Arrhythmias

Edward JN Ishac, Ph.D.
Smith Building, Room 742
eishac@hsc.vcu.edu
8-2127 or 8-2126

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Heart Physiology
Closed system
Supply nutrients/O2
Remove metabolites

Heart Physiology
P - atria depolarization
QRS - ventricle depolarization
PR - conduction A-V
T - ventricle repolarization
QT - duration ventricle of repolarization

Electrocardiogram (ECG)

Heart Physiology
Closed system
Pressure driven
Supply nutrients/O2
Remove metabolites

Heart Physiology
P - atria depolarization
QRS - ventricle depolarization
PR - conduction A-V
T - ventricle repolarization
QT - duration ventricle repolarization

Ion Permeability

<table>
<thead>
<tr>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

0 Na⁺ - open
1 Na⁺ - close
K⁺ - open/close
2 Ca²⁺ - open
K⁺ - leak
3 Ca²⁺ - close
K⁺ - open
4 K⁺ - close

Na⁺/Ca²⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)

Cardiac Action Potentials

<table>
<thead>
<tr>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

0 Na⁺ - open
1 Na⁺ - close
K⁺ - open/close
2 Ca²⁺ - open
K⁺ - leak
3 Ca²⁺ - close
K⁺ - open
4 K⁺ - close

Na⁺/Ca²⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)
Characteristics of Arrhythmias

Definitions:
- normal sinus rhythm (60-90bpm), SA node pacemaker
- arrhythmia: any abnormality of firing rate, regularity or site of origin of cardiac impulse or disturbance of conduction that alters the normal sequence of activity of atria and ventricles.

Occurrence:
- 80% of patients with acute myocardial infarctions
- 50% of anaesthetized patients
- less than 25% of patients on digitalis

Classification of arrhythmia

1. Characteristics:
   a. flutter – very rapid but regular contractions
   b. tachycardia – increased rate
   c. bradycardia – decreased rate
   d. fibrillation – disorganized contractile activity

2. Sites involved:
   a. ventricular
   b. atrial
   c. sinus
   d. AV node
   e. Supraventricular (atrial myocardium or AV node)

Examples of Arrhythmias

Mechanisms of arrhythmias

1. Abnormal impulse generation (abnormal automaticity)
   a. automaticity of normally automatic cells (SA, AV, His)
   b. generation of impulses in normally non-automatic cells
      - development of phase 4 depolarization in normally non-automatic cells
      - 'triggered activity' due to afterdepolarizations
      - early afterdepolarization
      - delayed afterdepolarization

2. Abnormal impulse conduction (more common mechanism)
   a. AV block – ventricle free to start own pacemaker rhythm
   b. Re-entry: re-excitation around a conducting loop, which produces tachycardia
      - unidirectional conduction block
      - establishment of new loop of excitation
      - conduction time that outlasts refractory period

Heart Physiology

Unidirectional Block

Damaged tissue is usually depolarized → ↓ conduction velocity
Strategy of Antidysrhythmic Agents

Suppression of dysrhythmias

A. Alter automaticity
   i. decrease slope of Phase 4 depolarization
   ii. increase the threshold potential
   iii. decrease resting (maximum diastolic) potential

B. Alter conduction velocity
   i. mainly the rate of rise of Phase 4 depolarization
   ii. decrease resting (maximum diastolic) potential
   iii. decrease membrane responsiveness

C. Alter the refractory period
   i. increase Phase 2 plateau
   ii. increase action potential duration

Classification of Antidysrhythmic Drugs

Vaughan-Williams classification (1970), subsequently modified by Harrison.

Helpful, But?
1. based on electrophysiological actions in normal tissue
2. presumes a mechanism of action of antidysrhythmic drugs
3. consists of four main classes and three subclasses
4. does not include actions of other agents (i.e., adenosine)

Vaughan-Williams Classification

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Mechanism</th>
<th>Prototype</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Mod. block Ph.0; slow conduction; ↑ ERP</td>
<td>Quinidine</td>
</tr>
<tr>
<td>IB</td>
<td>Min. block Ph.0; slow conduction; shorten Ph.3 repolarization</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>IC</td>
<td>Marked block Ph.0; slow conduction; no change</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Class II</td>
<td>Beta blockers; decrease adrenergic input; No effect APD, suppress Ph.4 depolarization</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Class III</td>
<td>Prolong repolarization/refractory period other means than exclusively this block (mainly K+ channel blockade)</td>
<td>Bretylium</td>
</tr>
<tr>
<td>Class IV</td>
<td>Ca channel blockers, Slower conduction and ↑ ERP, Phase 2 plateau in normal tissue (A-V node) and Ca-dependent slow responses of depolarized tissue (atria, ventricle, Purkinje)</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Others</td>
<td>Adenosine, Digoxin, Anticoagulants</td>
<td></td>
</tr>
</tbody>
</table>

Electrophysiological Properties Of Specialized Cardiac Fibers

<table>
<thead>
<tr>
<th>CLASS OF ANTIARRHYTHMIC DRUG</th>
<th>IA</th>
<th>IB</th>
<th>IC</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purkinje fibers</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Action potential amplitude</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Action potential duration</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Effective refractory period (ERP)</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>ERP/APD</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>Membrane responsiveness</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Automaticity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Quinidine (Class IA prototype)

Other examples: Propranolol, Disopyramide

- D-isomer of quinine
- Among the most common local anesthetics
- As with most of the Class I agents
  - moderate block of sodium channels
  - decreases automaticity of pacemaker cells
  - increases effective refractory period/AP duration
**Actions of Quinidine**

**Cardiac effects**
- a. ↓ automaticity, conduction velocity and excitability of cardiac cells.
- b. Preferentially blocks open Na channels.
- c. Recovery from block slow in depolarized tissue; lengthens refractory period (RP).
- d. All effects are potentiated in depolarized tissues.
- e. Increases action potential duration (APD) and prolongs AP repolarization via block of K channels; decreases reentry.
- f. Indirect action: anticholinergic effect (accelerates heart), which can speed A-V conduction.

**Extracardiac**
- a. Blocks alpha-adrenoreceptors to yield vasodilatation.
- b. Other strong antimuscarinic actions.

**Toxicity**
- "Quinidine syncope" (fainting) - due to disorganized ventricular tachycardia.
- Associated with greatly lengthened Q-T interval; can lead to Torsades de Pointes (precurser to ventricular fibrillation).
- Negative inotropic action (decreases contractility).
- GI - diarrhea, nausea, vomiting.
- CNS effects - headaches, dizziness, tinnitus (quinidine "Cinchonism").

**Quinidine: Pharmacokinetics/therapeutics**
- a. Oral, rapidly absorbed, 80% bound to membrane proteins.
- b. Hydroxylated in liver; T1/2 = 6-8 h.
- c. Drug interaction: displaces digoxin from binding sites; so avoid giving drugs together.
- d. Probably are active metabolites of quinidine.
- e. Effective in treatment of nearly all dysrhythmias, including:
  1) Premature atrial contractions.
  2) Paroxysmal atrial fibrillation and flutter.

**Procainamide (Class 1A)**

**Cardiac effects**
- a. Similar to quinidine, less muscarinic & alpha-adrenergic blockade.
- b. Has negative inotropic action.

**Extracardiac effects**
- a. Ganglionic blocking reduces peripheral vascular resistance.

**Toxicity**
- a. Cardiac: Similar to quinidine; cardiac depression.

**Pharmacokinetics/therapeutics**
- a. Administered orally, i-v and intramuscularly.
- b. Major metabolite in liver is N-acetylprocainamide (NAPA), a weak Na channel blocker with class III activity. Bimodal distribution in population of rapid acetylators, who can accumulate high levels of NAPA.
- c. T1/2 = 3-4 hours; necessitates frequent dosing; kidney chief elimination path. NAPA has longer T1/2 and can accumulate.
- d. Usually used short-term. Second choice in CCUs after lidocaine for ventricular dysrhythmias associated with acute MIs.

**Lidocaine (Class IB prototype)**

**Other examples:** Mexiletine, Phenytoin, Tocainide.

**General**
- a. Most commonly used antidysrhythmic agent in emergency care.
- b. Given i-v and i-m; widely used in ICU critical care units (DOC).
- c. Very low toxicity.
- d. A local anesthetic, works on nerve at higher doses.

**Lidocaine Actions**

**Cardiac effects**
- a. Generally decreases APD, hastens AP repolarization, decreases automaticity and increases refractory period in depolarized cells.
- b. Exclusively acts on Na channels in depolarized tissue by blocking open and inactivated Na channels.
- c. Potent suppresser of abnormal activity.
- d. Most Na channels of normal cells rapidly unblock from lidocaine during diastole; few electrophysiological effects in normal tissue.

**Toxicity**
- Least cardiotoxic, high dose can lead to hypotension.
- Tremors, nausea, slurred speech, convulsions.

**Pharmacokinetics/therapy**
- a. i.v., i-m since extensive first pass hepatic metabolism.
- b. T1/2 = 0.5-4 hours.
- c. Very effective in suppressing dysrhythmia associated with depol. tissue (block does not block Na channels).
- d. Suppresses ventricular tachycardia; prevents fibrillation after acute MI; test choice for this application; rarely used in supraventricular arrhythmias.
Phenytoin (Class IB)
1. Non-sedative anticonvulsant used in treating epilepsy ('Dilantin')
2. Limited efficacy as antidyssrhythmic (second line antidyssrhythmic)
3. Suppresses ectopic activation by blocking Na and Ca channels
4. Especially effective against digitalis-induced dysrhythmias
5. T1/2 = 24 hr - metabolized in liver
6. Gingival hyperplasia

Flecainide (Class IC prototype)
Other examples: Lorcainide, Propafenone, Indecainide, Moricizine
Depress rate of rise of AP without change in refractoriness or APD in normally polarized cells
1. Decreases APD, decreases automaticity, conduction in depolarized cells.
2. Marked block of open Na channels (decreases Ph. D), no change repolarization.
3. Used primarily for ventricular dysrhythmias but effective for atrial too
4. No antimuscarinic action
5. Suppresses premature ventricular contractions
6. Associated with significant mortality; thus, use limited to last resort applications like treating ventricular fibrillation.

Propranolol (Class II, beta adrenoreceptor blockers)
Other agents: Metoprolol, Esmolol, Sotalol (also Class III), Acebutolol
a. Slow A-V conduction
b. Prolong A-V refractory period
c. Suppress automaticity

Cardiac Action Potentials
Ion Flow

Clinical uses: Beta-Blockers
- Angina (non-selective or B1-selective)
  - Cardiac: ↓2 demand more than O2 supply
  - Exercise tolerance ↑ in angina patients
- Arrhythmia (B1-selective, LA-action)
  - ↓ catecholamine-induced increases in conductivity and automaticity
- Congestive Heart Failure
  - caution with use
- Glaucoma (non-selective)
  - ↓ aqueous humor formation (Timolol)
- Other
  - Block of tremor of peripheral origin (B2-AR in skeletal muscle)
  - Migraine prophylaxis (methyldopa)
  - hyperthyroidism, cardiac manifestation (only propranolol)
  - panic attacks, stage fright

β-Blockers: Untoward Effects, Contraindications
- Supersensitivity:
  - Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal
- Asthma:
  - Blockade of pulmonary β2-receptors increase in airway resistance (bronchospasm)
- Diabetes:
  - Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
Bretylium (Class III, K⁺ channel blockers)

*Others: Amiodarone, Ibutilide (Sotatol, also beta-blocker)*

**General:** originally used as an antihypertensive agent

**Cardiac effects:**
- a. Direct antidysrhythmic action
- b. Increases ventricular APD and increases refractory period; decreases automaticity
- c. Most pronounced action in ischemic cells having short APD
- d. Initially stimulates and then blocks neuronal catecholamine release from adrenergic nerve terminals
- e. Blocks cardiac K channels to increase APD

**Extracardiac effects:** Hypotension (from block of NE release)

**Pharmacokinetics/Therapeutics:**
- a. IV or intramuscular
- b. Excreted mainly by the kidney
- c. Usually for emergency use only: ventricular fibrillation when lidocaine and cardioversion therapy fail. Increases threshold for fibrillation.
- d. Decreases tachycardias and early extrasystoles by increasing effective refractory period

Amiodarone (Class III)

**General:**
- a. not frontline, prolongs refractory period by blocking potassium channels
- b. also member of Classes IA, III, IV since blocks Na, K, Ca channels and alpha and beta adrenergic receptors
- c. secondline agent because of its serious side effects
- d. effective against atrial, A-V and ventricular dysrhythmias
- e. very long acting (20 days)

Verapamil (Class IV, Ca²⁺ channel blockers)

*Other example: Diltiazem - Increasing use and importance*

- a. Blocks active and inactivated Ca channels, prevents Ca entry
- b. More effective on depolarized tissue, tissue firing frequently or areas where activity dependent on Ca channels (SA node, A-V node)
- c. Increases A-V conduction time and refractory period; directly slows SA and A-V node automaticity
- d. suppresses oscillatory depolarizing after depolarizations due to digoxin

Ca²⁺ Channel Blockers - Actions

**Extracardiac:**
- a. Peripheral vasodilatation via effect on smooth muscle
- b. Used as antihypertensive / antihypertensive
- c. Hypotension may increase HR reflexively

**Toxicity:**
- a. Cardiac:
  - Too negative inotropic for damaged heart, depresses contractility
  - Can produce full A-V block
- b. Extracardiac:
  - Hypotension
  - Constipation, Nervousness
  - Gingival hyperplasia

**Pharmacokinetics/Therapeutics:**
- a. T½ = 7h, metabolized by liver
- b. Oral administration; also available parenterally
- c. Great caution for patients with liver disease
- d. Blocks reentrant supraventricular tachycardia ("A-V nodal reentrant tachycardia"), decreases atrial flutter and fibrillation
- e. Only moderately effective against ventricular arrhythmias

Dysrhythmics - Others

1. **Adenosine**: i.v. (secs), activates P₁ purinergic receptors (A₁) coupled to K channels, ICV. Trefrectory period
2. **Potassium ions (K+)**: Depress ectopic pacemakers
3. **Digoxin**: used to treat atrial flutter and fibrillation - AV node inhibition, decreases atrial re-entrant activity. - myocardium, decreases atrial and AV node refractory period. - Purkinje fibers, decreases refractory period.
4. **Autonomic agents**: used to treat A-V block - β-agonists, anticholinergics
5. **Anticoagulant therapy**: prevent formation of systemic emboli & stroke

Cardiac Effects of Antiarhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>AV</th>
<th>CI</th>
<th>BP</th>
<th>APD</th>
<th>ARR effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>να̅-block</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Tocainide</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IIIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Tocainide</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>IIB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IIIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>β-block</td>
</tr>
</tbody>
</table>

More Important agents
Pharmacokinetic Properties of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Plasma Binding %</th>
<th>T1/2 (Hrs)</th>
<th>Drug Excretion Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>50</td>
<td>6</td>
<td>20-30%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td>15</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>20-85</td>
<td>5</td>
<td>50-70%</td>
</tr>
<tr>
<td>Indacrinol</td>
<td>II</td>
<td>45</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Tocainide</td>
<td>II</td>
<td>10</td>
<td>14</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>65</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IB</td>
<td>45</td>
<td>4</td>
<td>40%</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IA</td>
<td>65</td>
<td>8</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IB</td>
<td>95</td>
<td>4</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Acetylsalicylic Acid</td>
<td>IB</td>
<td>5</td>
<td>2</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>IB</td>
<td>8 days</td>
<td>8 hrs</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IA</td>
<td>95</td>
<td>20 days</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IA</td>
<td>90</td>
<td>6</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>

Drug Excretion

**Unchanged**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>T1/2 (Hrs)</th>
<th>Drug Excretion Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>50</td>
<td>20-30%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td>15</td>
<td>50%</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>20-85</td>
<td>50-70%</td>
</tr>
<tr>
<td>Indacrinol</td>
<td>II</td>
<td>45</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Tocainide</td>
<td>II</td>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>65</td>
<td>10%</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IB</td>
<td>45</td>
<td>40%</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IA</td>
<td>65</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IB</td>
<td>95</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Acetylsalicylic Acid</td>
<td>IB</td>
<td>5</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>IB</td>
<td>8 hrs</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IA</td>
<td>20 days</td>
<td>&gt;1%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IA</td>
<td>90</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>

**Agents used in the treatment of HT, CHF, Arrhythmia and Angina**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Tolerance</th>
<th>Flushing</th>
<th>Dizziness</th>
<th>Headache</th>
<th>Contraindications/Notes/Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Caution: CHF (inotrope), CHF (catecholamine-induced hypertension), or in patients with asthma (bronchospasm).</td>
</tr>
<tr>
<td>ACEI</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>CHF, GFR, hypertension.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Low GFR, renal insufficiency, hypokalemia.</td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>CHF, myocardial infarction.</td>
</tr>
<tr>
<td>Nitrates</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Headache, dizziness, headache, other toxic symptoms.</td>
</tr>
<tr>
<td>Non-Selective Beta-blockers</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Tolerance. Flushing, dizziness, headache.</td>
</tr>
</tbody>
</table>