Acute Heart Failure
Inotropes

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Indications

Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors		
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	IIb	C

Recommendations regarding management of patients with cardiogenic shock

Recommendations	Class[a]	Level[b]
Fluid challenge (saline or Ringer's lactate, >200 ml/15–30 min) is recommended as the first-line treatment if there is no sign of overt fluid overload.	I	C
Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output.	IIb	C
Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion.	IIb	B

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Indications

Table 27. Recommendations for Inotropic Support, MCS, and Cardiac Transplantation

Recommendations	COR	LOE
Inotropic support		
Cardiogenic shock pending definitive therapy or resolution	I	C
BTT or MCS in stage D refractory to GDMT	IIa	B
Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF/EF	IIb	B
Long-term support with continuous infusion palliative therapy in select stage D HF	IIb	B

2013 ACCF/AHA Guideline for the Management of Heart Failure

American Heart Association.

ndications: Hypotension & Hypoperfusion

Hypotension

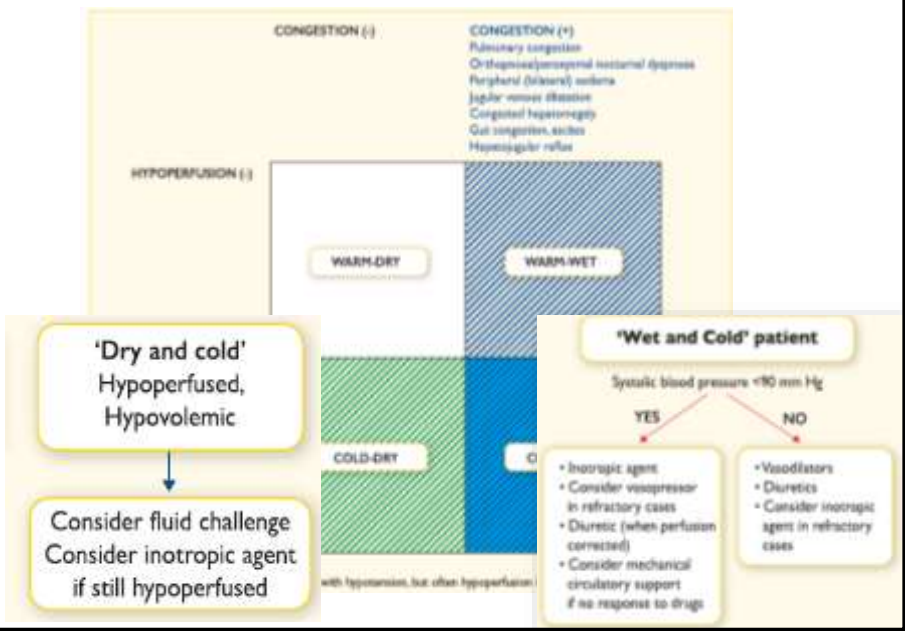
Hypoperfusion

ndications: Hypotension & Hypoperfusion

Hypotension
- < 90 mmHg

Hypoperfusion
- Extremities: cold, sweaty
- Oliguria
- Confusion
- Narrow pulse pressure
- Laboratories:
  - WRF
  - ↑ AST, ALT
  - Hyponatremia
  - ↑ Lactate

Indications



Use of inotropes in ADHF

	no	Inotropes/ vasopressor use
ESC-HF-LT registry	6926	12%
IN-HF Outcome registry	360	20%
ALARM-HF registry	1617	33%

Intensive Care Med 2011;37:290–301
J Heart Lung Transplant 2014;33:1056–1065.
Eur J Heart Fail 2017

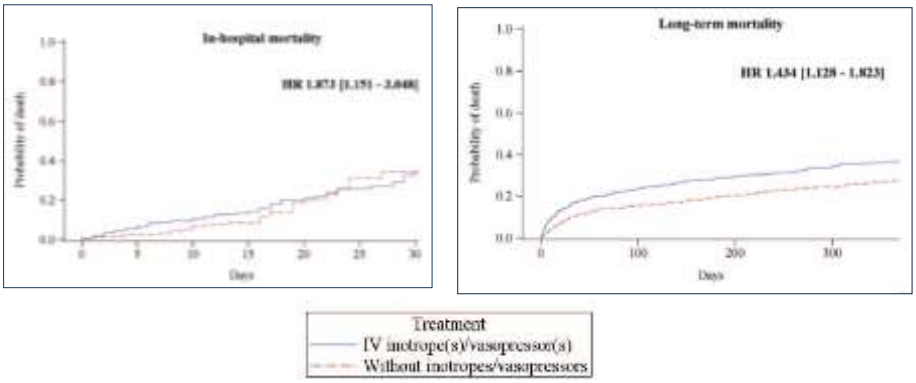
Use of inotropes in ADHF

ESC-HF LT	○ 12% have received inotropes ○ 54 % of pts on inotropes had no evidence of hypoperfusion ○ SBP = 112.1± 27.2 mmHg
ADHERE	9% have received inotropes ; only 2% were hypotensive

Eur J Heart Fail 2017

ESC Heart Failure Long-Term Registry

6926 ADHF from 21 countries



Mebazaa et al. European Journal of Heart Failure (2017)

OPTIME-CHF Study

949 patients with ADHF + no indication for inotropes

IV milrinone vs. placebo

Events	Placebo (N = 472)	Milrinone (N = 477)	*P* Value
Days of hospital for CV causes < 60d	12.5 (mean)	12.3 (mean)	.71
During Hospitalization			
New AF	7 (1.5%)	22 (4.6%)	.004
VT/VF	7 (1.5%)	16 (3.4%)	.06
Sustained hypotension	15 (3.2%)	51 (10.7%)	< .001
Death	11 (2.3%)	18 (3.8%)	.19

Cuffe MS, et al. JAMA 2002;287 (12):1541

Class III

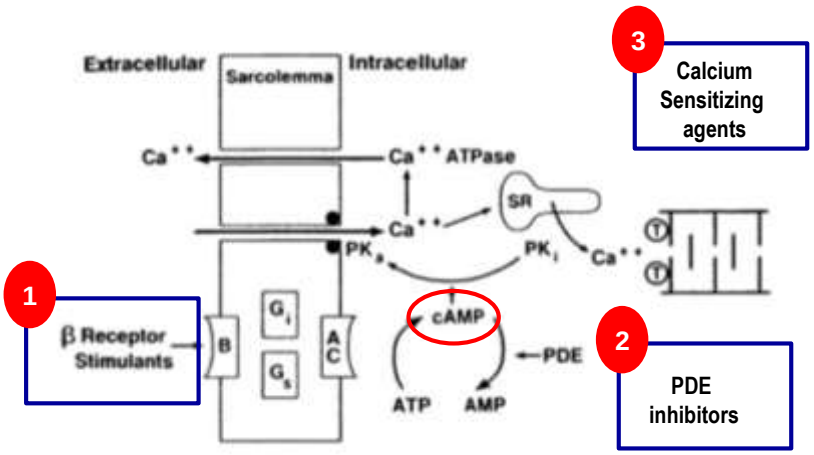
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	III	A

Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF	III: Harm	B
Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful	III: Harm	B

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

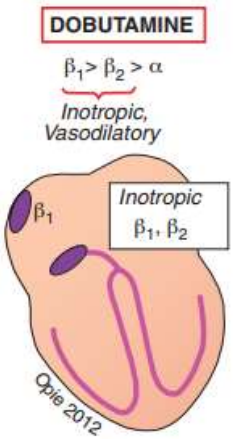
2013 ACCF/AHA Guideline for the Management of Heart Failure

Inotropic agents: Classification



Pharmacology: Dobutamine

CO	↑↑
SVR	↓
PCWP	↓
PVR	↔↓
HR	↑
Elim t1/2	**2-3 min** **H**
NBs	-Tachyphylaxis - Eosinophilc myocarditis -Fever - Nausea - Sulfite allergy - ≠ MAOI



In-Hospital Mortality in Patients With Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications

An Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE)

65,180 patient ADHF episodes

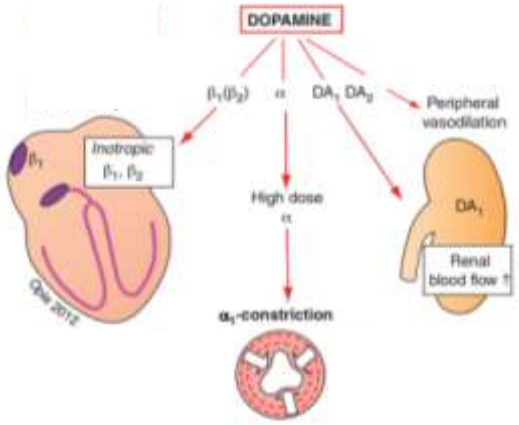
Table 4. Mortality Odds Ratios in Pair-Wise Treatment Comparis

Analysis*	NTG (n = 5,713) vs. DOB (n = 3,478)	NES (n = 4,270) vs. DOB (n = 3,301)
Unadjusted	0.24 (0.20–0.28)†	0.37 (0.32–0.44)†
Adjusted for covariates‖	0.46 (0.38–0.57)†	0.47 (0.39–0.56)†
Adjusted for covariates and propensity score¶	0.46 (0.37–0.57)†	0.47 (0.39–0.56)†

J Am Coll Cardiol 2005;46:57–64

Pharmacology: Dopamine

CO	↑	↑↔↓
SVR	↓↔	↑
PCWP	↔↓	↑
PVR	↔	
HR	↑	
Elim t1/2	**2-20 minutes R, H, P**	
NBs	**- MAOI -Tissue necrosis**	



ESC Heart Failure Long-Term Registry

6926 ADHF from 21 countries

Table 3 Duration and dosage of treatment with intravenous inotropes and/or vasopressors and their association with long-term all-cause death

Inotrope/vasopressor (whole cohort, n = 833)	Dobutamine (n = 354)	Dopamine (n = 206)	Levosimendan (n = 109)	Norepinephrine (n = 45)	Epinephrine (n = 14)
Hours of treatment					
Mean ± SD	42.3 ± 29.9	43.4 ± 32.3	24.8 ± 6.3	40.2 ± 28.3	37.6 ± 41.7
Median (IQR)	36.0 (23.0–72.0)	36.0 (20.0–72.0)	24.0 (24.0–24.0)	35.0 (17.0–60.0)	22.0 (1.0–72.0)
Long-term all-cause death, %	37.9	49.0	38.5	55.6	64.3
Inotrope/vasopressor (matched cohort, n = 606)	**Dobutamine (n = 512)**	**Dopamine (n = 314)**	**Levosimendan (n = 168)**	**Norepinephrine (n = 36)**	**Epinephrine (n = 16)**
HR (95% CI) for long-term all-cause death	1.055 (0.727–1.531)	1.628 (1.031–2.572)	1.229 (0.618–2.445)	3.762 (0.903–15.663)	NA

Mebazaa et al. European Journal of Heart Failure (2017)

ıdications (Dopamine+ diuresis)

Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis

IIb	B

American Heart Association.

Circulation. 2013;128:e240-e327;

ROSE-AHF

380 pts with ADHF and eGRF = 15-60 ml/min
Dopamine 2ug/kg/min versus placebo

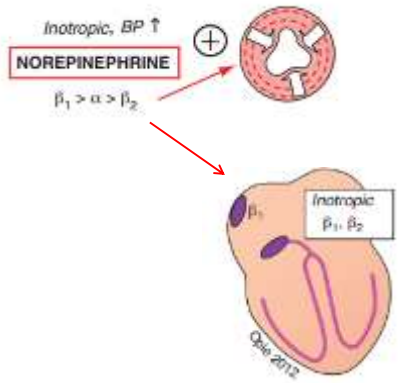
ROSE-AHF

	Placebo	Dopamine	P-value
N	119	122	
Urine volume (72h, mL)	8296	8524	0.59
Change in Cystatin C (mg/L)	0.11	0.12	0.72
Change in Creatinine (μmol/L)	1.8	0	0.78
WRF (%)	22	22	0.88
Sodium excretion (72h, mmol)	540	527	0.75
Weight change (72h, kg)	-3.5	-3.3	0.82

Chen et al, JAMA, 2013; 2533

Pharmacology: Norepinephrine

CO	↑
SVR	↑↑
PCWP	
PVR	↔↓
HR	↑↔
Elim t1/2	**3 minutes**
NBs	- Oliguria - Hepatic failure - Gangrene



SOAP II

1679 patients with shock

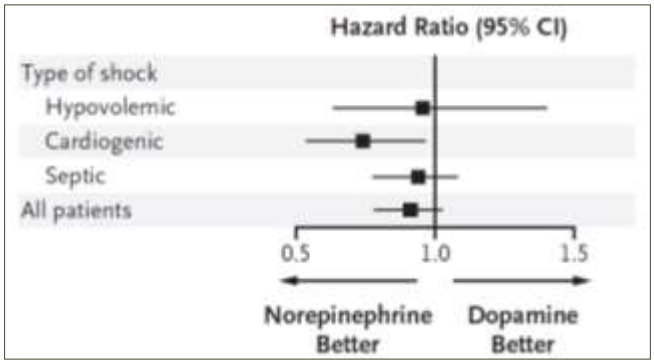
Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

N Engl J Med 2010;362:779-89.

SOAP II

1679patients with shock



N Engl J Med 2010;362:779-89.

NE in Cardiogenic shock

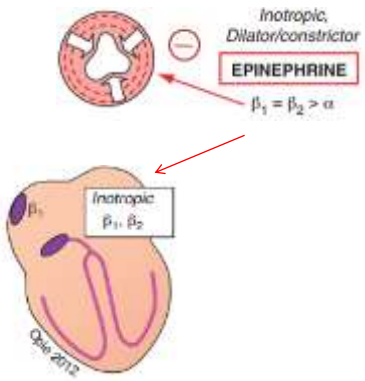
Recommendations regarding management of patients with cardiogenic shock

Recommendations	Class[a]	Level[b]
Fluid challenge (saline or Ringer's lactate, >200 ml/15–30 min) is recommended as the first-line treatment if there is no sign of overt fluid overload.	I	C
Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output.	IIb	C
Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion.	IIb	B

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

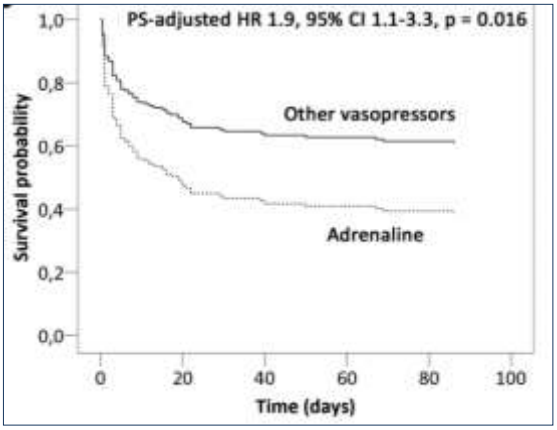
Pharmacology: Epinephrine

CO	↑↑
SVR	↑
PCWP	
PVR	
HR	↑↑
Elim t1/2	**2 minutes**
NBs	- **Cardiac arrest** - **After CBP**



CardShock

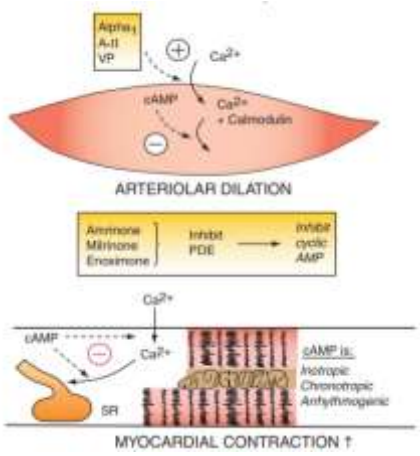
219 patients with CS



Crit Care 2016;20:208.

Pharmacology: Milrinone

CO	↑
SVR	↓↓
PCWP	↓↓
PVR	↓
HR	↑
Elim t1/2	**2.5 hour H**
NBs	**- ↑ LFT**



OPTIME-CHF Study

949 patients with systolic dysfunction and ADHF

IV milrinone vs. placebo

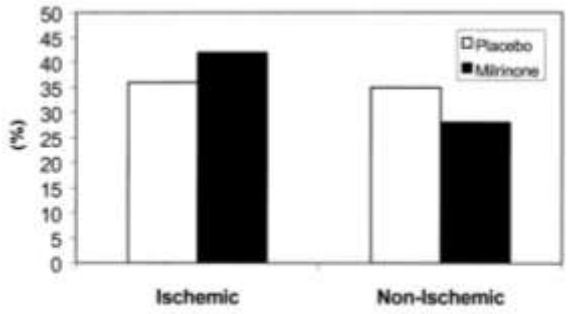


Figure 2. Composite end point of death + rehospitalization by heart failure etiology and treatment assignment. p = 0.01 for etiology-treatment interaction.

J Am Coll Cardiol 2003;41:997–1003

Pharmacology: Levosemindane

CO	↑
SVR	↓↓
PCWP	↓
PVR	↓
HR	↑
Elim t1/2	Levo: 1 hour Metab: 80 hour
NBs	

Calcium sensitization of cardiomyocytes
Open K ATP channels in vascular smooth muscle cells
Open K ATP channels in mitochondria of cardiomyocytes

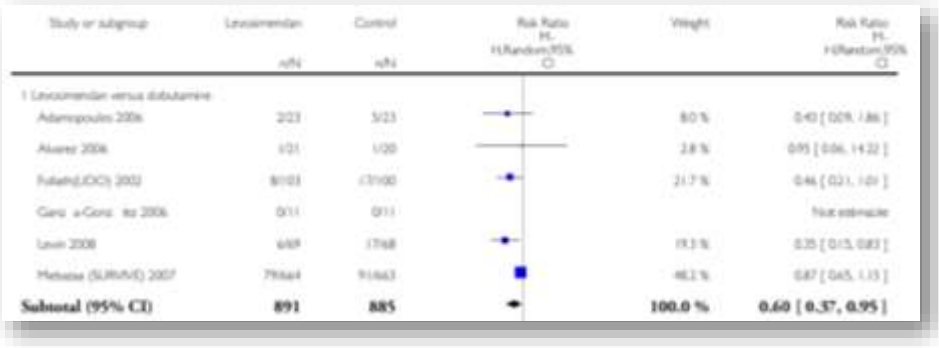
Levosimendan

Study	Patients	Primary End Point
Calcium Sensitizer (Levosimendan)		
LIDO	203	Change CI 24 h and PCWP 24 h
CASINO	299	Mortality 30 d and Mortality 180 d
REVIVE II	600	Composite global assess. at 6 h, 24 h 5 d
SURVIVE	800	Mortality 180 d

Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome (Review)

Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H, Werdan K, Frantz S, Unverzagt S

Levosimendan vs. Dobutamine: All cause short term mortality



NNT: 16 (patients with moderate risk)
NNT: 5 (patients with CS)

Cochrane Library

Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD009669.

Indications (+BB)

An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.	IIb	C

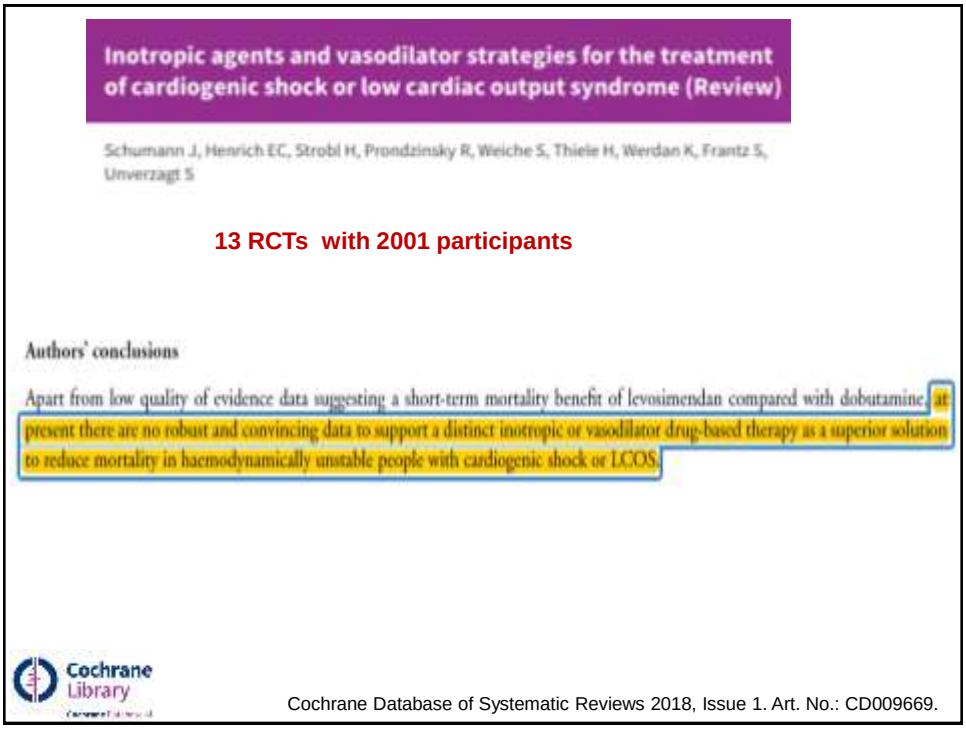
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Choice of specific agent

Situation	Agent
Chronic BB use	Levosimendan - Milrinone
Pulmonary hypertension	Levosimendan - Milrinone
Acute renal dysfunction	Dopamine - Levosimendan - Dobutamine
IHD	Levosimendan - Dobutamine
Septic HF	Dobutamine - Levosimendan
Hepatic dysfunction	Levosimendan

Continuing Cardiology Education, 2017; 3(3), https://doi.org/10.1002/cce2.59

Choosing the Best Inotrope….



Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome (Review)

Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H, Werdan K, Frantz S, Unverzagt S

13 RCTs with 2001 participants

Authors' conclusions

Apart from low quality of evidence data suggesting a short-term mortality benefit of levosimendan compared with dobutamine, at present there are no robust and convincing data to support a distinct inotropic or vasodilator drug-based therapy as a superior solution to reduce mortality in haemodynamically unstable people with cardiogenic shock or LCOS.

Cochrane Library

Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD009669.

Inotropes in ADHF: Rules

- Only in hypotension / hypoperfusion + adequate filling
- Early initiation
- Dose: as low as possible
- Duration: as short as possible
- Goal oriented (Until Therapy) perfused/ diuresed / recovery from insult / Tx death
- Careful selection of agents

Practical

- Central line

It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension.	I	C
In such cases intra-arterial blood pressure measurement may be considered.	IIb	C

Outcome

- Ade

Data on : Dopamine

TABLE 33-6 Common Intravenous Vasoactive Agents for Heart Failure

AGENT	INITIAL DOSE	EFFECTIVE DOSE RANGE
Vasodilators		
Nitroglycerin	20 μg/min	40-400 μg/min*
Nitroprusside	10 μg/min	30-350 μg/min* Usually <4 μg/kg/min
Nesiritide	With or without 1- to 2-μg/kg bolus	0.005-0.03 μg/kg/min
Inotropic Agents†		
Dobutamine	1-2 μg/kg/min	2-10 μg/kg/min for inotropy and vasodilation
Dopamine		
To augment diuresis	2 μg/kg/min	2-4 μg/kg/min for vasodilation and inotropy
To treat hypotension	4-5 μg/kg/min	5-15 μg/kg/min for inotropy and vasoconstriction
Milrinone	50- to 75-μg/kg bolus may be administered over 10 min	0.10-0.75 μg/kg/min for vasodilation and inotropy

*Customarily titrated to effect, using absolute doses rather than per kilogram.
†These inotropic agents also cause vasodilation. The more potent inotropic agents epinephrine and norepinephrine and the pressor agent vasopressin are rarely used for chronic decompensated heart failure but are discussed in the Use of Specific Intravenous Agents during Hospitalization section.

Data on : Adrenaline

Dosing & Packing:

- Emergency situation (eg, cardiac arrest & shock), iv bolus 0.05-1 mg, depending on the severity of cardiovascular compromise
- Major anaphylactic reactions 100-500µg (repeated, if necessary) followed by infusion
- To improve myocardial contractility or HR, a continuous infusion is prepared (1 mg in 250 ml [4µg/ml]) & run @ 2-20µg/min

Weaning

- Adequate filling pressure, euvolemia, SVR, stable SCr
- Dopamine
- Milrinone
- Oral medications

- discontinuation of BB. RAAS blockers
- Digoxin
- Nitrates + Hydralazine

Choice of Agents: **SVR**

Data on : Dobutamine

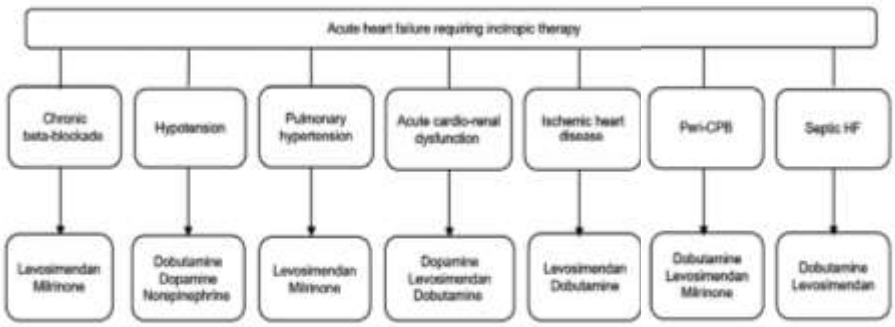
- Q1. What is the practical Dose?
- Q2. When HR slows down with dobutamine?
- Q3. Duration of infusion; Tachycardia
- Q4. Cn we use Dob + PDE-I? yes
- Q5. Is hypotension common?

Data on : IV Digoxin

Data on : Vasopressin

Inotropic versus vasodilator therapy

Choice of specific agent



Continuing Cardiology Education, 2017; 3(3), https://doi.org/10.1002/cce2.59

Pharmacology

Table 17–9 Hemodynamic Effects of Positive Inotropic Agents

	+dP/dt	PCWP	SVR	CO
Dobutamine	↑↑	↓	↓	↑
Dopamine (low dose)	↔	↔	↓	↔↑
Dopamine (high dose)	↑↑	↑	↑↑	↑↔↓
Milrinone	↑	↓↓	↓↓	↑

Pharmacology

Table 6-3

Sympathomimetic Inotropes for Acute Cardiac Failure Therapy

Drugs and Mediating Receptors	Dobutamine $\beta_1 > \beta_2 > \alpha$	Dopamine (Dopaminergic > β_1 High Dose α)	Norepinephrine $\beta_1 > \alpha > \beta_2$	Epinephrine $\beta_1 = \beta_2 > \alpha$	Isoproterenol $\beta_1 > \beta_2$	Milrinone PDE inhibitor
Dose infusion mcg/kg/min	2-15	2-5 renal effect 5-10 inotropic 10-20 SVR ↑	0.01-0.03 max. 0.1	0.01-0.03 max. 0.1-0.3	0.01-0.1	Bolus 50-75 (10 min) Drip 0.375-0.75
Elim t½ minutes	2.4	2.0	3.0	2.0	2.0	150
Inotropic effect	↑↑	↑↑	↑	↑↑	↑↑↑	↑
Arteriolar vasodilation	↑	↑↑	0	↑	↑	↑↑
Vasoconstriction	HD ↑	HD ↑↑	↑↑	HD ↑	0	0
Chronotropic effect	↑	0, ↑	↑	↑↑	↑↑↑	0
Blood pressure effect	↑	HD ↑	↑	0, ↑	↑	↓
Diuretic effect (direct)	0	↑↑	↑	0	0	0
Arrhythmia risk	↑↑	HD ↑	↑	↑↑↑	↑↑↑	↑

Elim t½, Elimination half-life; HD, high dose; PDE, phosphodiesterase; SVR, systemic vascular resistance.
↑, increase; 0, no change; ↓, decrease.

Conclusion

- Ade