse conduction**
  - Suppression of **contractility**
  - Acts to block Na channels in open state
- **Indirect effects:**
  - Anticholinergic
    - **Increases** HR and conduction through AV node
    - $\alpha$–adrenergic blockade
    - **Decreases** vascular resistance
Quinidine

- **EKG Effects:**
  - Prolongation of P-R interval
  - Prolongation of Q-T interval
    - Up to 25%
    - Caution in long Q-T syndrome
  - Widening of QRS
- **Absorption 73-80%**
- **Rapidly distributed**
  - No CNS penetration
- **Excreted unchanged in urine**
  - Weak base (positively changed)
  - Quinidine and metabolites filtered at glomerulus and secreted by PCT
Quinidine

• Metabolism
  – Hepatic metabolism
  – Oxidation by CYP3A
  – Metabolites generally not active
  – Inhibits CYP2D6
    • Involved in oxidation of β-blockers, encainide
    • Responsible for metabolism of debrisoquin

• 70-95% protein bound

• Therapeutic drug levels 2 to 6 μg/ml
  – Narrow therapeutic index

• Drug Interactions
Quinidine

• Clinical Use
  – Paroxysmal supraventricular tachycardia
  – Atrial fibrillation and flutter
    • Maintains sinus rhythm after conversion
  – Ventricular premature complexes
  – Ventricular tachycardia

• Oral therapy
  – 3-4 times per day
  – Long-acting dosage forms exist
  – Monitor for increase in QT interval
Quinidine: Adverse Effects

– **Cardiotoxicity**
  • Sinus arrest, AV block
  • Torsade de pointes

– **Increase in ventricular response**
  • Due to anticholinergic effects
  • Pretreatment with A-V nodal blocker essential

– **Diarrhea**
  • Occurs in up to 40%

– **Cinchonism**
  • Tinnitus
  • Headache
  • Vertigo

– **Thrombocytopenia**

**Use often limited by adverse effects:**
30% stop drug
Procainamide

• Action similar to quinidine
  – Similar effects on open Na channels and outward K channels
• Weakly anticholinergic
  – No increase in ventricular response in AF
• Less suppression of myocardial contractility
• Similar effects on EKG
Procainamide

• Clinical Use:
  – Atrial fibrillation
    • Conversion to sinus rhythm in patients with normal left atrial size
    • Atrial fibrillation of long duration or associated with anatomical abnormality resistant to drug treatment
  – Atrial flutter
  – Wolff-Parkinson-White syndrome
  – PVCs and ventricular tachycardia
    • Efficacy 15 to 50%
    • Efficacy enhanced by concurrent therapy with agents acting by different mechanisms
Procainamide: Metabolism

- 75-85% oral absorption
- 15% protein binding
- Hepatic metabolism (16-33%)
  - Acetylation
    - N-acetyl-procainamide (NAPA)
      - Possesses Class I and III effects
      - Increases effective refractory period
- Renal excretion
- Half-life 3 hours
  - Sustained release dosage forms exist
Procainamide: Adverse Effects

- **Systemic lupus erythematosus**
  - Chronic administration results in + ANA in most
  - Particularly seen in slow acetylators
  - Lupus-like syndrome seen in up to 1/3 of patients
  - Clinical manifestations remit when drug is discontinued or changed to N-acetyl-procainamide
    - Suggests important pathogenetic role for aromatic amine acid group on procainamide

- **Granulocytopenia (Agranulocytosis)**

- **Cardiac toxicity**
  - Prolonged QRS, PR and/or QT intervals
  - Arrhythmias, e.g., torsades
  - Depression of LV function
Procainamide: Use

• Oral and IV dosage forms
  – IV form associated with hypotension when given by rapid infusion
    • Secondary to ganglionic blocking effect
  – Oral dosing every 3-4 hours
  – Oral dosing every 6-8 hours with sustained release form

• Therapeutic level
  – 4 to 12 μg/ml
Disopyramide

• Effects similar to quinidine
• Marked suppression of contractility
• Marked anticholinergic effects
• EKG effects similar to quinidine
Class IB agents:

- Block Na channels in depolarized tissues
- Less prominent Na channel blocking activity at rest
- Tend to bind to inactivated state
  - Induced by depolarization
  - “Use-dependent” effect
- Dissociate from Na channel more rapidly than other Class I drugs
- More effective with tachycardias than with slow arrhythmias
Class IB agents:

- Lidocaine
- Tocainide
- Mexilitene
Lidocaine

- Use widely as a local anesthetic
- Reduces ventricular automaticity
- No effect on heart rate, PR interval or QRS complex
- Produces no changes on EKG
- No atrial affects
- No anticholinergic effects
Lidocaine: Clinical Use

• Extremely effective against ventricular arrhythmias
  – Ventricular tachycardia
    • Particularly after myocardial infarction
  – Ventricular fibrillation
• No role in treatment of supraventricular arrhythmias
• Well tolerated hemodynamically
Lidocaine: Pharmacokinetics

- IV administration only
  - Poor oral bioavailability (3%)
- Use via continuous infusion following bolus to raise levels to therapeutic
- Rapid hepatic metabolism
  - Toxicity may occur in liver disease or CHF
  - Clearance = hepatic blood flow
Lidocaine: Adverse Effects

- Central Nervous System
  - Drowsiness
  - Nystagmus
  - Confusion
  - Slurred speech
  - Paresthesias
- Toxic levels (> 6 mg/L) result in seizures
- Generally very low toxicity
  - Primarily with liver disease or CHF
Tocainide

- Oral agent
- Effects similar to lidocaine
- 10 to 15% response
- Interstitial pneumonitis
  - Occurs after months of therapy
  - Neutrophilic alveolitis with organizing pneumonia
  - Irreversible fibrosis may occur with continuing inflammation
- Introduced 1984; Discontinued 2004
Class IC agents:

- All preferentially bind to inactivated Na channel
  - Slow dissociation
  - Results in increased effect at more rapid rate
    - Use-dependence
    - Contributes to proarrhythmic effects
- **Encainide**
  - Withdrawn after increased death rate seen in CAST (late occurrence)
- **Flecainide**
- **Propafenone**
- **Moricizine**
  - Phenothiazine with modest efficacy, premature mortality
Flecainide

- Flecainide acetate (Tambocor)
Propafenone

- Class IC agent
  - Also weak β-blocking and Ca channel blocking effects
- Slows conduction in atria, ventricles, AV node, His-Purkinje system and accessory pathways
  - Increases atrial and ventricular refractoriness
- Negative inotropic effect
- Useful in ventricular tachycardia and for prevention and termination of supraventricular reentrant tachycardias involving accessory pathways
- Extensive first-pass metabolism, dose-dependent
  - 2 active metabolites
- Dysgeusia occurs; proarrhythmic effects
Mexiletine

- Mexiletine HCl (Mexitil)
Bretylium tosylate

- Initially introduced as antihypertensive
- Delays repolarization in Purkinje fibers and ventricular muscle
- Prolongs effective refractory period
  - Most pronounced in ischemic cells
- No effect on automaticity, conduction velocity or EKG
- Used only in severe ventricular arrhythmias
- Hypotension occurs in 2/3
  - Blocks release of catecholamine after initial uptake
  - See brief period of sympathetic stimulation
- IV use
- Renal clearance, half-life 4-16 hours
Amiodarone

- Similar in action to bretylium
  - Also has Class IA, II and IV effect
- Antiarrhythmic effects may not be seen for days to weeks
- Lipid soluble drug
- Distribution described by multi-compartmental model
  - Enters tissues at different rates
  - Drug first distributes to extravascular sites (10-1000x conc)
  - Cannot give loading dose, then maintenance dose
  - Steady state then exists in which tissue stores are saturated
    - Takes weeks to months to achieve
  - After one month or more, can reduce dose to maintenance
    - Represents drug eliminated from body without additional tissue accumulation
Amiodarone

- Administered via oral or IV route
- Hepatic metabolism
  - Desethylamiodarone major metabolite
    - Possesses antiarrhythmic properties similar to parent drug (Type Ib effects)
    - Accumulates in lipid-rich tissue (myocardium)
  - Large amount of iodine released during metabolism (3 mg organic I per 100 mg amiodarone per day)
- Wide range of bioavailability
  - 22 to 86%
- Negligible amount excreted unchanged
- Protein binding 96%
Amiodarone

- Half-life = 20-100 days
- Excreted by skin, lacrimal glands and into bile
- Little proarrhythmic effects
- Large $V_D = 70 \text{L/kg}$

- Not dialyzable
Amiodarone: Clinical Use

• **Useful for ventricular arrhythmias as well as for atrial fibrillation**
  – First-choice antiarrhythmic for persistent VF/pulseless VT
• Also used in WPW syndrome
• Delays repolarization and prolongs refractory period
  – Atria
  – A-V node
  – Ventricles
• Decreases myocardial contractility
  – Antianginal
• EKG effects
  – Widens QRS
  – Prolongs PR interval
  – Prolongs QT interval
Amiodarone: Adverse Effects

- **Corneal micro-deposits**
  - Occurs in most patients receiving long-term medication
  - Dose-dependent and reversible
  - Rarely cause visual disturbances

- **Cutaneous effects**
  - Photosensitivity
  - Blue-gray discoloration

- **Hepatic dysfunction**
  - Elevation in serum transaminase levels
Amiodarone: Adverse Effects

- **Pulmonary Disease**
  - Pulmonary involvement occurs in 5 to 15%
  - Toxic effect responsible for deaths (5-10% fatal)
  - Symptoms can occur one month to five years after therapy started
  - Incidence lower with lower maintenance doses
  - Chronic interstitial pneumonitis most common
    - Foamy macrophages characteristic finding in alveoli
    - Cells filled with amiodarone-phospholipid complex
  - Pathogenesis unclear
    - Direct drug cytotoxicity
    - Hypersensitivity reaction
    - Dose related
Amiodarone: Adverse Effects

• **Thyroid Abnormalities**
  – Most common complication of therapy
  – Occurs even with low doses
  – 3 mg inorganic I released/100mg amiodarone
  – Changes due to **impaired deiodination of T4 to T3**
  – Inhibits outer ring mono-deiodination of T4, decreasing T3 production, and of reverse T3
    • Serum **TSH** usually rises after initiation of therapy
      – Returns to normal after 2 to 3 months
    • Serum T4 rises 20 to 40% during first month, then gradually falls towards baseline
    • Serum T3 falls by up to 30% within few weeks and remain at this level
Amiodarone: Adverse Effects

- **Neurologic Dysfunction**
  - Tremor
  - Ataxia
  - Peripheral neuropathy
  - Fatigue
  - Dose-dependent

- **Cardiac effects**
  - Bradycardia and AV nodal block
    - Primarily due to Ca channel blocking effect
  - Prolongation of repolarization and QT interval
    - Proarrhythmic effect
      - Likely in face of hypokalemia, hypomagnesemia

Ejection Fraction usually unaffected despite negative inotropic effect
Amiodarone: Drug interactions

• Interferes with hepatic metabolism of many drugs
  – Quinidine
  – Procainamide
  – Digoxin
  – Warfarin
  – Theophylline

• Effects may persist for months after discontinuation of amiodarone

• Crosses placenta and into breast milk
Ibutilide fumarate

• Predominant Class III properties
  – Prolongation of action potential
  – Increases refractoriness
    • Atrial
    • Ventricular
  – Mild slowing of sinus rate
  – No effect on QRS
  – Dose related QT prolongation
  – No effects of Cardiac output or BP
Ibutilide fumarate

- High plasma clearance
  - = hepatic blood flow
- Multiple metabolites
  - One active metabolite
- Indicated in conversion of atrial fibrillation/flutter of recent onset
- Proarrhythmic effect
  - Torsades de pointes
    - Develops quickly
    - Not to be used with Class IA or III agents
- IV infusion with continuous EKG monitoring
Adenosine

- Endogenous nucleoside
- Slows AV nodal conduction velocity
- Slows rates of SA node firing
- Increases AV nodal refractory period
- Decreases duration of action potential
Adenosine

- Interacts with A1 receptors on extracellular surface of cardiac cells
  - Causes activation of potassium channels
  - Causes increase in K conductance
  - Inhibits cAMP-induced Ca^{++} influx

- No direct effect on ventricular tissue
  - Acts exclusively in atrium, AV node and SA node

- In patients with dual AV nodal pathways and typical AV nodal reentrant tachycardia, fast pathway more sensitive than slow pathway to effects of adenosine
Adenosine

• EKG effects
  – Prolongation of P-R interval
  – Slowing of sinus rate
  – Prolongation of A-H interval

• Usual dose without hemodynamic effects
Adenosine: Pharmacokinetics

• Rapidly removed from circulation
  – Taken up by RBCs and vascular endothelial cells
  – $t_{1/2} < 10$ seconds
  – Degraded by intra and extracellular deaminases
    • Metabolized to inosine
• Antagonized by theophylline, caffeine
• Potentiated by dipyridamole
  – Adenosine uptake inhibitor
• Administer via rapid IV bolus
• Flushing and dyspnea major adverse effects
Adenosine: Clinical Use

- Paroxysmal supraventricular tachycardia
  - At least as effective as verapamil
  - Effective in patients who do not respond to verapamil

- Pharmacologic stress testing
  - Used in patients with suspected coronary artery disease with limited exercise capacity
  - Adenosine activates A2 receptors resulting in vasodilatation of resistance coronary vessels.
  - Increase in coronary blood flow leads to flow mediated release of NO producing epicardial coronary artery dilatation
  - Dipyridamole and dobutamine also used