Inotropes and Vasodilators

Inotropic agents

Inotropes are drugs that basically alter the contractility of the cardiac or heart muscle. There are positive and negative inotropes. The positive inotropes act by enhancing cardiac contractility thus increasing the cardiac output. Negative inotropes, on the other hand, reduce or weaken the heart's contractility reducing cardiac output.

For the purpose of this article, we shall mainly cover positive inotropes.
All inotropes mainly act by altering calcium concentration that enhances the contractility of cardiac muscle.

All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with heart failure with reduced ejection fraction due to coronary artery disease. For this reason, these drugs, with the exception of digoxin, are only used for a short period mainly in the inpatient setting.

The classes of drugs under inotropes are:

A. Digitalis glycosides

The cardiac glycosides are often called digitalis or digitalis glycosides because most of the drugs come from the digitalis (foxglove) plant.

They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating heart failure.

The digitalis glycosides have a low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The most widely used agent is digoxin.
Digitoxin is seldom used due to its considerable duration of action.

1. Mechanism of action:

These drugs work by;

a. Regulation of cytosolic calcium concentration:

By inhibiting the Na + /K + -adenosine triphosphatase (ATPase) enzyme, digoxin reduces the ability of the myocyte to actively pump sodium ions from the cell. This decreases the Na + concentration gradient and, consequently, the ability of the Na + /
Ca 2+ -exchanger to move calcium out of the cell.

Further, the higher cellular Na + is exchanged for extracellular Ca 2+ by the Na +/Ca 2+ exchanger, increasing intracellular Ca 2+.

A small but physiologically important increase occurs in free Ca 2+ that is available at the next contraction cycle of the cardiac muscle, thereby increasing cardiac contractility.

When Na + /K + -ATPase is markedly inhibited by digoxin, the resting membrane potential may increase (?70 mV instead of ?90 mV), which makes the membrane more excitable, increasing the risk of arrhythmias (toxicity).

b.Increased contractility of the cardiac muscle:

Digoxin increases the force of cardiac contraction, causing the cardiac output to more closely resemble that of the normal heart
Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand and decrease.

Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation.
In the normal heart, the positive inotropic effect of digitalis glycosides is counteracted by compensatory autonomic reflexes.

c. Neurohormonal inhibition:

Although the exact mechanism of this effect has not been elucidated, low-dose digoxin inhibits sympathetic activation with minimal effects on contractility. This effect is the reason a lower serum drug concentration is targeted in HfrEF.

Therapeutic uses:

Digoxin therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, ?-blocker, and diuretic therapy.

A low serum drug concentration of digoxin (0.5 to 0.8 ng/ mL) is beneficial in HFrEF. At this level, patients may see a reduction in HF admissions, along with improved survival. At higher serum drug concentrations, admissions are prevented, but mortality likely increases.

Digoxin is not indicated in patients with diastolic or right-sided HF unless the patient has concomitant atrial fibrillation or flutter.

Patients with mild to moderate HF often respond to treatment with ACE inhibitors, ?-blockers, aldosterone antagonists, direct vaso- and venodilators, and diuretics and may not require digoxin.

3. Pharmacokinetics:

Digoxin is available in oral and injectable formulations. It has a large volume of distribution because it accumulates in muscle.

The dosage is based on lean body weight. In acute situations such as symptomatic atrial fibrillation, a loading dose regimen is used. Digoxin has a long half-life of 30 to 40 hours. It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

4. Adverse effects:

At low serum drug concentrations, digoxin is fairly well tolerated. However, it has a very narrow therapeutic index, and digoxin toxicity is one of the most common adverse drug reactions.

Anorexia, nausea, and vomiting may be initial indicators of toxicity. Patients may also experience blurred vision, yellowish vision (xanthopsia), and various cardiac arrhythmias.

Toxicity can often be managed by discontinuing digoxin, determining serum potassium levels, and, if indicated, replenishing potassium.

Decreased levels of serum potassium (hypokalemia) predispose a patient to digoxin toxicity since digoxin normally competes with potassium for the same binding site on the Na + /K + -ATPase pump.

Patients receiving thiazide or loop diuretics may be prone to hypokalemia.
Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug.

Digoxin is a substrate of P-gp, and inhibitors of P-gp, such as clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin.

Digoxin should also be used with caution with other drugs that slow AV conduction, such as ?-blockers, verapamil, and diltiazem.

B. ?-Adrenergic agonists

?-Adrenergic agonists, such as dobutamine and dopamine, improve cardiac performance by causing positive inotropic effects and vasodilation.
Dobutamine is the most commonly used inotropic agent other than digoxin.

?-Adrenergicagonists lead to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase.
Protein kinase then phosphorylates slow calcium channels, thereby increasing the entry of calcium ions into the myocardial cells and enhancing contraction. Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting
Phosphodiesterase inhibitors

Milrinone is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP.

Like ?-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.

Long-term, milrinone therapy may be associated with a substantially increased risk of mortality. However, short-term use of intravenous milrinone is not associated with increased mortality in patients without a history of coronary artery disease, and some symptomatic benefit may be obtained in patients with refractory heart failure.

High yield take away

1. **Inamrinone lactate** (formerly known as amrinone) and **milrinone.**

Inamrinone lactate and milrinone reduce LV filling pressure and vascular resistance and enhance cardiac output.
Inamrinone lactate and milrinone act by inhibiting phosphodiesterases in cardiac and vascular muscle, especially phosphodiesterase Type 3. This causes an increase in cyclic AMP (cAMP), thereby activating calcium channels leading to elevated intracellular Ca21 levels and enhanced excitation-contraction.

These drugs are used in patients who do not respond to digitalis; they are most effective in individuals with elevated left ventricular filling pressure.

Inamrinone lactate and milrinone produce considerable toxicity on extended administration; they are administered intravenously only for short-term therapy.

The most common adverse effects are
Transient thrombocytopenia

- Hypotension.
- Fever and gastrointestinal disturbances occur occasionally.

Fewer and less severe adverse effects are seen with milrinone than with inamrinone.

2. Dobutamine

Dobutamine hydrochloride is a synthetic catecholamine derivative that increases contractility; it acts primarily on myocardial ?1-adrenoceptors with lesser effects on ?2- and ?-adrenoceptors.

Dobutamine hydrochloride increases cAMP-mediated phosphorylation and the activity of Ca21 channels.
Moderate doses of dobutamine hydrochloride do not increase heart rate.

Dobutamine hydrochloride does not activate dopamine receptors.
This drug is administered only by the IV route.

Dobutamine hydrochloride is used in short-term therapy in individuals with severe chronic cardiac failure and for inotropic support after myocardial infarction and cardiac surgery.