Vasoactive drugs

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Q1

58y o male came with sever chest pain, typical had one spray of nitroglycerinn became severally hypotensive received 2 liters of NS
history of sildenafil 12 hs ago what is your next action??

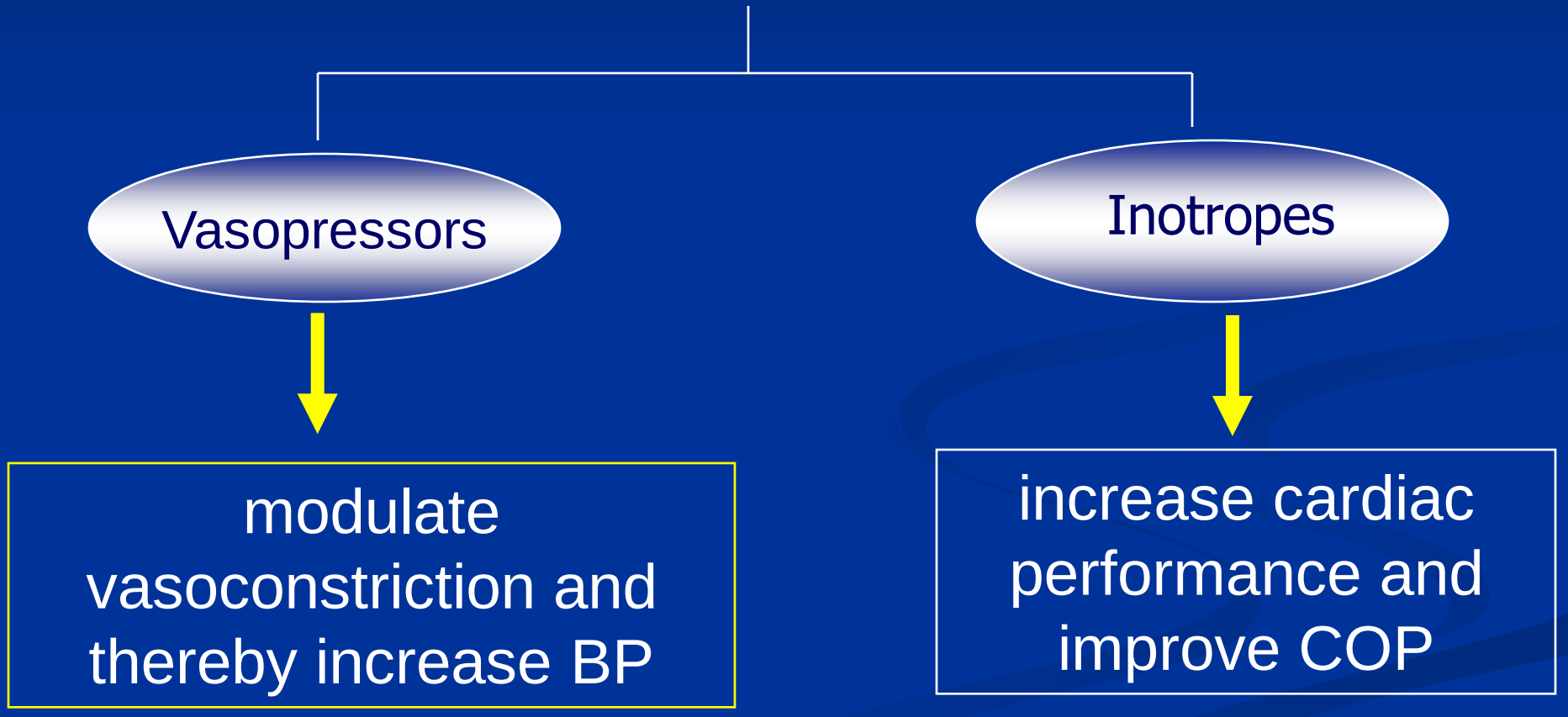
1. Epinephrine
2. Dobutamine
3. Norepinephrine
4. Phenylephrine

Q2

- 60 y o m with stemi cardiogenic shock going for ptci, remain hypotensive despite fluid resuscitation
- What is you first appropriate choice????

1. Epin
2. Dobutamine
3. Milrinon
4. Dopamine and dobutamine

Vasoactive drugs



α-adrenergic and β-adrenergic effects of vasoactive catecholamines

Isoproterenol

Dopexamine

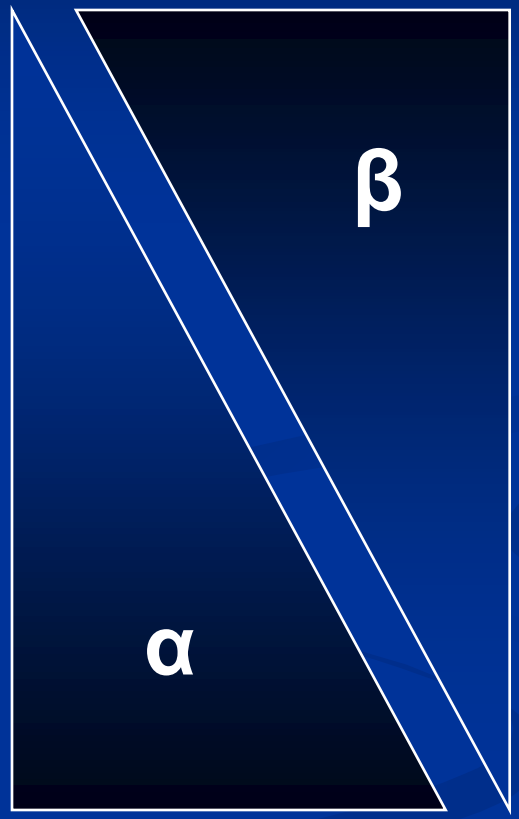
Dobutamine

Dopamine

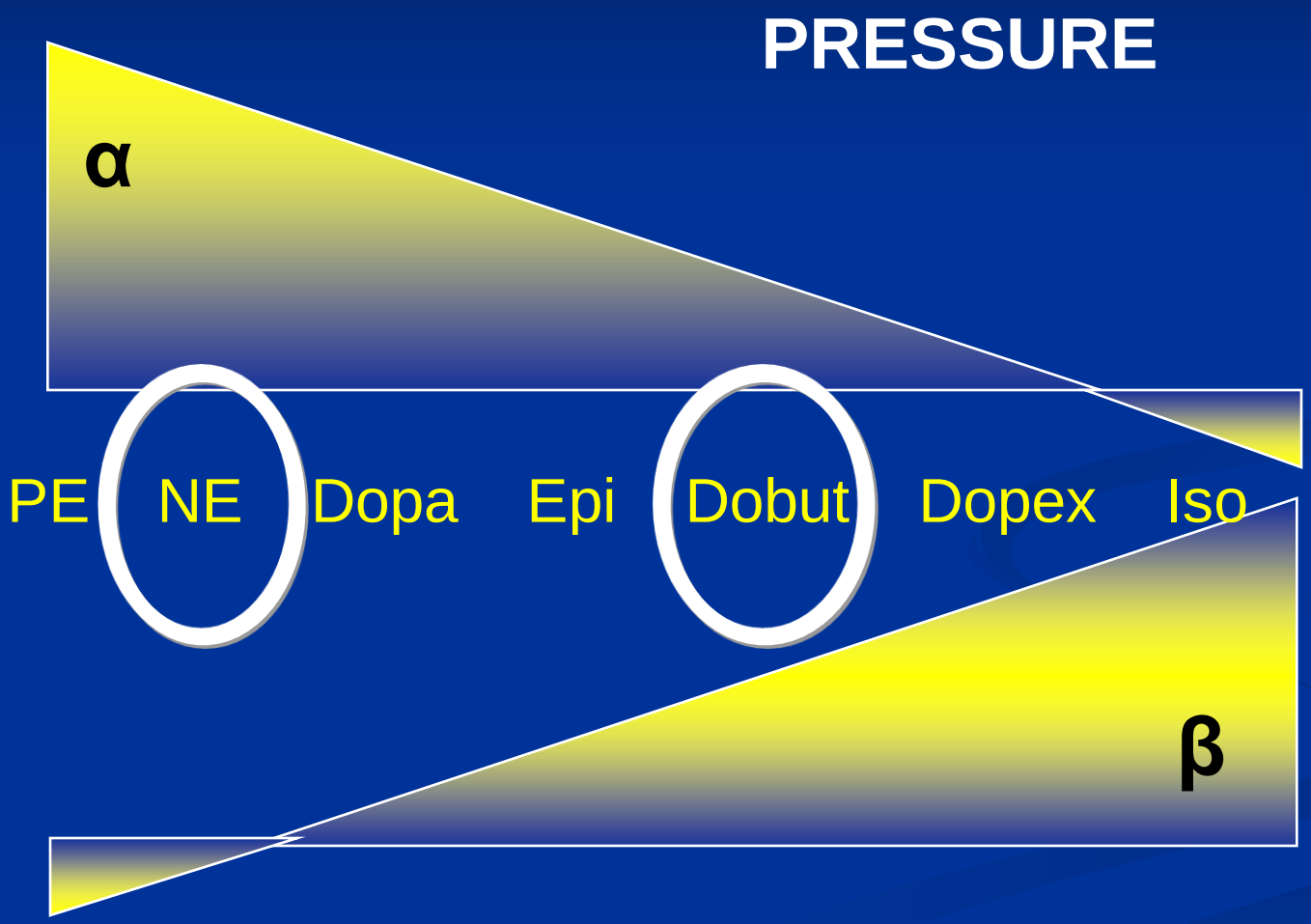
Epinephrine

Norepinephrine

Phenylephrine



Effects of vasoactive catecholamines on pressure and blood flow



Shock

Dosing of Vasoactive Therapy

Drug	Dose
Dobutamine	5–15 µg/kg/min
Dopamine	2–20 µg/kg/min
Epinephrine	5–20 µg/min
Norepinephrine	5–20 µg/min
Phenylephrine	40-180 µg/min

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- 1-Adrenergic receptor stimulation results in enhanced myocardial contractility through Ca2-mediated facilitation of the actin-myosin complex binding with troponin C and enhanced chronicity through Ca2 channel activation

Vasoactive drugs

- Activation of 1-adrenergic receptors on arterial vascular smooth muscle cells results in smooth muscle contraction and an increase in systemic vascular resistance

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- 2-Adrenergic receptor stimulation on vascular smooth muscle cells through a different intracellular mechanism results in increased Ca2 uptake by the sarcoplasmic reticulum and vasodilation

Vasoactive drugs

- Stimulation of D1 and D2 dopaminergic receptors in the kidney and splanchnic vasculature results in renal and mesenteric vasodilation through activation of complex second-messenger systems.

Facts

- Adrenergic receptors can be desensitized and downregulated in certain conditions such as in chronic heart failure .

Tilley DG, Rockman HA. Role of beta-adrenergic receptor signaling and desensitization in heart failure: new concepts and prospects for treatment. *Expert Rev Cardiovasc Ther.* 2006;4:417– 432.

Facts

- Hypoxia or Acidosis can alter The relative binding affinities of individual inotropes and vasopressors to adrenergic receptors

Li HT, Long CS, Rokosh DG, Honbo NY, Karliner JS. Chronic hypoxia differentially regulates 1-adrenergic receptor subtype mRNAs and inhibits 1-adrenergic receptor-stimulated cardiac hypertrophy and signaling. *Circulation*. 1995;92:918 –925.

Modest VE, Butterworth JF IV. Effect of pH and lidocaine on betaadrenergic receptor binding: interaction during resuscitation? *Chest*. 1995;108:1373–1379.

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Dobutamine

- Dobutamine is a synthetic catecholamine with a strong affinity for both 1- and 2-receptors, which it binds to at a 3:1 ratio

- Vasoconstriction progressively dominates at higher infusion rates only.

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Norepinephrine

- is a potent 1-adrenergic receptor agonist ----powerful vasoconstrictor
- less potent direct inotropic properties.
- Coronary flow is increased owing to elevated diastolic blood pressure

Vasoactive drugs

Phenylephrine

- With its potent synthetic -adrenergic activity
- primarily as a rapid bolus for immediate correction of sudden severe hypotension.

- no direct heart rate effects

Vasoactive drugs

Phosphodiesterase Inhibitors

- increase the level of cAMP by inhibiting its breakdown within the cell, which increased myocardial contractility
- potent inotropes and vasodilators
- Milrinone is the PDI most commonly used
- has a longer half-life (2 to 4 hours) than many other inotropic medications.

Vasoactive drugs

Ephedrine

- a sympathomimetic agent with a structure similar to the other synthetic derivatives of epinephrine.
- Ephedrine acts on alpha and beta receptors with less potency than epinephrine and also stimulates the release of norepinephrine accounting for additional indirect alpha and beta effects
- Ephedrine's combined receptor activity causes an increase in systolic blood pressure and a modest inotropic effect.
- Ephedrine is rarely used in a continuous infusion and its clinical use is mainly limited to treatment of acute hypotension episode

Vasoactive drugs

vasopressin or “antidiuretic

- released after increased plasma osmolality or hypotension, as well as pain, nausea, and hypoxia

Vasoactive drugs

Calcium-Sensitizing Agents

- inotropic agents
- levosimendan being the most well known
- improved contractile performance and vasodilation

Vasoactive drugs

- Combination of dopamine and dobutamine at a dose of 7.5 g kg1 min1 each was shown to improve hemodynamics and limit important side effects

Richard C, Ricome JL, Rimailho A, Bottineau G, Auzepy P. Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. *Circulation*. 1983;67:620–626.

Vasoactive drugs

- When response to a medium dose of dopamine or dopamine/ dobutamine in combination is inadequate, or the patient's presenting systolic blood pressure is 70 mm Hg, the

- use of norepinephrine has been recommended.

ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004;44:E1–E211.

Vasoactive drugs

- One study to date that examined vasopressin use in cardiogenic shock after AMI, this agent was found to increase MAP without adversely impacting cardiac index and wedge pressure.

Jolly S, Newton G, Horlick E, Seidelin PH, Ross HJ, Husain M, Dzavik V. Effect of vasopressin on hemodynamics in patients with refractory cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol*. 2005;96:1617–1620.

Vasoactive drugs

- In hypotension and peripheral hypoperfusion, particular agents may be indicated with slightly different levels of recommendation (dobutamine and levosimendan, class IIa; PDIs and dopamine, class IIb).

Nieminen MS, Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:384–416.

Levosimendan

- Two early studies demonstrated a mortality benefit in patients given levosimendan versus placebo

- early (within 14 days) in the setting of LV failure complicating AMI

Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction: a randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J*. 2002;23:1422–1432.

Levosimendan

- in larger multicenter randomized trials in the setting of acute decompensated HF levosimendan use significantly improved symptoms but not survival.

Packer M. REVIVE II: multicentre placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Presented at: 78th Scientific Sessions of the American Heart Association; November 13–16, 2005; Dallas, Tex.

Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R Padley RJ, Poder P, Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA*. 2007;297:1883–1891.

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

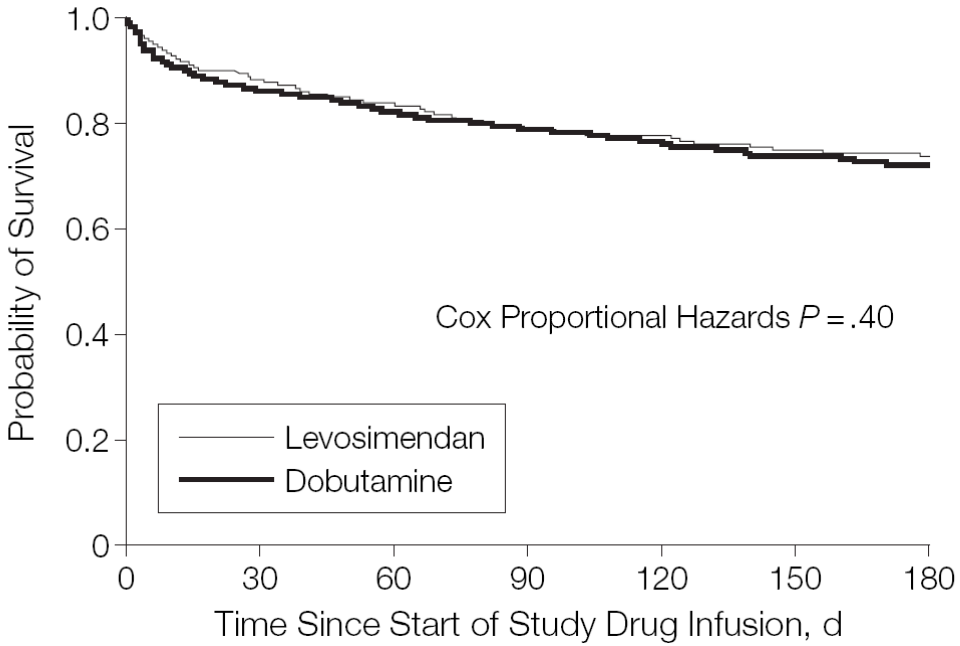
The SURVIVE Randomized Trial

- **Design, Setting, and Patients**

- comparing the efficacy and safety of intravenous levosimendan or dobutamine in 1327 patients hospitalized with acute decompensated heart failure who required inotropic support.

- *JAMA. 2007;297:1883-1891*

Figure 2. Effect of Dobutamine and Levosimendan Treatment on All-Cause Mortality During 180 Days Following the Start of Study Drug Infusion



No. at Risk					
Levosimendan	664	608	586	525	462
Dobutamine	663	596	568	519	454

LEVOSIMENDAN VS DOBUTAMINE IN ACUTE HEART FAILURE

Table 2. Primary, Secondary, and Post Hoc All-Cause Mortality End Points*

	No. (%) of Patients†			
	Levosimendan (n = 664)	Dobutamine (n = 663)	HR (95% CI)	*P* Value
Primary end point				
All-cause mortality at 180 d	173 (26)	185 (28)	0.91 (0.74-1.13)	.40‡
Secondary end point				
All-cause mortality at 31 d	79 (12)	91 (14)	0.85 (0.63-1.15)	.29‡
Mean change in BNP at 24 h from baseline, pg/mL	(n = 628) −631	(n = 611) −397		<.001§
Mean No. of days alive and out of the hospital during 180 d	120.2	116.6		.30‖
Dyspnea assessed at 24 h; ≥mild improvement¶	544 (82)	550 (83)		.96‖
Global assessment at 24 h; ≥mild improvement¶	531 (80)	537 (81)		>.99
Cardiovascular mortality during 180 d	157 (24)	171 (26)	0.90 (0.72-1.12)	.33‡
Post hoc all-cause mortality				
5 d	29 (4)	40 (6)	0.72 (0.44-1.16)	.17‡
14 d	59 (9)	69 (10)	0.84 (0.59-1.19)	.33‡
90 d	139 (21)	138 (21)	0.99 (0.78-1.25)	.91‡

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; HR, hazard ratio.
*Survival differences were tested for significance by the Cox proportional hazard regression model with treatment as the only covariate. Comparison of categorical variables such as dyspnea assessment, patients' global assessment, and days alive and out of the hospital were performed by the Cochran-Mantel-Haenszel test with effect for treatment only. Changes in BNP levels were analyzed using the Kruskal-Wallis test.
†Unless otherwise indicated.
‡Cox proportional hazards model was used for treatment effect only.
§Analysis of covariance model used with baseline value as covariate and treatment for main effect.
‖Cochran-Mantel-Haenszel mean score test with effect for treatment only.
¶Distribution from markedly improved to markedly worse.

ACC/AHA PRACTICE GUIDELINES—FULL TEXT

ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)

Developed in Collaboration With the Canadian Cardiovascular Society

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- SBP 70 to 100 mm Hg who are
  - less sick and show no signs of shock, dobutamine infusion (2–20 μg/kg/min)
  - In shock states with signs of hypoperfusion, begin with a dopamine infusion (5–15 μg/kg/min) to provide inotropic and vasoconstrictive support.
- SBP <70 mm Hg) norepinephrine is recommended as a 0.5 to 30 μg/min

	Receptor activity						
Vasoactive agent	**α1**	**α2**	**β1**	**β2**	**Dopamine**	**Other**	**Clinical effect**
Epinephrine	+++++	+++(+)	+++	0(+)	0		▲ in SVR predominates, vasodilator in low dose ▲CO by ▲**inotrope** and ▲HR
Ephedrine	++	0	++(+)	++	0		▲ in SVR predominates Mild ▲CO by ▲**inotrope**
Norepinephrine	+++++	+++	+++	0(+)	0		▲▲ in SVR predominates because of alpha effects ▼CO s/t ▲ in SVR offset by **inotrope** ▲*HR at higher doses may limit clinical effectiveness*
Phenylepherine	+++	0	0	0	0		▲▲ in SVR predominates CO neutral at low doses s/t ▲venous return offsets the ▲SVR effect on CO *At high doses, ▲ in SVR predominates with ▼CO*

Vasoactive agent	α1	α2	β1	β2	Dopamine	Other	Clinical effect
Dopamine							
0.5–2 μg/kg/min	0	(+)	+	+	++	Dopamine	Dose 1-▲CO by ▲**inotrope**
3.0–10 μg/kg/min	+	(+)	++	+	++		Dose 2-▲SVR and ▲CO by ▲**inotrope** and ▲HR
10–20 μg/kg/min	+(++)	(+)	++(++)	+(+)	++		Dose 3-▲ in SVR predominates
Dobutamine	0(+)	0(+)	++++	+++	0		▲*HR* ▲SVR▲CO by ▲
Vasopressin	0	0	0	0	0	V1 receptor	▲▲ in SVR predominates
Amrinone /milrinone	0	0	0	0	0	PDE inhibition	▾SVR ▲CO by phosphodiesterase inhibition

Shock state	First-tier agents	Second-tier agents
Anaphylactic shock	Epinephrine, 1 mL of 1:10,000 solution (100 μg), can be given as a slow IV push, then (5–15 μg/min)	Norepinephrine infused at 0.1–1 μg/kg/min (0.5–30 μg/min)
Cardiogenic shock, left ventricular	SBP <70, norepinephrine at 0.1–1 μg/kg/min (0.5–30 μg/min) SBP 70–90, dopamine at 15 μg/kg/min SBP >90, dobutamine at 2–20 μg/kg/min	Amrinone, 0.75 mg/kg then 5–10 μg/kg/min (not recom. post-MI) Milrinone, 50 μg/kg, then 5–10 μg/kg/min (not recommended post-MI) Although they are less arrhythmogenic and chronotropic, they have prolonged half-lives and may cause hypotension
Cardiogenic shock, PE	Dobutamine 5 μg/kg/min Norepinephrine 0.1–1 μg/kg/min	Phenylephrine infused at 10–20 μg/kg/min
Hemorrhagic shock	Volume resuscitation	Dopamine 5–15 μg/kg/min as a temporizing adjunct

Shock state	First-tier agents	Second-tier agents
Neurogenic shock	Dopamine infused at 5–15 μg/kg/min	Norpinephrine infused at 0.1–1 μg/kg/min Phenylephrine infused at 10–20 μg/kg/min
Septic shock	Norepinephrine 0.1–1 μg/kg/min Dobutamine 5 μg/kg/min	Dopamine infused at 5–15 μg/kg/min Epinephrine infused at 0.02 μg/kg/min
Toxic drug overdose with shock	Norepinephrine infused at 0.1–1 μg/kg/min	Phenylephrine 10–20 μg/kg/min Glucagon given as a 5-mg IV bolus, then a 1–5 mg/h infusion calcium gluconate, 0.6 mL/kg bolus, then a 0.6–1.5 mL/kg/h infusion Insulin started at 0.1 units/kg/h IV and titrated to a goal of 1 unit/kg/h

Thank you