The inotropic agent in the context of heart failure and angina is classified into a positive and negative inotropic agent. The positive agent increases the contractility and will be discussed in detail in this article. A brief about the negative inotropic agent, which decreases the myocardial contractility, is mentioned. The inotropic agent, when mentioned alone without any prefix, stands for a positive inotropic agent in this article.

Heart Failure and Angina

Heart failure is the inability of the heart to fill the blood and pump to all parts of the body. There are different types of heart failure, namely normal ejection fraction heart failure and reduced ejection fraction heart failure.

Inotropes are especially useful in reduced ejection fraction heart failure. The role of the inotropic agents is to increase the ejection fraction of the heart. Ejection fraction determines the amount of blood pumped from the heart with each heartbeat. In the case of heart failure, this fraction is reduced. The reduction might be because of the structural changes in the heart or because of any functional defect.
The normal value of the left ventricular ejection fraction is 55-70%. In the case of heart failure, the ejection fraction reduces to 40%. These percentages represent the amount of blood that is pumped out from the left ventricle with each heartbeat. If heart failure is not properly treated, in addition to morbidity, the chances of sudden cardiac death and cardiac arrest occur.

An Outline of the Pharmacological Treatment

Positive inotropic agents include

1. Digoxin
2. Phosphodiesterase inhibitors like amrinone, milrinone, enoximone, and vesnarinone
3. Beta-receptor agonists like dopamine, dobutamine, and xamoterol
4. Growth hormone somatotropin
5. Calcium-sensitizing agents like pimobendan and levosimendan

The role of inotropes as an acute intravenous agent in patients with severe dysfunction of the myocardium, especially in the systolic phase, is well established. Digoxin remains the only drug that is used orally and widely for long-term chronic treatment with an inotropic agent. The other inotropic agents generally are given during the acute HF, or acute exacerbation, of chronic heart failure (CHF)+.

<table>
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<th>Inotropes</th>
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<th>Cardiac remodeling/neurohormonal activity</th>
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Digoxin

Mechanism of action of Digoxin

The increase in calcium concentration leads to an increase in contractility. Digoxin achieves this by inhibiting the sodium-potassium-ATPase pump in the myocardial cell. The inhibition of this channel leads to an increase in the concentration of intracellular sodium. In order to balance the concentrations of sodium, the sodium-calcium exchange pump is activated, which, in turn, causes an increase in the influx of calcium. Digoxin also reduces the activation of the sympathetic system. This is achieved by means of increasing the sensitivity of the baroreceptor.

![Chemical structure of digoxin created with ChemDraw.](https://via.placeholder.com/150)

Pros & cons and the main indication of Digoxin

Digoxin is available in the oral form for the treatment of chronic heart failure. The serum digoxin level correlates with the safety of digoxin in the patients. The optimal level, to which digoxin is to be maintained, is from 0.5 to 0.8 ng/ml.

In patients with heart failure with reduced ejection fraction, along with atrial fibrillation and who do not have an additional conducting accessory pathway, IV digoxin might be used.

In addition to heart failure, it is also used in the case of supraventricular tachyarrhythmia.

Adverse and side effects related to Digoxin

Atrial tachycardia, with or without associated block, first, second and third-degree heart block ventricular bigeminy, ST-segment depression, ventricular tachycardia, rashes (especially maculopapular), nausea, diarrhea, edema in the laryngeal region, and visual disturbances (yellow vision).
Digoxin toxicity

This occurs, especially after the **serum digoxin level is greater than 2 ng/ml**.

The symptoms include **loss of appetite**, the **sensation of vomiting**, **visual changes**, and **cardiac arrhythmias**. The electrolyte imbalances like **hypokalemia**, **hypomagnesemia**, **old age**, and **thin and lean body weight**, are some of the risk factors for digoxin toxicity.

Phosphodiesterase-3 Inhibitors

Classification and mechanism of action of phosphodiesterase-3 inhibitors

![Image](https://via.placeholder.com/150)

Image: "Chemical formula of the PDE3 inhibitor Meribendan" by Anypodetos - Own work,
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The ultimate effects of the PDE-3 inhibitor are to **increase the inotropic effect** by increasing the influx of calcium from the **sarcoplasmic reticulum**. The drug also causes a **positive relaxation of the heart** by causing the reflex of calcium into the sarcoplasmic reticulum.

The drug achieves this by means of inhibiting the **PDE-3 enzyme**, which is responsible for the degradation of CAMP. The inhibition leads to the increase in the amount of CAMP, which, in turn, activates the **cardiac calcium channels** causing an increase in the influx of calcium from the sarcoplasmic reticulum by means of increasing **phosphorylation** through **protein kinase A**. In addition to just direct activation, the drug also has a **calcium-induced calcium release (CICR) potentiation action**. The additional action of **vasodilation** seen is because of the inhibition of the **phosphodiesterase** present in the vascular bed.

Pros & cons and the main indication of PDE-3 inhibitors

These drugs are especially used for the treatment of heart failure, along with the presence of **cardiogenic shock**. For **intravenous Milrinone**, though studies have shown that it improves the functional status of the heart in patients with advanced heart failure with reduced ejection fraction along with the reduction of hospitalization, some big trials like OPTIME-CHF have shown that it is associated with an increase in the risk of **arrhythmia**, **hypotension**, and **in-hospital mortality**. In OPTIME-CHF, the drug was investigated against the acute exacerbation of chronic CHF.

In a Cochrane review in which 21 clinical trials were reviewed, it was shown that the chronic use of phosphodiesterase inhibitors is to be discouraged and avoided. The use of PDE inhibitors was associated with an increase in the relative risk of 1.17 when compared
to that of a placebo. The findings are confirmed in large trials like the PROMISE trial. The increase in the risk with chronic oral use is hypothesized due to the increase in the arrhythmia, though the exact mechanism is not known.

The combination of a beta-blocker and PDE inhibitor has shown good outcomes when used in advanced refractory and class 4 heart failure patients.

**Adverse and side effects related to PDE-3 inhibitors**

The drugs in this group cause a decrease in the platelets (thrombocytopenia), an abnormality of rhythm (arrhythmia), sudden death, vertigo, and the increase in the level of liver enzymes like transaminase. Though overall, Milrinone is deemed beneficial, and there are some studies to suggest that there is an increase in the arrhythmia risk following its use in cardiac surgery.

**Beta Receptor Agonists**

**Classification and mechanism of action of Beta Receptor Agonists**

Dobutamine, Dopamine and beta-blocker with intrinsic sympathomimetic activity like Xamoterol.

![Chemical structure of Xamoterol](image)


The Dopamine effect varies according to the dose. At therapeutic doses, the drug has an effect on both dopaminergic and beta 1 adrenergic receptors. This leads to renal vasodilation and the stimulation of the cardiac tissue. At lower doses, the drug has a predominant action on the dopaminergic receptor causing renal vasodilation (this will cause an increase in the urine output). At larger doses, the drug takes action on the Alpha adrenergic receptors causing vasoconstriction.

**Dobutamine** is a racemic mixture of a positive and a negative enantiomer. The beta,adrenergic receptor is stimulated by the positive enantiomer and is responsible for the contraction of the myocardium. The negative enantiomer shows the agonistic action on the alpha receptor. In addition, it also stimulates the beta, and alpha, receptor in the blood vessel, with the predominant action being beta, leading to the vasodilation of the blood vessel.
Pros & cons and the main indication of beta receptor agonists

In a landmark paper published in Circulation (although the sample size was less), it showed the effect of Dobutamine when given in a short duration of 3 days (rate of 5 microg/min), had the beneficial effect lasted for up to 4 weeks. This phenomenon is described as a ‘Dobutamine holiday’.

There are concerns regarding the use in the short term in acutely decompensated patients following a report of an increase in the mortality with the drug. Dobutamine and Milrinone are to be used as a bridge therapy before the instrumental (mechanical), and surgical therapy is started in advanced stage 4 heart disease patients. It can also be used as palliative therapy in non-responsive patients.

Adverse and side effects related to beta-receptor agonists

Side effects of Dopamine include anxiety, headache, the sensation of vomiting, angina, atrial fibrillation, widening of the QRS complex on the ECG and the extravasation of the drug, during administration, needs to be avoided.

The side effects of Dobutamine include ventricular premature contractions, palpitation, variation in blood pressure (both hypotension, as well as an increase in blood pressure), difficulty in breathing (dyspnoea), anginal pain, headache, nausea, and fever in some cases.

Calcium Sensitising Agents

Classification and mechanism of action of calcium sensitizing agents

Levosimendan and pimobendan are the two drugs under this category. The troponin c in the sarcomere is responsible for binding to the calcium to bring about the contraction of the myocardial tissue.

The levosimendan, by binding to the troponin c in a calcium-dependent manner, increases the calcium sensitivity of the myocytes. Thus, it is described as a calcium-sensitizing agent. The drug also has an agonistic action on the ATP-dependent potassium channel and activates it. This leads to the efflux of potassium leading to hyperpolarization and relaxation of the blood vessel. This decreases the preload and the afterload on the heart.

In addition to the calcium-sensitizing effect, Pimobendan has the PDE-3 inhibitory activity. It is mainly approved for veterinary usage and is approved only in Japan for human use.

Pros & cons and the main indication of calcium sensitizing agents

The main indication for the use of Levosimendan is in severe CHF patients who are
Acutely decompensated. A recent meta-analysis conducted in 2016 clearly shows the beneficial effect of Levosimendan in terms of decreasing the mortality in patients with heart failure.

Adverse and side effects related to calcium sensitizing agents

- A decrease in blood pressure
- Arrhythmias
- Ischemic attack of the myocardium
- A decrease in the serum potassium level
- Nausea
- Headache

Newer Drug for Heart Failure: Sacubitril/Valsartan

Mechanism of action of Sacubitril/Valsartan

The drug is a 1:1 combination of Angiotensin II receptor type 1 inhibitor, namely valsartan and the neprilysin inhibitor namely sacubitril. The neprilysin is involved in the breakdown of substances which causes vasodilation, like bradykinin and natriuretic peptide. The sacubitril causes an increase in the concentration of these substances.

The inhibition of the AT-II leads to the decrease in the aldosterone concentration and decreases the ECF volume with additional dilation of the blood vessel.

Pros & cons and the main indication of Sacubitril/Valsartan

This class of drug has recently been approved by the FDA and has shown a decrease in the mortality, as well as hospitalization, of patients with heart failure. It was evaluated in a trial containing 8442 patients, named the PARADIGM-HF trial, and was compared with that of Enalapril alone.

Adverse and side effect related to Sacubitril/Valsartan

- Hypotension
- Hyperkalemia
- Impairment of the kidney function
- Increased risk of an allergic reaction like angioedema (the risk of which increases with the co-administration with the ACE inhibitors). There is also a risk of dementia (due to neprilysin inhibition).

Negative Inotropic Agent in the Angina

These positive inotropic agents, which are discussed above, should not be used in angina, as it will increase the workload on the heart and will aggravate angina or may precipitate a new attack. The agents with a negative inotropic effect are used in the case of angina, and these include drugs such as beta-blockers, calcium channel blockers (which includes Verapamil and Diltiazem), the class 1a antiarrhythmic agent (according to the Vaughan-Williams classification) such as Quinidine, Procainamide, Disopyramide, and Flecainide which is the class 1c antiarrhythmic agent.

The mechanism of action of the negative inotropic
agents

The **beta-blocker** acts directly on the beta 1 receptor of the myocardium. The **calcium channel blocker** decreases the concentration of the calcium by blocking the calcium channel. In addition, the conduction along the conduction pathway is mainly dependent on the calcium, which will be decreased by this drug. The **class 1 antiarrhythmic** act by means of inhibiting the sodium channel with the 1a showing intermediate association/dissociation to the sodium channel and the 1c showing the slow association/dissociation to the sodium channel.

Among the ionotropic agent in heart failure, not a single drug stands as a clear superior drug. There is a daring need for new drugs that can afford the cardio-protectivity, along with the mortality and morbidity benefit. A small ray of hope has come with the arrival of Sacubitril/Valsartan, though it is too early to conclude.

**References**


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