Pharmacology in Shock

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Objectives

- Define the mechanism of action of vasoactive medications and resultant hemodynamic effects
- Review pertinent literature comparing vasoactive medications in cardiogenic shock
- Compare patient presentation and characteristics that influence choice of vasoactive medication in cardiogenic shock

Background

- Vasopressors administered in 90% of patients with cardiogenic shock
- Limited literature comparing vasoactive medications in cardiogenic shock

Pathophysiology of Vasopressor Use

Mechanism of Action and Hemodynamic Effects of Vasopressors

Medication	Usual Dosing	Receptor Binding				Hemodynamic Effect
		α_1	β_1	β_2	DA	
Dopamine	0.5 – 2 mcg/kg/min	-	+	-	+++	↑ CO
	5 - 10 mcg/kg/min	+	+++	+	++	↑↑ CO ↑ SVR
	10 - 20mcg/kg/min	+++	++	-	++	↑↑ SVR ↑ CO
Norepinephrine	0.05 – 0.4 mcg/kg/min	++++	++	+	-	↑↑ SVR ↑ CO
Epinephrine	0.01 – 0.5 mcg/kg/min	++++	++++	+++	-	↑↑ CO ↑↑ SVR
Phenylephrine	0.1 – 10 mcg/kg/min	+++	-	-	-	↑↑ SVR
Vasopressin	0.02 – 0.04 units/min	Stimulates V1 in vascular smooth muscle				↑↑ SVR

Circulation. 2017;136e232-268.

SOAP II (2010)

- Dopamine vs Norepinephrine for shock (n = 1679)

- Outcomes
  - No significant difference in rate of death at 28 days
    - (52.5% vs 48.5%; OR 1.17 95% CI 0.97 – 1.42; p = 0.10)

  - Subgroup analysis
    - Increased 28 day mortality in cardiogenic shock with Dopamine

N Engl J Med 2010;362(9):779-89.

SOAP II (2010)

	Dopamine (n = 858)	Norepinephrine (n = 821)	p-value
Arrhythmia n,(%)	207 (24.1)	102 (12.4)	<0.001
Atrial Fibrillation n,(%)	176 (20.5)	90 (11)	
Ventricular Tachycardia n,(%)	21 (2.4)	8 (1)	
Ventricular Fibrillation n,(%)	10 (1.2)	4 (0.5)	

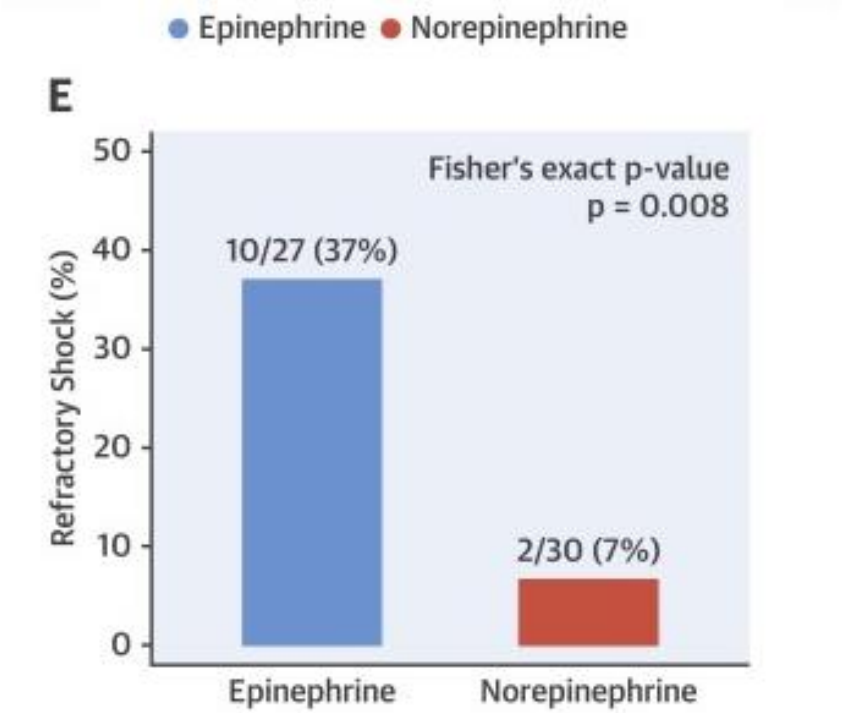
OptimaCC (2018)

- Epinephrine vs Norepinephrine in MI complicated by cardiogenic shock (n = 57)

- Outcomes
  - No difference in increase in MAP from H0 to H72 (p=0.25)
  - No difference in increase in cardiac index from H0 to H 72 (p = 0.43)

J Am Coll Cardiol. 2018;72:173-182

OptimaCC (2018)



J Am Coll Cardiol. 2018;72:173-182

Epinephrine versus norepinephrine in cardiac arrest patients with post-resuscitation shock

- Patients admitted alive to ICU with post-resuscitation shock after out-of-hospital cardiac arrest (n = 766)

- All-cause hospital mortality higher in the epinephrine group (83% vs 61%)
  - (OR 2.6;95% CI 1.4-4.7; p = 0.002)

- CV hospital mortality higher in the epinephrine group (41% vs 11%)
  - (aOR 5.5; 95% CI 3.0-10.3; p< 0.001)

Intensive Care Med. 2022; 48:300-310.

Choosing a Vasopressor

Norepinephrine

- 1st line for most patients in shock

Epinephrine

- 2nd line in most patients in shock
- Can consider in bradycardia

Dopamine

- Dose dependent effects
- Can consider in bradycardia
- More tachyarrhythmias than norepinephrine

Phenylephrine

- Arrhythmias w/ other agents
- HCM and LVOT

Vasopressin

- Minimize catecholamine requirement
- Maintains effect in acidosis
- Severe PH
- Arrhythmias w/ other agents

Mechanism of Action and Hemodynamic Effects of Inotropes

Medication	Usual Dosing	Receptor Binding				Hemodynamic Effect
		α_1	β_1	β_2	DA	
Dobutamine	2.5 – 20 mcg/kg/min	+	++++	++	-	↑↑ CO ↓ SVR ↓ PVR
Milrinone	0.125 – 0.75 mcg/kg/min	PD-3 inhibitor				↑ CO ↓ SVR ↓ PVR

Circulation. 2017;136e232-268.

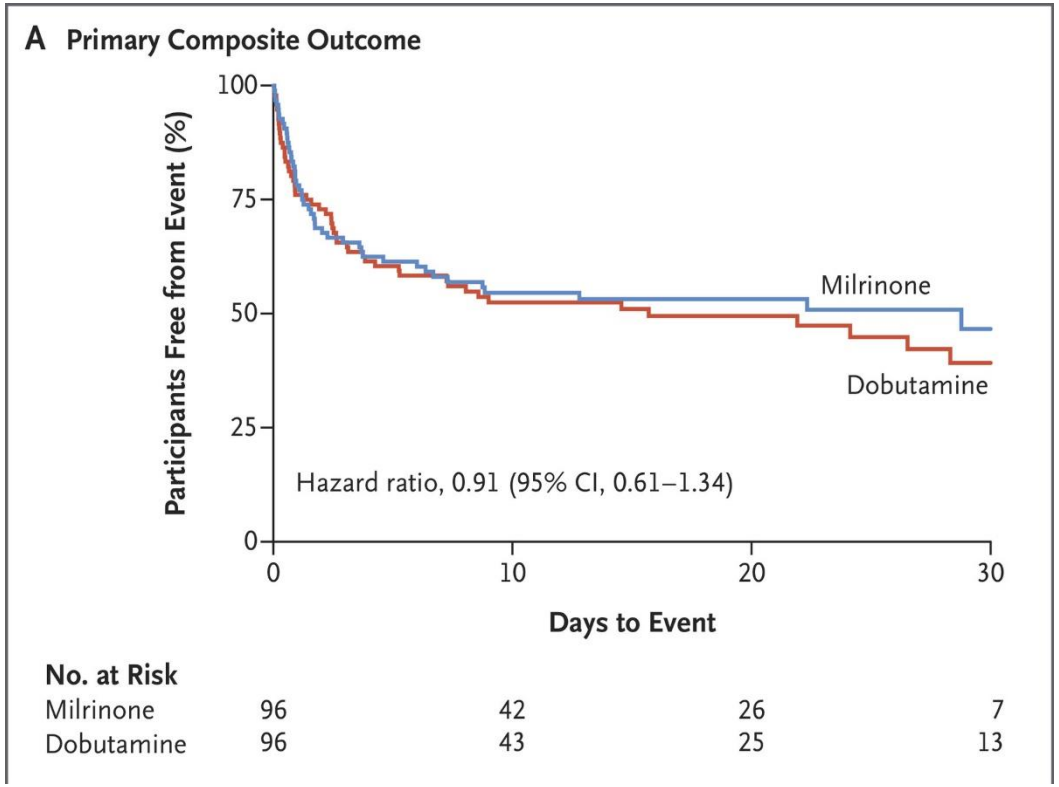
DOREMI (2021)

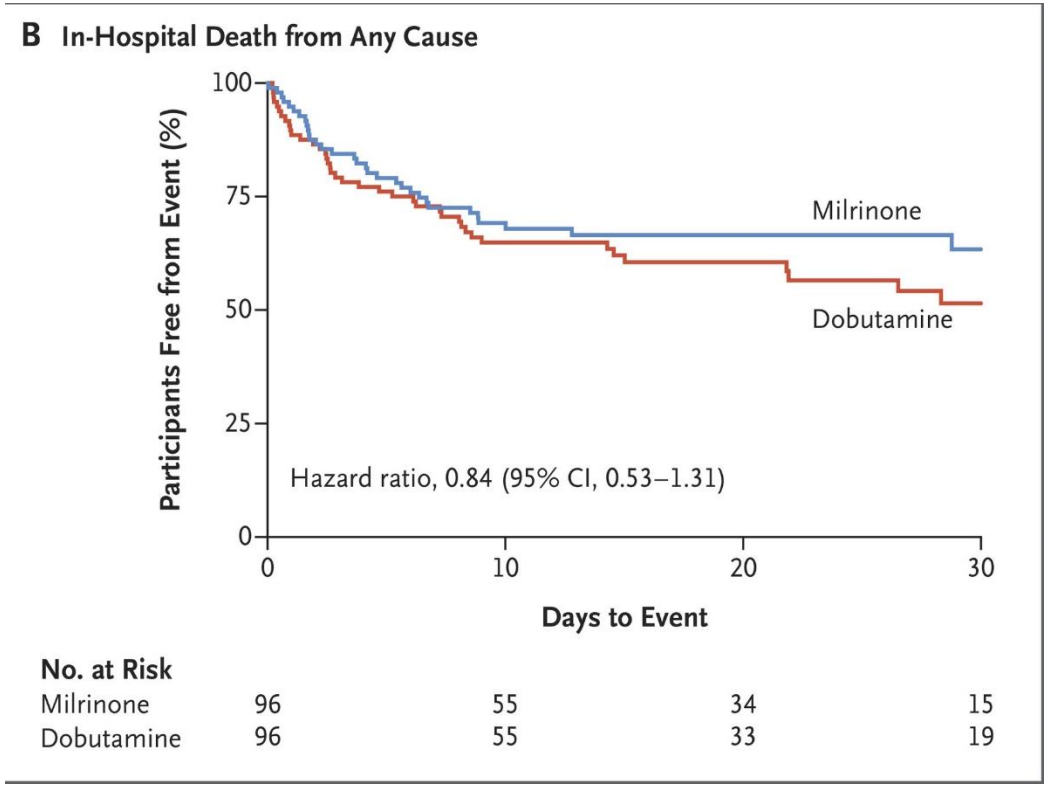
- Milrinone vs Dobutamine for Cardiogenic shock (n = 192)

- Outcomes
  - No difference in composite (in-hospital death, resuscitated cardiac arrest, receipt of cardiac transplant or MCS, non-fatal MI, TIA/stroke, or renal replacement therapy initiation)
    - 49% vs 54%; RR = 0.9, 95% CI 0.69-1.19; p = 0.47)

N Engl J Med 2021; 385:516-525

DOREMI (2021)





N Engl J Med 2021; 385:516-525

Choosing an Inotrope

Milrinone

- Pulmonary Hypertension
- Normotensive, High SVR

Dobutamine

- Hypotensive with Milrinone
- Renal Dysfunction
- Hypotensive, low to normal SVR

Am Heart J 2001;142(6):998-1002.
Am Heart J 2003;145:324-29.
J Cardiovasc Pharmacol Ther. 2015;20: 249-260.

Initial Vasoactive Management

Cause/Presentation of Cardiogenic Shock	Vasoactive Management Consideration
Classic (wet and cold)	Norepinephrine or Dopamine
	Inotrope
Euvolemic (cold and dry)	Norepinephrine or Dopamine
	Inotrope
	Small fluid bolus
Vasodilatory (warm and wet) or mixed	Norepinephrine
RV shock	Fluid bolus
	Norepinephrine, dopamine, or vasopressin
	Inotrope
	Inhaled pulmonary vasodilator
Normotensive	Inotrope

Circulation. 2017;136e232-268.

Conclusion

- Consider patient specific factors when choosing vasoactive therapy
  - Etiology of cardiogenic shock
  - Hemodynamic profile
  - Ability to tolerate adverse effects