



Inotropes: Effect on the Heart, microcirculation & other organs

By

Prof. Dr. Ahmed Shafie Ammar

Professor of cardiology

Zagazig University

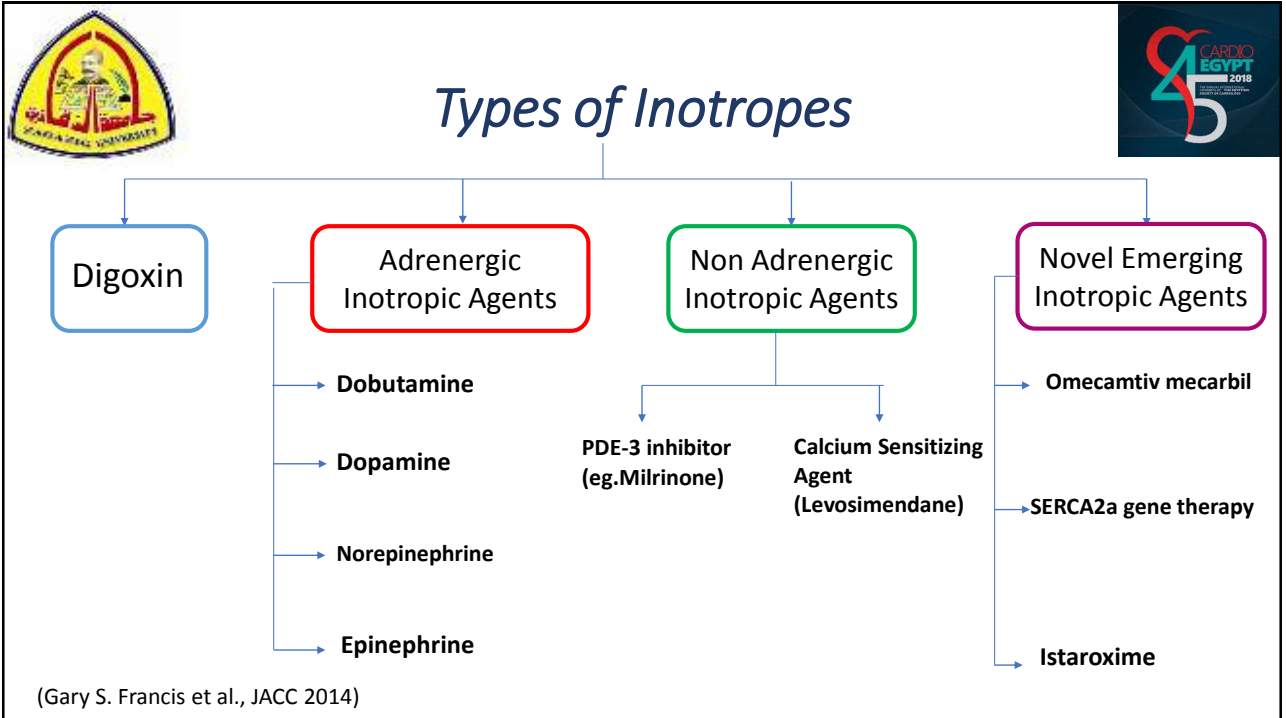
2018



Definition of Inotropes

- ***Inotropic drugs may be strictly defined as*** therapies that enhance myocardial contractile performance independent of changes in heart rate and loading conditions.
- ***However,*** Many inotropic drugs increase heart rate, and some have direct or indirect vasodilator properties.
- ***Therefore,*** some of the improved systolic performance generated by inotropic agents may also be due to changes in loading conditions and heart rate inherent to many of these drugs.

(Gary S. Francis et al., JACC 2014)



Section 1:

Effect of Inotropes on the Heart



Effect of Inotropes on the Heart



1- Digoxin

- Digoxin improves hemodynamics without adversely affecting heart rate or blood pressure.
- It tends not to increase myocardial oxygen demand and does not reduce coronary perfusion.
- It further diminishes neurohormonal activation, does not impair kidney function, and is available in both intravenous and oral form.
- Perhaps **most importantly**, digoxin can improve symptoms and tends to reduce hospitalization rate

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



1- Digoxin

- Digoxin was once widely used to treat patients with systolic heart failure.
- However, in 1997, results from the **DIG** (Digitalis Investigation Group) study indicated that digoxin had a neutral effect on mortality, although reductions were seen in overall rates of hospitalization and heart failure progression.
- The 20 years that followed the DIG study have seen a substantial decrease in its use for the treatment of heart failure.
- However, we believe there is still a role for digoxin in patients with heart failure

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



2- Dopamine:

- Dopamine, the immediate precursor to norepinephrine in the catecholamine synthetic pathway.
- It has been used intravenously to treat cardiogenic and septic shock since the 1970s.
- At low doses (<3 mg/kg/min), dopamine activates dopaminergic (D1) receptors that subserve vasodilation in various vascular beds, including the coronary and renal arteries.
- The benefits of “renal doses” of dopamine have remained controversial.

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



2- Dopamine:

- **The ROSE AHF** (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial recently found that neither nesiritide nor low-dose dopamine was better than placebo when added to standard care.
- Intermediate doses of dopamine (3 to 10 mg/kg/min) activate B-adrenergic receptors that cause increased inotropy and heart rate and also promote release and inhibit reuptake of norepinephrine in presynaptic sympathetic nerve terminals
- At higher infusion rates (10 to 20 mg/kg/min), dopamine acts primarily as an a-adrenergic agonist resulting in peripheral vasoconstriction.

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



3- Dobutamine:

- Dobutamine was introduced in the late 1970s as a new, synthetic, intravenously administered catecholamine that had a direct agonist effect on B1- and B2- adrenergic receptors with no vasoconstrictor properties and less tachycardia.
- It was suggested that dobutamine might have an advantage over dopamine, as it does not increase sympathetic norepinephrine signaling or peripheral vasoconstriction.
- Dobutamine raises blood pressure solely by increasing cardiac output, whereas dopamine raises blood pressure via peripheral vasoconstriction

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



3- Dobutamine:

- Dobutamine exhibits a peripheral vasodilatory effect, most likely caused by B2-adrenergic stimulation in the peripheral vasculature in combination with reflex withdrawal of intense vasoconstriction.
- With time and experience, however, it became clear that dobutamine infusions lasting longer than 72 h were associated with **pharmacodynamic tolerance**.
- Short-term infusion for 72 h selectively improves vascular endothelial function for 2 weeks

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



4- Norepinephrine:

- Norepinephrine is an endogenous catecholamine normally synthesized, stored, and released from sympathetic neurons.
- Norepinephrine is an endogenous agonist at α 1- and α 2- adrenoreceptors, with only very modest effects on β 1- adrenoreceptors.
- It increased chronotropy, heightened inotropy, and increased peripheral vasoconstriction

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



5- Epinephrine:

- Epinephrine is a direct-acting sympathomimetic agent, exerting its effect on β 1-, β 2-, and α 1-adrenoreceptors.
- It is a potent inotropic, chronotropic, and vasoconstricting agent.
- Generally, it does not have a role in the management of AHF.
- It is known to increase myocardial O₂ demand and is proarrhythmic, due to raised intracellular cAMP and Ca²⁺ concentrations.

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



6- Milrinone:

- Milrinone, is a phosphodiesterase (PDE) - 3 inhibitor.
- PDE-3 is an intracellular enzyme that breaks down cyclic adenosine monophosphate (cAMP).
- cAMP is a second messenger that modulates intracellular calcium.
- In the Heart, PDE-3 inhibitors thus increase cAMP, which increases calcium entry into the cardiac myocytes as well as the rate of removal, which in turn *leads to increased myocardial contractility*.
- In vascular smooth muscle, heightened cAMP primarily increases removal of calcium from the vascular smooth muscle cell, leading to *cellular relaxation and vasodilation*.

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



7- Levosimendan:

- Levosimendan is a calcium sensitizing drug widely used in Europe but is not approved for use in the United States.
- The drug appears to enhance troponin C sensitivity to intracellular calcium, thereby enhancing cardiac inotropy and lusitropy.
- Levosimendan also causes peripheral vasodilation by opening smooth muscle adenosine triphosphate (ATP)-dependent potassium channels.
- It may also have some PDE-3 inhibitor activity

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



8- Omecamtiv mecarbil:

- Omecamtiv mecarbil is the first selective cardiac myosin activator to be studied in humans.
- The small omecamtiv mecarbil molecule increases the efficiency of heart muscle contraction via selectivity for a subset of cardiac myosins.
- It increases the occupancy time of myosin on actin, leading to increased numbers of myosin molecules bound to actin, which causes prolongation of the contractile force without increasing left ventricular pressure development (dP/dt)

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



8- Omecamtiv mecarbil:

- The calcium transient remains unchanged with omecamtiv mecarbil in contrast to conventional inotropic agents such as dobutamine, which increase intracellular cAMP and thereby increase the calcium transient.
- By this mechanism, it appears that omecamtiv mecarbil does not increase the heart's demand for energy, rather, it improves systolic performance by allowing the myocardium to **make more efficient use of energy**

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



9- SERCA2a gene therapy:

- Sarcoplasmic reticulum Ca²⁺-ATPase (SERCA2a) *is an enzyme responsible for both:*

Myocardial relaxation

by reuptake of calcium into the sarcoplasmic reticulum (SR)

Myocardial contractility

by controlling the amount of calcium in the SR.

- SERCA2a *is downregulated in the failing human heart*, resulting in contractile dysfunction and arrhythmia

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



9- SERCA2a gene therapy:

- CUPID Trial** provided first in-human data for the gene transfer of SERCA2a cDNA (adeno-associated virus [AAV1]/SERCA2a).
- The cDNA was delivered by intracoronary infusion.
- The CUPID trial *demonstrates that* SERCA2a is a potential therapeutic target in patients with heart failure and provides supportive evidence for additional, larger randomized trials.

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



10-Istaroxime:

- Istaroxime is a novel intravenous drug that both:

Inhibits the activity of sodium-potassium ATPase

Stimulates sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a).

- This dual mechanism of action results in Istaroxime having both inotropic action by allowing the accumulation of cytosolic calcium during contraction and a lusitropic effect (improvement in diastolic relaxation) by sequestering calcium during relaxation

(Gary S. Francis et al., JACC 2014)



Effect of Inotropes on the Heart



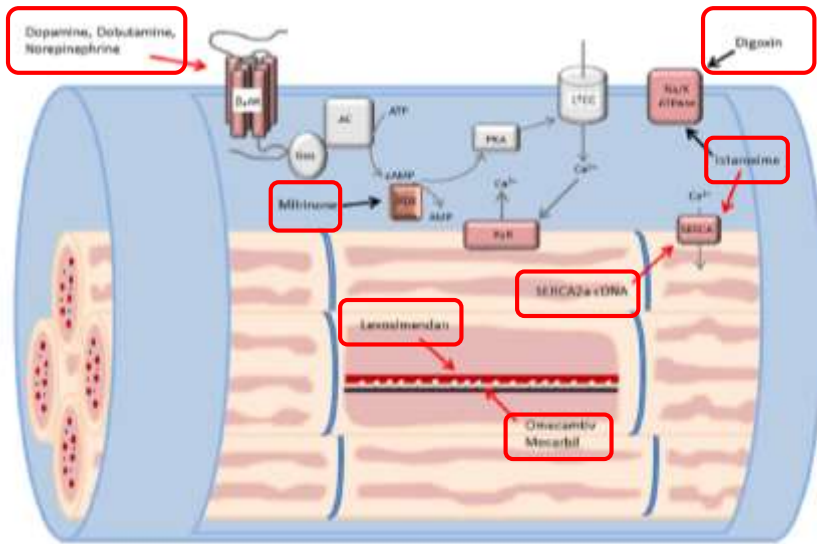
9-Istaroxime:

- The HORIZON-HF study assessed the hemodynamic effects of Istaroxime in a double-blind, placebo- controlled phase II trial in patients hospitalized with acute heart failure.
- It showed reduction in pulmonary capillary wedge pressure compared to placebo.
- There was a dose-dependent reduction in heart rate, a distinguishing feature from traditional intravenous inotropes.
- Additionally, there was an increase in systolic blood pressure but no effect on neurohormones, renal function, or troponin levels

(Gary S. Francis et al., JACC 2014)



Mechanisms of Inotropes on the heart



Section 2:



Effect of Inotropes on the Microcirculation



Effect of Inotropes on the microcirculation



Journal of Cardiac Failure Vol. 14 No. 5 2008

Inotropic Agents Improve the Peripheral Microcirculation of Patients With End-Stage Chronic Heart Failure

SERAFIM NANAS, MD,¹ VASILIKI GEROVASIL, MD,¹ STAVROS DIMOPOULOS, MD,²
 CHARALAMPOS PIERRAKOS, MD,² SOULTANA KOURTIDOU, MD,¹ ELISSAVET KALDARA, MD,²
 SERAFIM SARAFIOGLOU, MD,² JOHN VENETSANAKOS, MD,² CHARIS ROUSSOS, MD, MRCP, PhD,¹
 JOHN NANAS, MD, PhD,² AND MARIA ANASTASIOU-NANA, MD²

Athens, Greece



Effect of Inotropes on the microcirculation



- An indirect evaluation of peripheral microcirculation can be performed by near-infrared spectroscopy (NIRS), a simple, reproducible technique that monitors tissue oxygen saturation (StO₂) continuously and noninvasively.
- The aim of this study was to use the NIRS occlusion technique to evaluate the skeletal muscle microcirculation status of patients with CHF and determine peripheral microcirculation changes before and after 6 hours of inotropic infusion.
- It concluded that Peripheral muscle microcirculation as assessed by NIRS is impaired in patients with CHF & ***This impairment is partially reversed by infusion of inotropic agents in patients with ESCHF***



Effect of Inotropes on the microcirculation



- The effect of inotropic drugs on microcirculation was assessed by **De Backer et al.** who assessed effect of Dobutamine on Sublingual microcirculation.
- He found that dobutamine improved microcirculatory flow and that was not related to its systemic effects.
- This was surprising because microcirculation is devoid of B adrenergic receptors.
- **Possible explanation** was that B agonists may increase microcirculatory flow by limiting adhesion of WBCs to the endothelium or possibly through promoting endothelial integrity.

Year book of intensive care and emergency 2010



Section 3:

Effect of Inotropes on other organs





Effect of Inotropes on the other organs



- 1-Kidney
- 2-GIT
- 3-Metabolic
- 4-Coagulation system & platelets
- 5-Bacterial growth



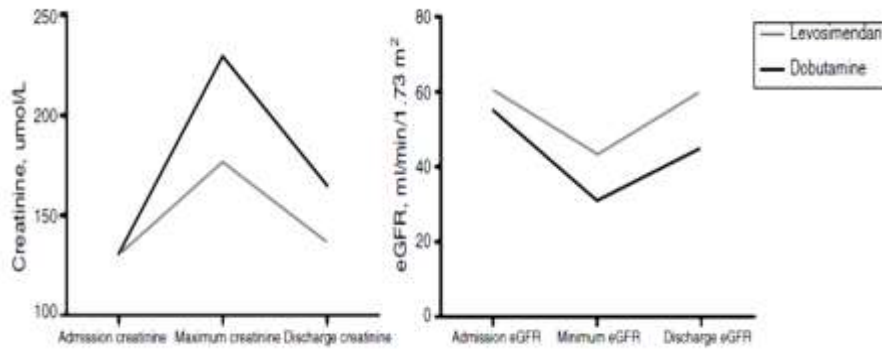
Effect of Inotropes on the Kidney



- Inotropes such as *dobutamine and levosimendan* improve cardiac output and thus renal perfusion.
- In addition, *levosimendan* also has a *vasodilatory effect on the renal arteries and veins, which may explain its renoprotective effect.*
- In their study, Madeira et al. 2017 retrospectively assessed the incidence of CRS in 108 consecutive patients admitted for acute HF and requiring inotropes, dividing their sample into two groups according to the inotrope used (levosimendan vs. dobutamine), in order to determine the predictors of CRS.
- *The incidence of CRS was higher in the dobutamine group than in the levosimendan group (49% vs. 77%, p<0.01)*



Effect of Inotropes on the Kidney



Madeira et al, 2017 Portuguese Journal of cardiology



Metabolic Effect of Inotropes



- Alpha adrenoceptors inhibit the pancreatic release of insulin whereas B- adrenoceptors stimulate glucagon release, and hepatic glycogenolysis and gluconeogenesis.
- This increases serum glucose concentration.
- Catecholamines also stimulate lipolysis, increasing plasma free fatty acids.

(Levy et al., 2008)



Bacterial Growth Effect of Inotropes



- Iron is required for several intracellular processes essential for the growth of bacteria.
- Catecholamines, particularly noradrenaline, can **increase bacterial iron uptake**, stimulating growth.
- There is also some evidence that catecholamines act as host signals to enhance virulence factors and gene transfer in commensal organisms such as *Escheria coli*.

Peterson *et al.*, 2011.



Effect of Inotropes on coagulation system and platelets



- Both α and β adrenoceptors mediate the exocytosis of vonWillebrand factor (vWF), clotting factor VIII, tissue plasminogen activator and chemoattractant IL-8 from Weibel–Palade bodies in endothelial cells.
- The aggregation of platelets is enhanced only in the presence of very high levels of circulating catecholamines.
- Platelet activation may impede microvascular flow and tissue oxygen delivery by a combination of enhanced platelet-leucocyte-endothelial interactions

(von Hundelshausen *et al.*, 2009)



Effect of Inotropes on GIT



- The gut is richly innervated and is, therefore, responsive to neuronally released and circulating catecholamines.
- Catecholamines have all been shown to directly inhibit motility in the colon, ileum and upper gastrointestinal tract.

(Fruhwald *et al.*, 2000)

Thank You

