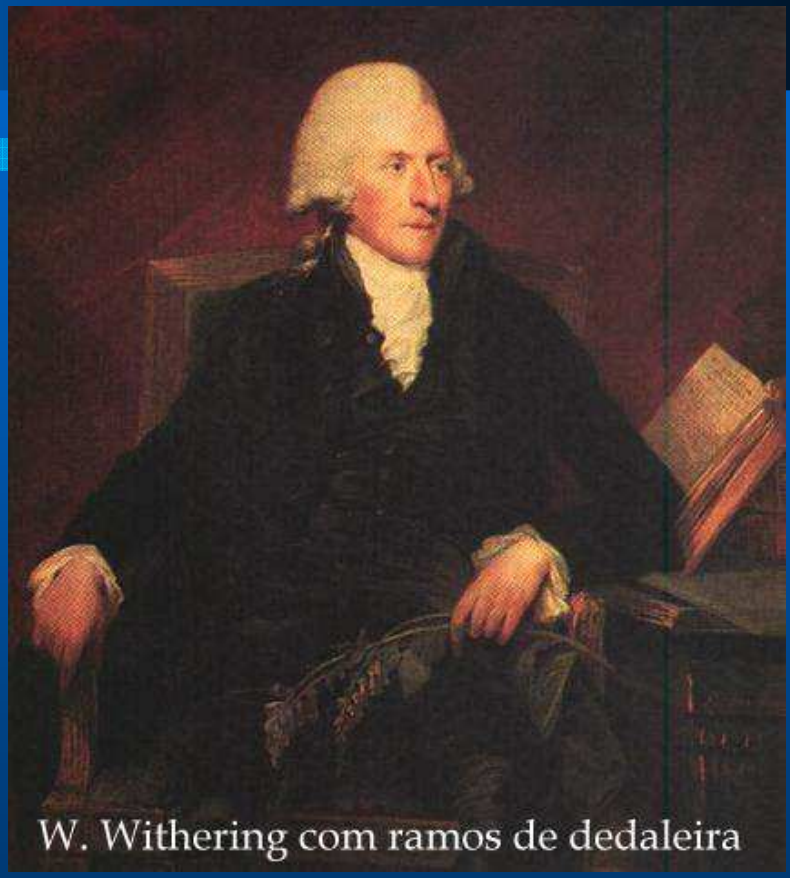
Drugs for Congestive Heart Failure



W. Withering com ramos de dedaleira

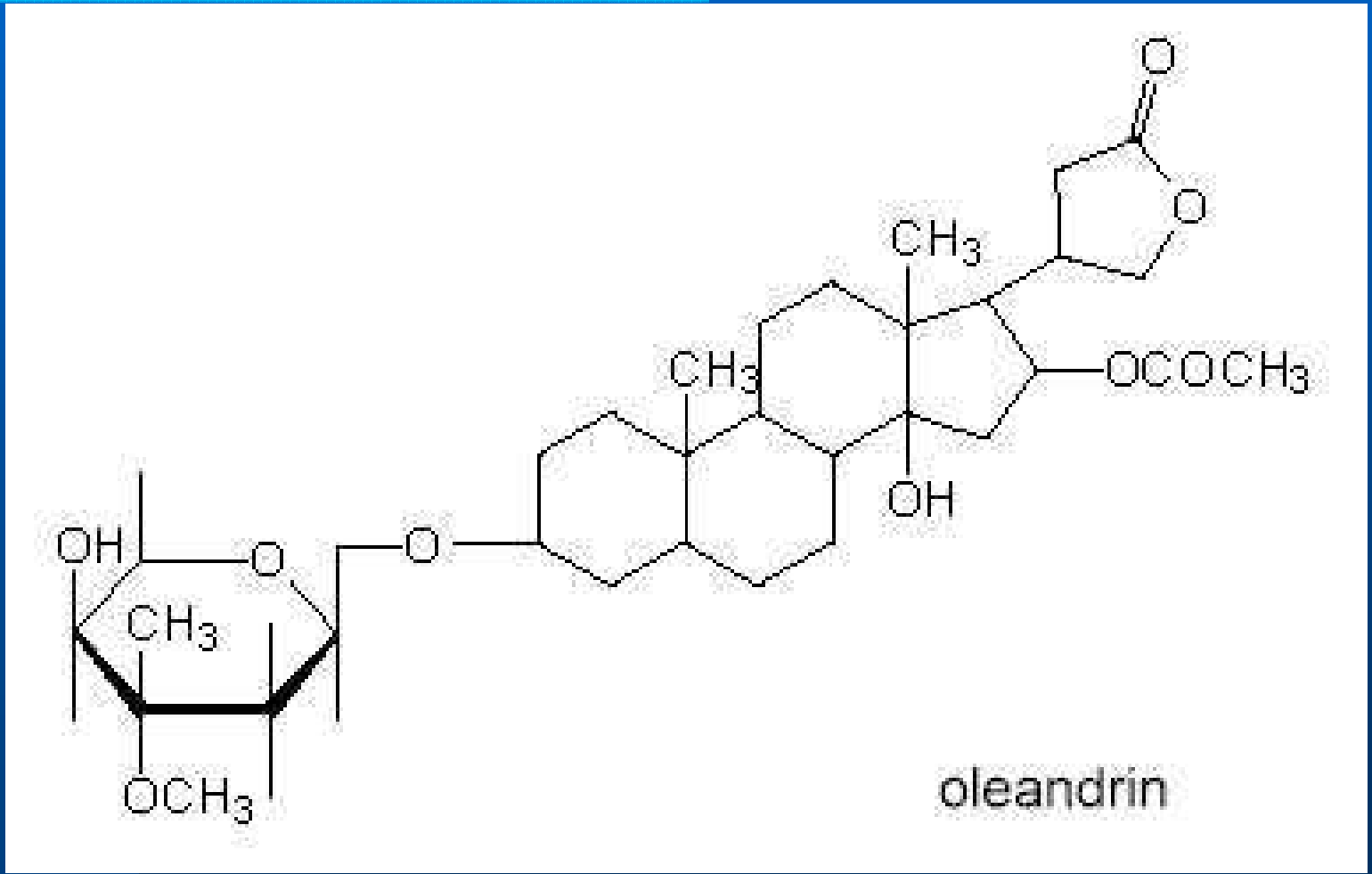
William Withering
1741-1799

Foxglove

Digitalis purpurea

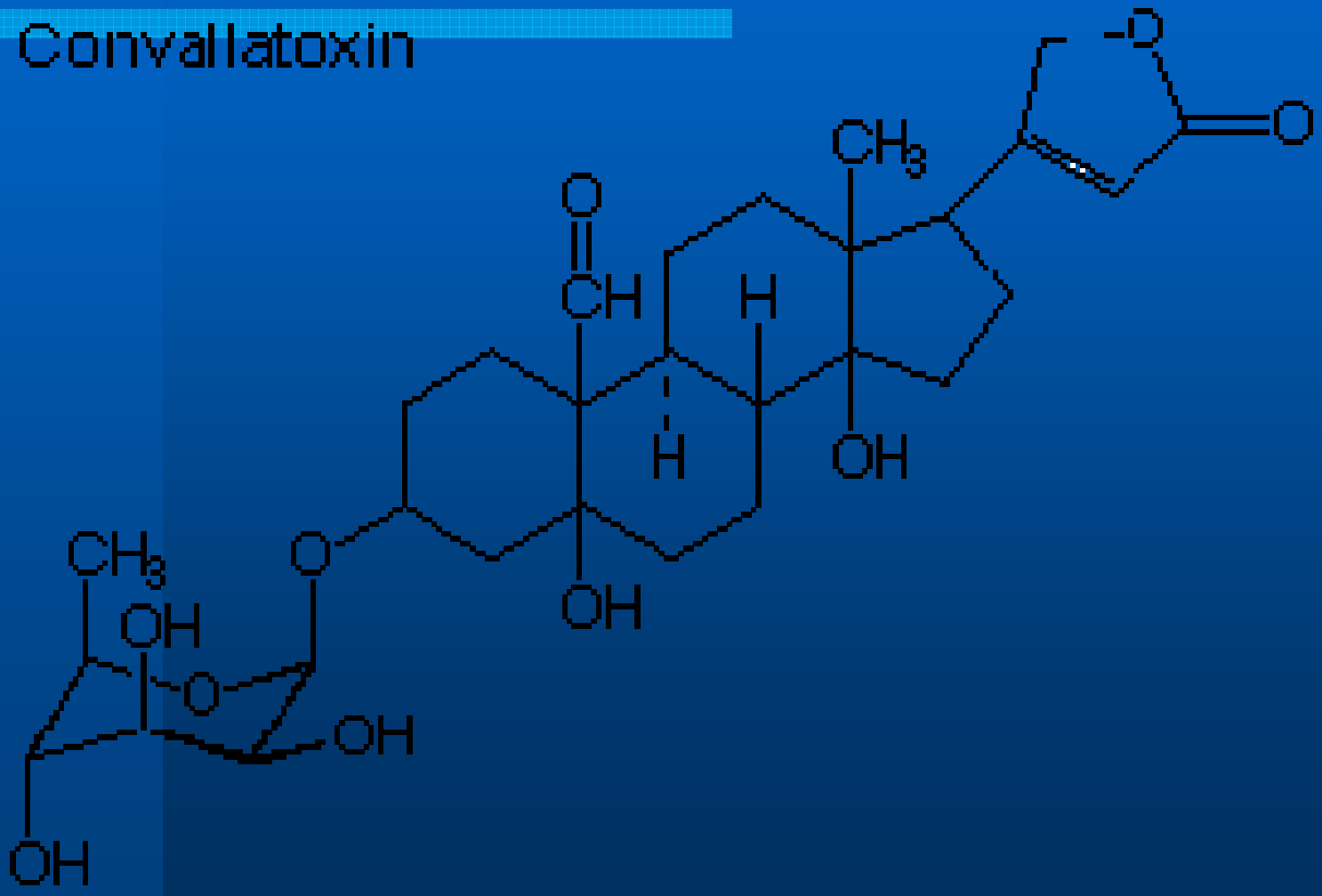
Oleander

Oleandrin



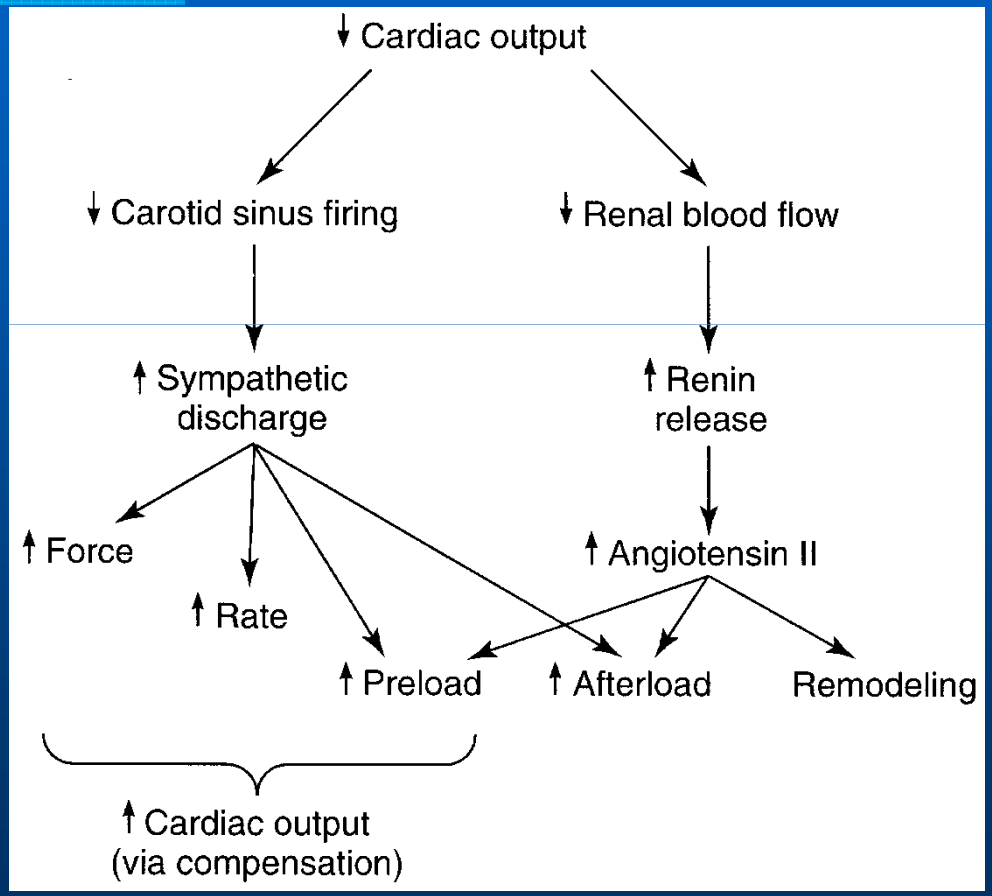
Convallaria majalis

Convallatoxin



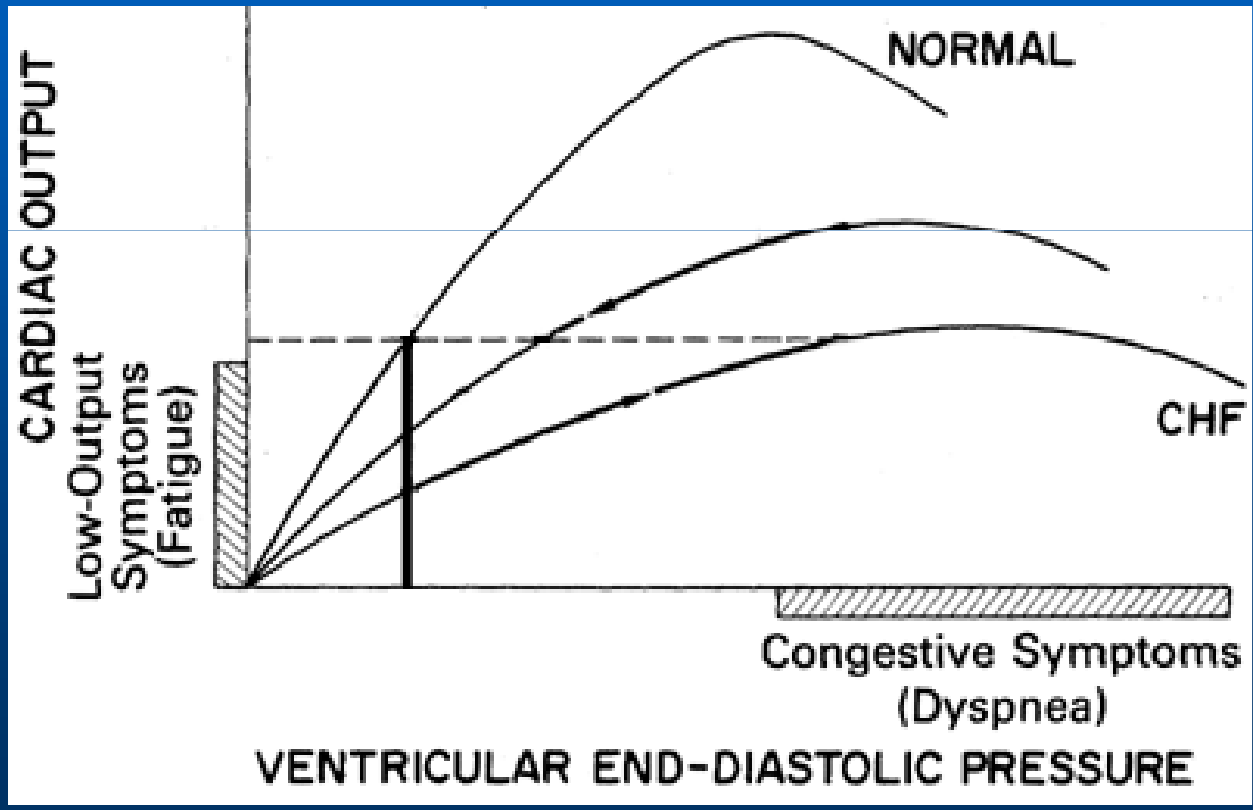
Compensatory Mechanisms in Heart Failure

- **Mechanisms designed for acute loss in cardiac output**
- **Chronic activation of these mechanisms worsens heart failure**



Potential Therapeutic Targets in Heart Failure

- **Preload**
- **Afterload**
- **Contractility**

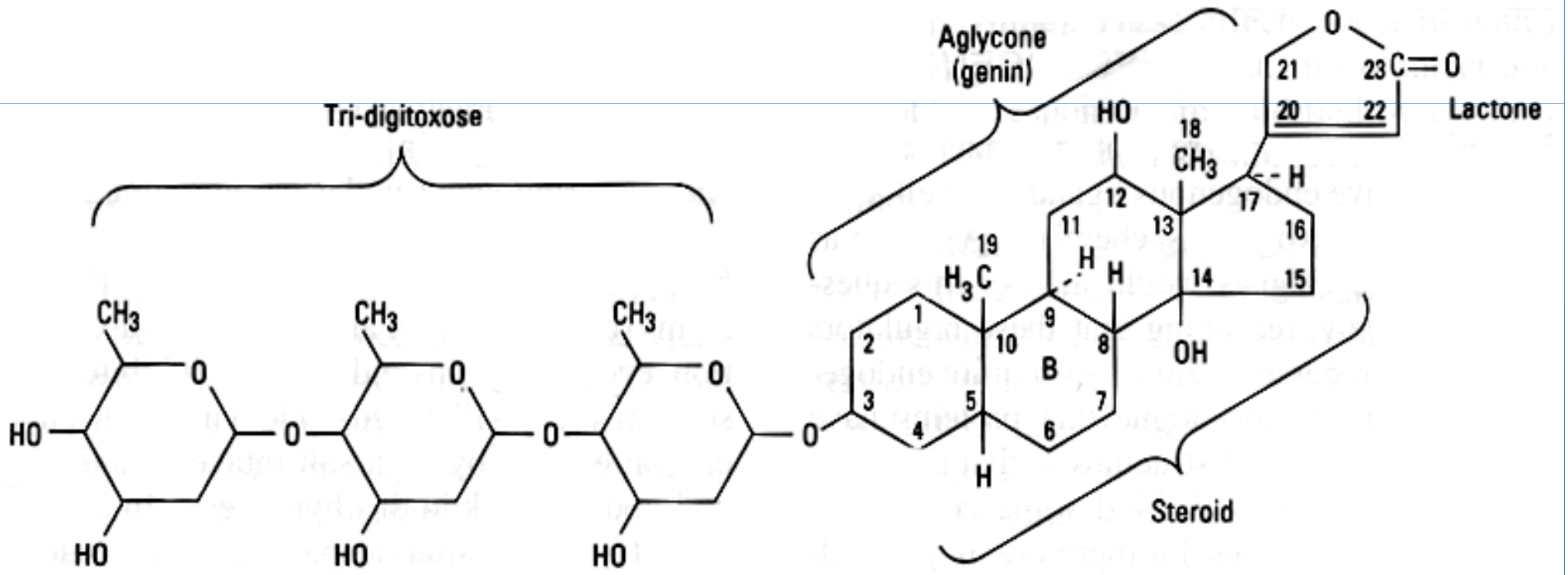


Positive Inotropic Agents

- **Cardiac Glycosides**
- **β-adrenoceptor agonists and dopamine receptor agonists**
- **Phosphodiesterase inhibitors**
- **Ca sensitizers**

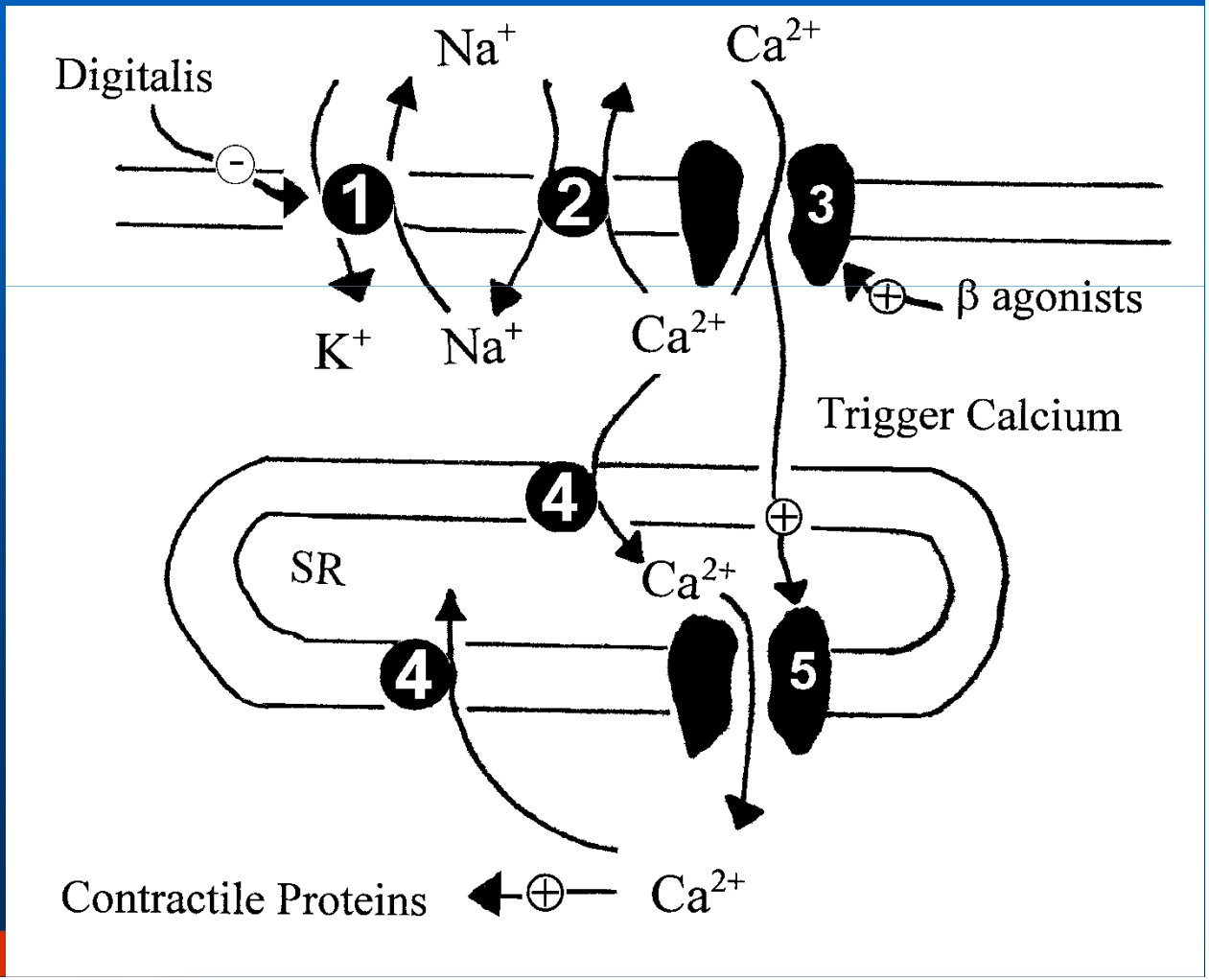
Cardiac Glycosides

- digoxin
- digitoxin
- deslanoside
- ouabain



Mechanism of Digitalis Action: Molecular

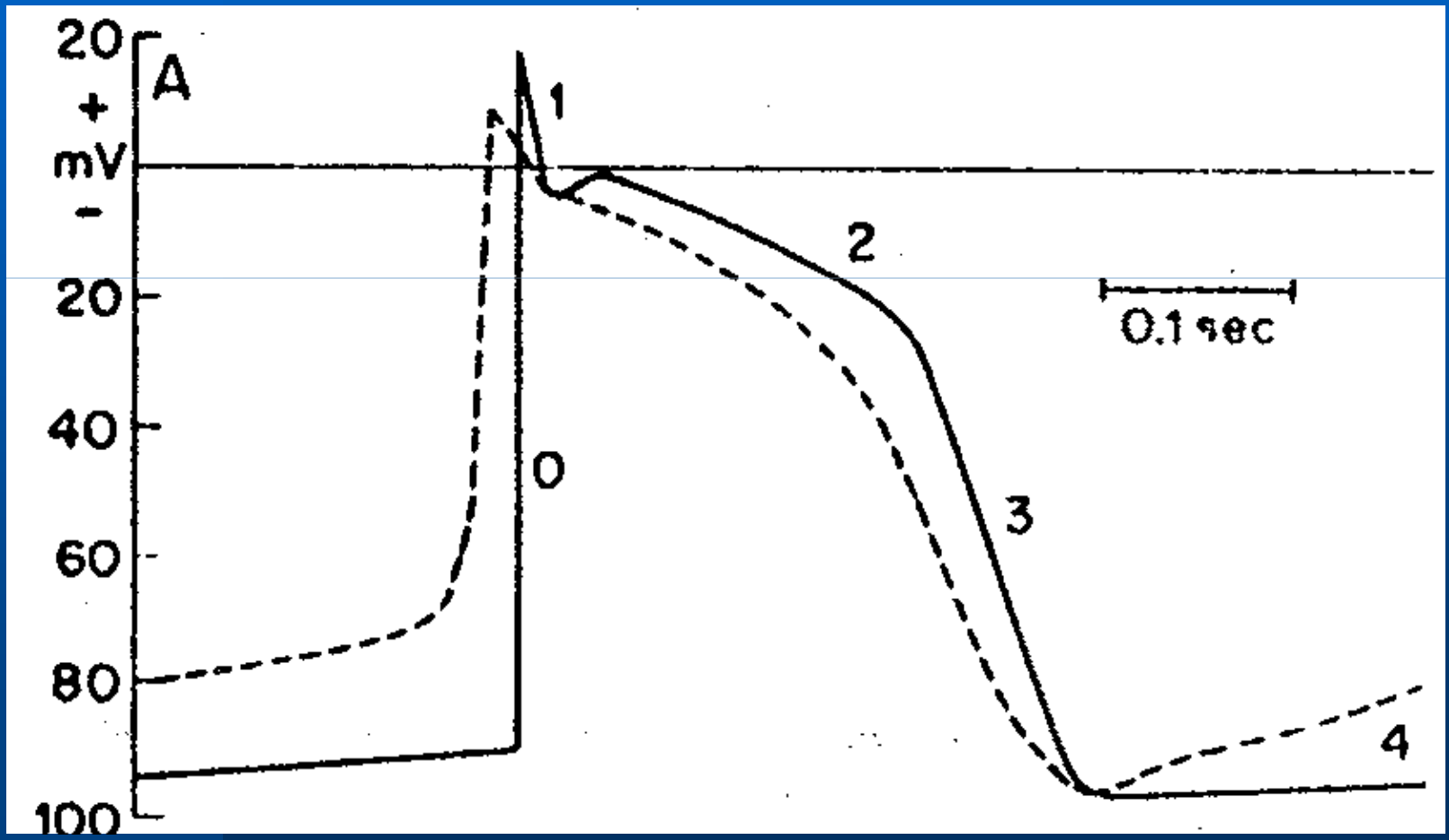
- **Inhibition of Na/K ATPase**
- **blunting of Ca^{2+} extrusion**
- **↑ Ca^{2+}_i**
- **↑ sarcomere shortening**



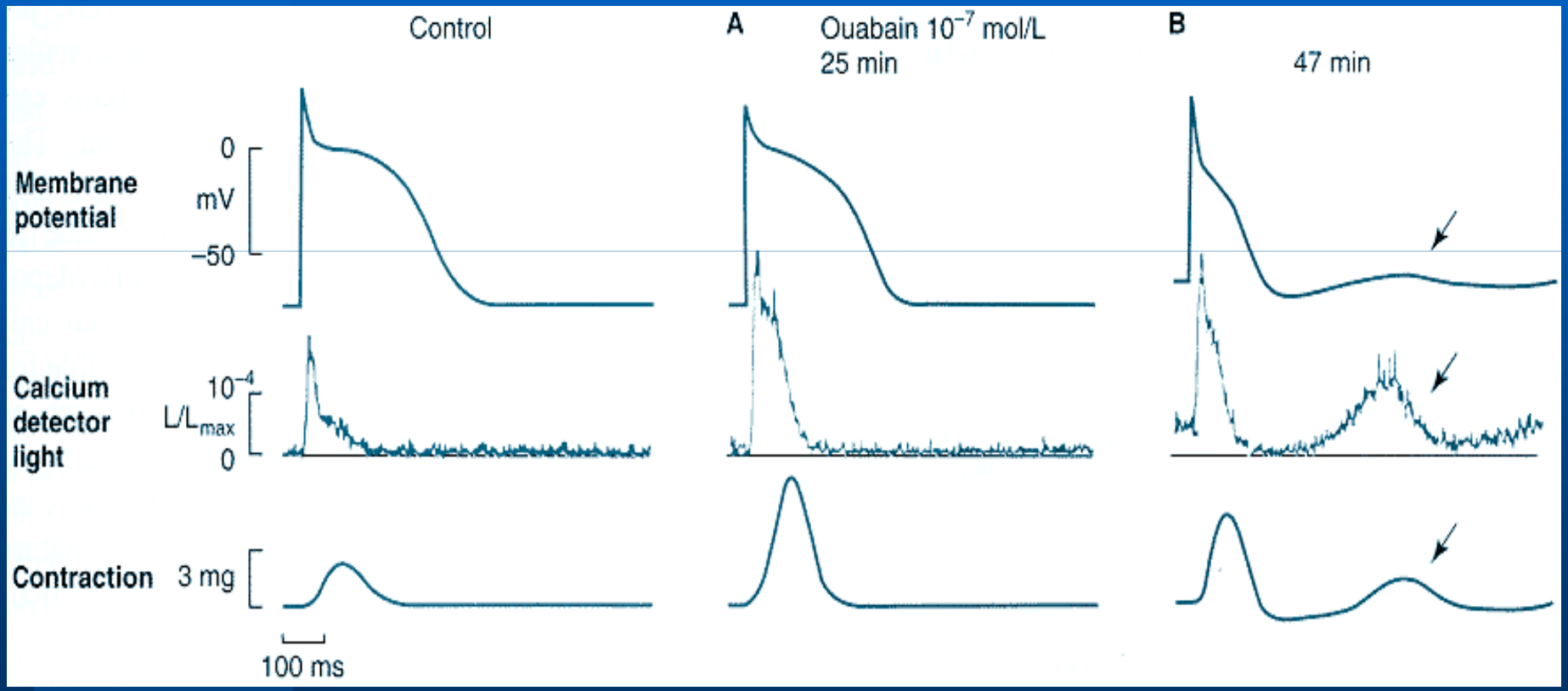
Effects on Cardiac Function

- **Positive inotropy**
- **Direct electrophysiological effects**
- **Effects mediated through increased vagal tone**

Direct Electrophysiological Effects:
Cellular Action Potential



Afterdepolarizations



Summary Direct Electrophysiological Effects

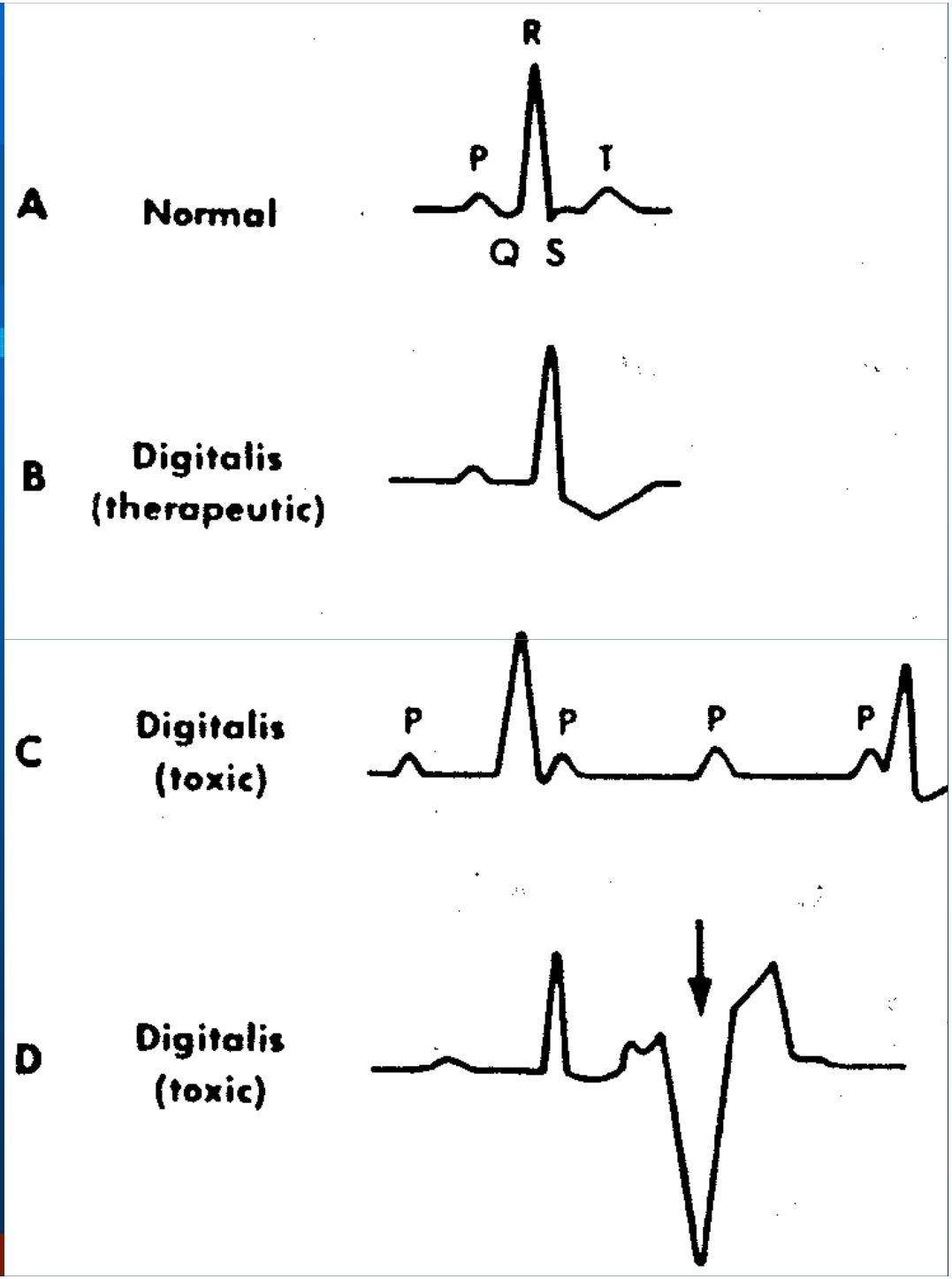
- **Less negative membrane potential: decreased conduction velocity**
- **Decreased action potential duration: decreased refractory period in ventricles**
- **Enhanced automaticity due to**
  - **Steeper phase 4**
  - **Afterdepolarizations**

Parasympathomimetic Effects (Vagomimetic effect)

- **Decreased conduction velocity in the AV node**
- **increased effective refractory period in the AV**
- **Heart block (toxic concentrations)**

ECG Effects of Digitalis

- decrease in R-T interval
- inversion of T wave
- Uncoupled P waves (Toxic concentrations)
- Bigeminy (toxic concentrations)



Therapeutic Uses of Digitalis

- **Congestive Heart Failure**
- **Atrial fibrillation**

Overall Benefit of Digitalis to Myocardial Function

- ↑ **cardiac output**
- ↑ **cardiac efficiency**
- ↓ **heart rate**
- ↓ **cardiac size**

NO survival benefit

Other Beneficial Effects

- **Restoration of baroreceptor sensitivity**
- **Reduction in sympathetic activity**
- **increased renal perfusion, with ↓ edema formation**

Administration

- **Digoxin has a long enough half life (24-36 hr.) and high enough bioavailability to allow once daily dosing**
- **Digoxin has a large volume of distribution and dose must be based on lean body mass**
- **Increased cardiac performance can increase renal function and clearance of digoxin**
- **Eubacterium lentum**

Adverse Effects

- **Cardiac**
  - **AV block**
  - **Bradycardia**
  - **Ventricular extrasystole**
  - **Arrhythmias**
- **CNS (anorexia, nausea, vomiting)**
- **GI**

Therapeutic index is ~ 2!

Serum Electrolytes Affect Toxicity

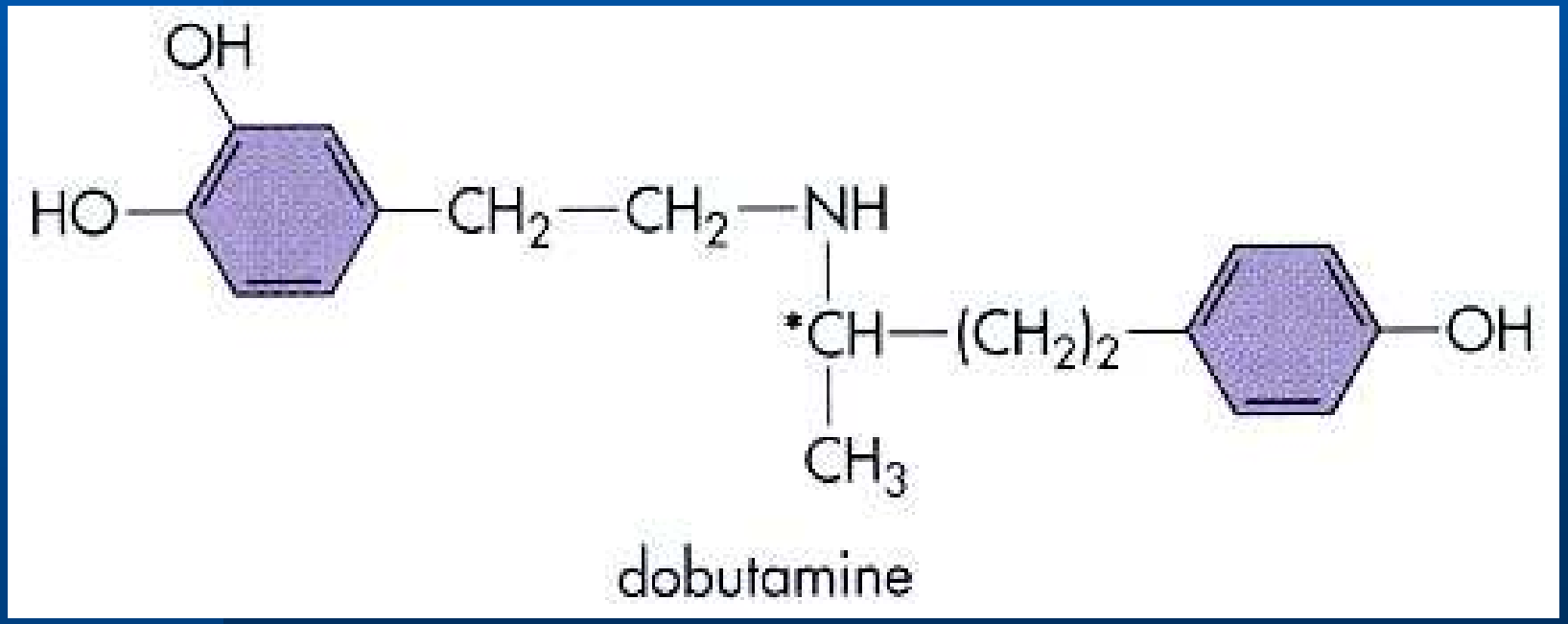
- K^+
  - Digitalis competes for K binding at Na/K ATPase
  - Hypokalemia: increase toxicity
  - Hyperkalemia: decrease toxicity
- Mg^{2+}
  - Hypomagnesemia: increases toxicity
- Ca^{2+}
  - Hypercalcemia: increases toxicity

Treatment of Digitalis Toxicity

- **reduce dose: 1st degree heart block, ectopic beats**
- **Atropine: advanced heart block**
- **KCl: increased automaticity**
- **Antiarrythmics: ventricular arrhythmias**
- **Fab antibodies: toxic serum concentration; acute toxicity**

β-Adrenoceptor and Dopamine Receptor Agonists

- **Dobutamine**
- **Dopamine**



dobutamine

Mechanism of Action: Dobutamine

- **Stimulation of cardiac β_1–adrenoceptors: ↑ inotropy > ↑ chronotropy**
- **peripheral vasodilatation**
- **↑ myocardial oxygen demand**

Mechanism of Action: Dopamine

- **Stimulation of peripheral postjunctional D1 and prejunctional D2 receptors**
- **Splanchnic and renal vasodilatation**

Therapeutic Use

- **Dobutamine: management of acute failure only**
- **Dopamine: restore renal blood in acute failure**

Adverse Effects

- **Dobutamine**
  - **Tolerance**
  - **Tachycardia**
- **Dopamine**
  - **tachycardia**
  - **arrhythmias**
  - **peripheral vasoconstriction**

Phosphodiesterase Inhibitors

- **amrinone**
- **milrinone**

Mechanism of Action

- inhibition of type III phosphodiesterase
  - ↑ intracellular cAMP
  - ↑ activation of protein kinase A
    - Ca^{2+} entry through L type Ca channels
    - inhibition of Ca^{2+} sequestration by SR
- ↑ cardiac output
- ↓ peripheral vascular resistance

Phosphodiesterase Inhibitors: Therapeutic Use

- **short term support in advanced cardiac failure**
- **• PROMISE (Prospective Randomized Oral Milrinone Survival Evaluation) long term use not possible**

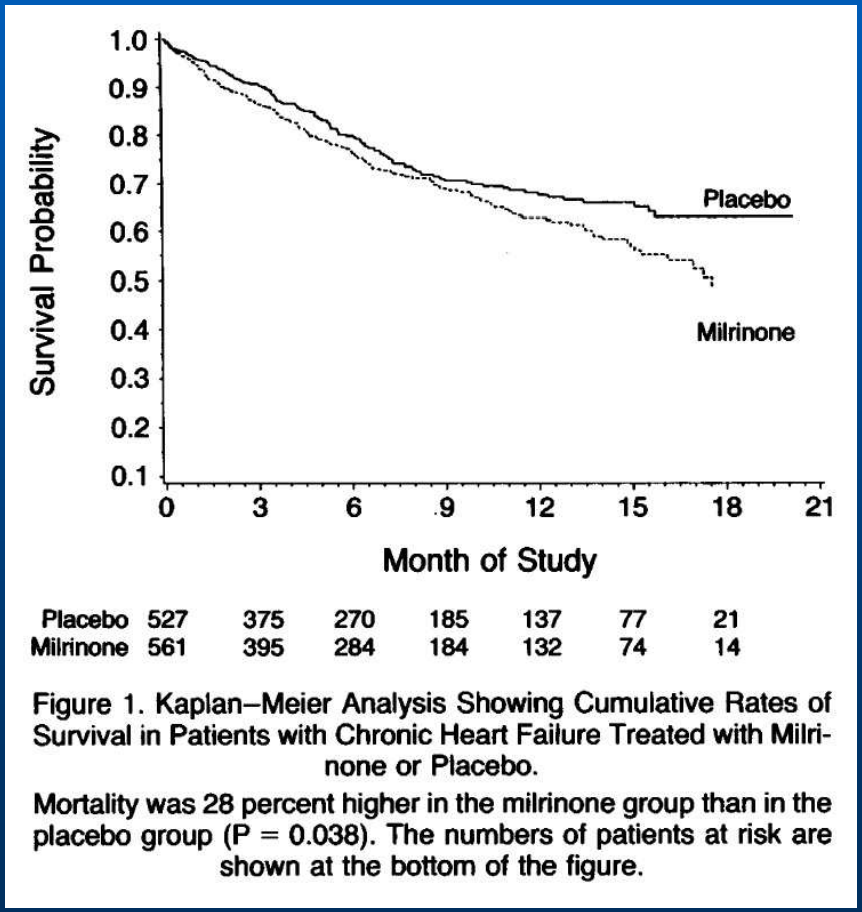


Figure 1. Kaplan–Meier Analysis Showing Cumulative Rates of Survival in Patients with Chronic Heart Failure Treated with Milrinone or Placebo.

Mortality was 28 percent higher in the milrinone group than in the placebo group (P = 0.038). The numbers of patients at risk are shown at the bottom of the figure.

Adverse Effects of Phosphodiesterase Inhibitors

- **Cardiac arrhythmias**
- **GI: Nausea and vomiting**
- **Sudden death**

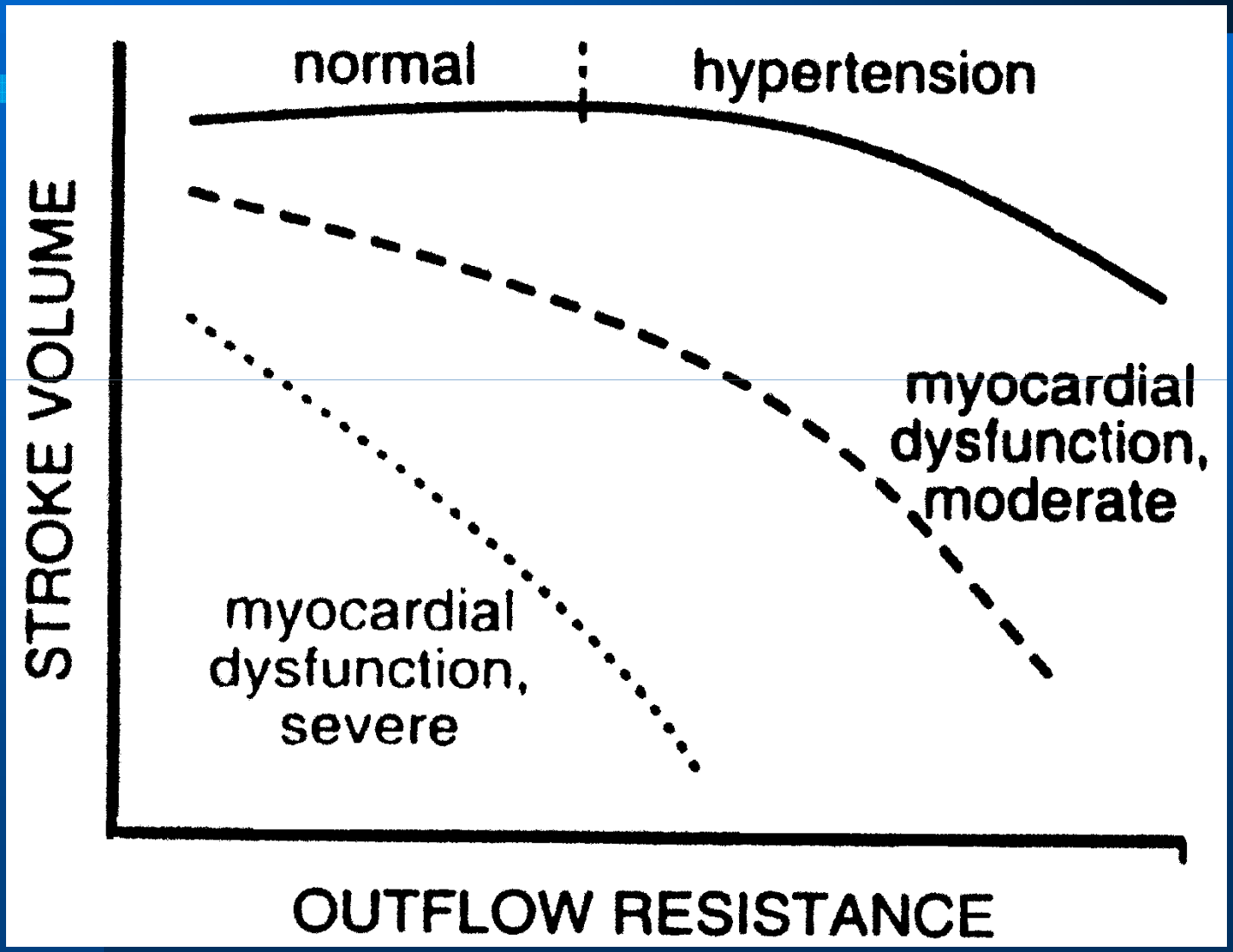
Ca sensitizers

- **Sensitizes troponin C to Ca**
- **Has some PDE3 inhibitory effect**
- **Prolong AP (delayed outward K+ current is inhibited)**
- **Reduces cytokine production**

Ca sensitizers

- **Levosimendan (SIMDAX)**
  - **Has K_{ATP} opener effect**
- **Pimobendan**

ACE Inhibitors in Heart Failure



Mechanism of Action

- **Afterload reduction**
- **Preload reduction**
- **Reduction of facilitation of sympathetic nervous system**
- **Reduction of cardiac hypertrophy**

ACE Inhibitors: Therapeutic Uses

- **Drugs of choice in heart failure (with diuretics)**
- **Current investigational use: Acute myocardial infarction**
- **ATII antagonists**

Diuretics: Mechanism of Action in Heart Failure

- **Preload reduction: reduction of excess plasma volume and edema fluid**
- **Afterload reduction: lowered blood pressure**
- **Reduction of facilitation of sympathetic nervous system**

Vasodilators

- **Mechanism of action: reduce preload and afterload**
- **Drugs used**
  - **Sodium nitroprusside**
  - **Hydralazine**
  - **Ca^{2+} channel blockers**
  - **Prazosin**

β-Blockers in Heart Failure: Mechanism of Action

- **Standard β-blockers:**
  - **Reduction in damaging sympathetic influences in the heart (tachycardia, arrhythmias, remodeling)**
  - **inhibition of renin release**
- **Carvedilol:**
  - **Beta blockade effects**
  - **peripheral vasodilatation via α_1-adrenoceptor blockade (carvedilol)**

Spironolactone

- Aldosterone antagonist, K-sparing diuretic
- Prevention of aldosterone effects on:
  - Kidney
  - Heart?
- Aldosterone inappropriately elevated in CHF
- Mobilizes edema fluid in heart failure
- Prevention of hypokalemia induced by loop diuretics (protection against digitalis toxicity?)
- Prolongs life in CHF patients