AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
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Vaso-active Agents in the Emergency Department: When and How Hard to Squeeze

Emergency physicians can choose from a wide array of vasoactive agents to treat patients in shock. However, when to begin therapy, the optimal drug or drug combination to select, and the dose to administer are not always clear. With the use of case-based presentations, the indications and dosing strategies for currently available pressor agents will be reviewed. When to add a second agent and which one to choose will also be discussed.

- List the currently available vaso-active drugs and describe their mechanisms of action.
- Discuss the indications and dosages for these agents.
- Select appropriate vaso-active agents for the management of typical emergency department patients presenting in shock.

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FACULTY

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Vaso-active Agents in the Emergency Department: When and How Hard to Squeeze

Peter M.C. DeBlieux, MD, FACEP

I. Course Description

Emergency physicians can choose from a wide array of vaso-active agents in the management of shock. Utilizing a case based format, the indications and dosing strategies of currently available agents will be reviewed.

II. Objectives

A. List the currently available vaso-active drugs and describe their mechanism of action.
B. Discuss the indications and dosages for these agents.
C. Select appropriate vaso-active agents for the management of typical emergency department patients presenting in shock.

III. Target Audience

The target audience is emergency medicine physicians with a basic knowledge of cardiovascular shock and therapeutic goals of cardiovascular shock management.

IV. Outline

A. Shock - inadequate tissue perfusion that impairs cellular metabolism.

1. Hemorrhagic – decreased hemoglobin transport of oxygen.

2. Cardiogenic – primary pump failure.

3. Septic – diminished perfusion at the tissue level and/or diminished systemic vascular resistance with a presumed infectious etiology.

4. Anaphylactic – allergen response resulting in a histamine release that causes decreased systemic vascular resistance.

5. Neurogenic – loss of normal sympathetic tone resulting in bradycardia and diminished systemic vascular resistance

.

B. Assessment of Shock

1. Blood Pressure

   - Mean Arterial Blood Pressure correlates best with perfusion pressures. Maintenance of MABP 65-75 mmHg is essential for cerebral perfusion.

2. Organ Perfusion

   - Mental status impairment may be the first sign of perfusion abnormalities.

   - Hourly urinary output is a quick reference for organ perfusion. A standard of 0.5 – 1 cc/kg hourly output for adults without renal disease is expected.

3. Skin

   - Cyanosis and decreased capillary refill are late and inconsistent signs.

C. ABCs

1. Airway assessment and control may be indicated in patients with impaired mental status and/or hemodynamic instability.

2. Breathing may be labored as a result of pulmonary pathology or in a response to poor perfusion. Assisted ventilation may compensate for poor cardiopulmonary reserve.

3. Circulatory support with two large bore intravenous lines is the fastest way to administer fluids in the E.D. setting. Central venous access with a Cordis or triple lumen catheter should follow the secondary survey if peripheral lines are established.

D. Fluid Resuscitation

1. Establishing a need for fluid resuscitation

   - Physical exam evidence of dehydration can be confounding.
   - Lab evidence of dehydration can be delayed and confounding.

2. Crystalloids are the fluid of choice over colloids for emergent resuscitation of shock states.

   - Advantages to crystalloids include reduced cost, similar outcome in comparison to colloids.
   - Advantages to colloids include more rapid expansion of intravascular volume, decreased incidence of pulmonary edema.

D. Measuring a Response to Fluid Therapy

1. Fluid bolus in hypotensive patients should consist of NS or RL fluid bolus 250 - 500 cc over 10 - 15 min.

2. Assessment of: heart rate, respiratory rate, blood pressure, urine output, mental status, $SA0_2$.

3. Consider repeat fluid bolus if no response is seen.

4. Discontinue fluid boluses for decreasing blood pressure, increasing respiratory rate, decreasing oxygen saturation.

5. Establishing a trend is vital to assessing critically ill patient's response to therapy.

- Obtain data
- Organize data
- React to data

6. If no change following 2L crystalloid consider vaso-active agents.

E. Role of Vaso-active Agents in Hemodynamic Support

Table I
Indications for Vaso-active Therapy

Indication	*Goal*	Primary *Receptor Type*
Bradycardia	Increased heart rate	Beta
Hypotension		
Hypovolemic*	Vasoconstriction	Alpha
Cardiogenic	Increased contractility	Beta
Vasogenic	Vasoconstriction	Alpha
Mixed	Vasoconstriction. and increased contractility	Alpha and Beta
Selective organ Hypoperfusion	Vasodilation or Vasoconstriction	Dopamine or alpha

*Used as temporizing measure until intravascular volume is replete.

F. Cardiovascular Actions and Receptors

Table 2
Cardiovascular Actions and Signal Pathways Activated by Adrenergic Receptors

Receptor Type	*Cardiovascular Actions*	*Signal Pathway*
Alpha 1	Vasoconstriction	Activation of phospholipase C
Alpha 2	Decreased central sympathetic outflow; feedback inhibition of norepinephrine release; vasoconstriction	Inhibition of adenyl cyclase
Beta 1	Increased heart rate,	Activation of

	contractility, and conduction velocity	adenyl cyclase
Beta 2	Vasodilation	Activation of adenyl cyclase
Dopamine	Vasodilation	Activation of adenyl cyclase

G. Commonly Used Vaso-active Agents

Table 3
Ability of Commonly Used Vaso-active Agents to Stimulate Adrenergic Receptors

	Receptor Type			
	a	B1	B2	Dopamine
Phenylephrine	++++			
Norepinephrine	++++	++++	+/++	
Epinephrine	+++	++++	+++	
Dopamine	++/+++	++++	++	++++
Dobutamine	+	++++	++	

G. Case Presentations

Case One

A 32 year-old female, status post C-section delivery 4 days ago, returns from radiology waving the results of her high probability VQ scan. She suddenly becomes agitated and her oxygen saturation drops. Her blood pressure is now 80/40, pulse rate 132, and respiratory rate of 34. A fluid bolus of 2L NS results in no increase in her blood pressure.

What are the options for vaso-active agents in pulmonary embolism?

1. Pathophysiology – pulmonary hypertension and subsequent right ventricular failure following the release of vaso-active amines. Reduction in cardiac output is due to a combination of decreased right heart performance and impingement of left ventricular filling.

2. Treatment – limited animal data supports the use of norepinephrine linked to improved survival, cardiac output and coronary blood flow with minimal effect on pulmonary vascular bed. Epinephrine, Dobutamine and Amrinone have all been utilized with some degree of success in animal models and anectdotal

Case Two

A 64 year-old male presents with a change in mental status and flank pain. His initial vital signs reveal a pulse of 142, blood pressure of 70/30, respiratory rate of 36 and a temperature of 41°C. A Foley catheter is placed and 200 cc of pus/urine returns. He has received four serial boluses of 500 cc NS without improvement to his blood pressure.

What are the options for vaso-active agents in the treatment of septic shock?

1. Pathophysiology – septic shock results in a decrease in systemic vascular resistance and a systemic inflammatory response syndrome with diffuse capillary leak. Cardiac output is typically elevated, but may be depressed in some cases.

2. Treatment – practice habit supports the use of Dopamine as the initial vaso-active agent of choice in fluid unresponsive septic shock. Evidence based medicine supports Norepinephrine as the vaso-active agent of choice with resultant improved splanchnic blood flow, and achievement of hemodynamic goals when compared to Dopamine. Other options include combining Dobutamine and Dopamine, Dobutamine and Norepinephrine, Epinephrine, Epinephrine and Dopamine, replacing Dobutamine with Amrinone.

Case Three

A 28 year-old female has ingested her freshly filled prescription of Elavil. She presents with a depressed mental status and vital signs of pulse 138, blood pressure 76/38, and respiratory rate of 6. She has been intubated, lavaged/charcoal, and given 2L NS without improvement in her blood pressure.

What are the options for vaso-active agents in the treatment of tricyclic antidepressant overdoses?

1. Pathophysiology – hypotension results because of neuronal blockade of norepinephrine uptake, decreased myocardial contractility, and peripheral postsynaptic alpha adrenergic receptor blockade.
2. Treatment – initial cautious fluid administration with NS, for decreased cardiac output Dobutamine is the agent of choice. For hypotension due to a decreased systemic vascular resistance, Norepinephrine is the drug of choice. Dopamine should be avoided due to beta 2 stimulation resulting in a decreased systemic vascular resistance.

Case Four

A 19 year-old male has sustained a high cervical spine injury at C-2 due to a trampoline accident. His neurological injury is complete at the C-2/C-3 level and he is intubated. Vital signs are pulse rate of 62, blood pressure of 82/44, and respiratory rate of 18. He has been given 4 L of NS and his blood pressure has not responded.

What are the options for vaso-active agents in the treatment of spinal shock?

1. Pathophysiology – hypotension associated with spinal shock is due to the loss of sympathetic tone to the heart and vasculature. Resultant bradycardia and diminished systemic vascular resistance may further exacerbate spinal cord injury.
2. Treatment – mean arterial blood pressure has been restored with Phenylephrine, but bradycardia and diminished cardiac output has been associated with this management. Epinephrine has improved heart rate, cardiac output, but did not alter diastolic blood pressure or mean arterial blood pressure. Maximizing mean arterial blood pressure with fluids, and Dopamine, +/- Norepinephrine offers the best choice for improvement in neurological outcome without adverse events.

H. Cautious Use of Vaso-active Agents in:

1. Right-sided myocardial infarction

2. Valvular heart disease

3. Myocardial schema

I. Potential Side effects of Vaso-active Agents

1. Tachyarrhythmias

2. Myocardial ischemia

3. Hypoperfusion

4. Hyperglycemia

J. Dosages of Common Agents

1. Norepinephrine - start at 2 mcg/min and titrate

2. Dobutamine - start at 2 mcg/kg/min and titrate

3. Epinephrine - start at 1 mcg/min and titrate

4. Dopamine - start at 2 mcg/kg/min

5. Phenylephrine – start at 20 mcg/min and titrate

K. Dose-Response Curves

1. Variability

   - Patient to patient
   - Drug to drug

2. Clinical response

   - Blood pressure
   - Heart rate

- Urine output
- Mental status
- Oxygen saturation

L. Treatment Plan

1. Each patient is unique
2. Avoid dogmatism, "fixed recipe"
3. Evaluate the need for ongoing therapy
4. Use minimum dose required
5. Identify finite end points

References

1. Buchman AL, Dauer J, Geiderman J. The use of vasoactive agents in the treatment of refractory hypotension seen in tricyclic antidepressant overdose. J Clin Psychopharm 10(6):409-13, 1990.
2. Marshall JB, Forker AD. Cardiovascular effects of tricyclic antidepressant drugs: therapeutic usage, overdose, and management complications. Amer Heart J. 1982;103(3):401-11.
3. Ducas J, prewitt RM. Pathophysiology and therapy of right ventricular dysfunction due to pulmonary embolism. Cardiovasc Clin. 1987;17:191-202.
4. Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. Chest.1997;111:218-24.
5. Deboisblanc BP.Treatment of massive pulmonary embolism. Clin Pulm Med. 1995;2:353-58.
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7. Brooker RF, et al. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia;a randomized, double blinded, cross-over comparison of phenylephrine and epinephrine. Anesthesiol. 1997;86(4):797-805.
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9. Desjars P, Pinaud M, et al. A reappraisal of norepinephrine therapy in human septic shock. Crit Care Med. 1987;15:134-37.
10. Martin C, Papaz. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest. 1993;103(6):1826-31.

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I. Fluid Resuscitation

A. History

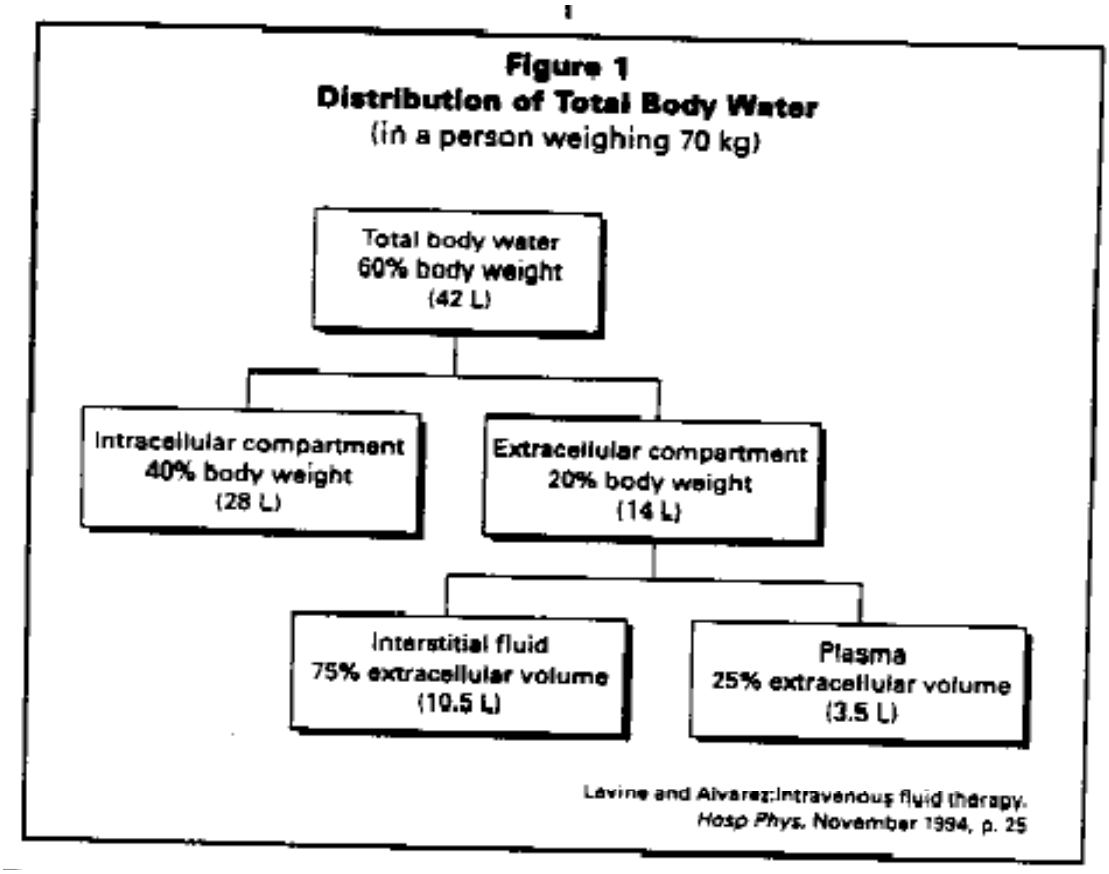
1. WW I - crystalloids and colloids

2. WW 11 - blood and plasma

3. Today - the controversy continues

III. Maintenance Fluid Requirements

A. Crystalloids are fluids of choice



B. Formula based on body weight in kg:

1st 10 kg are 4 cc/kg/hr

2nd 10 kg are 2 cclkg/hr

Every kg thereafter is 1 cc/kg/hr

C. Example 70-kg person:

10 kg x 4 cc = 40 cc

10 kg x 2 cc = 20 cc

50 kg x *1 cc = 50 cc*

Total fluid maintenance requirements are: 40 + 20 + 50 = 110 cc

IV. Types and Composition of Crystalloids

VII. Fluid and Blood Requirements in Hemorrhage

Table 4
Estimated Fluid and Blood Requirements
(based on patient's initial presentation)

	Class I	Class 11	Class III	Class IV
Blood loss (mL)	up to 700	750-1500	1500-2000	> 2000
Blood loss (% blood volume)	*up to 15%*	*15-30%*	*30-40%*	*>40%*
Pulse rate	< 100	> 100	> 120	> *140*
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiratory rate	*14-20*	*20-30*	*30-40*	*> 35*
Urine output (ml/hr)	< 30	20-30	5-15	Negligible
CNS-mental status	Slightly anxious	Mildly anxious	Anxious and con-fused	Confused, lethargic
Fluid replacement *(3:1* rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood
*for a 70-kg patient				

VIII. Clinical Disorders Associated With Increased Vascular Permeability

Table 5
Conditions Associated with Increased Microvascular Premeability

- Adult respiratory distress syndrome
- Amniotic fluid embolism
- Anaphylaxis
- Aspiration pneumonia
- Bacterial or viral pneumonia
- Burns
- Disseminated intravascular coagulation
- Drug overdose (salicylates, cocaine, narcotics)
- Inhalation injury
- Massive blood transfusion
- Near drowning
- Head injury
- Pancreatitis
- Sepsis

- Thromboembolism
    - Trauma
- Venom Injuries

IX. Crystalloids Versus Colloids

Table 6
Crystalloids versus Colloids

	Crystalloids	Colloids
Advantages	Inexpensive More rapid expansion of IV volume	Effective if given in sufficient amounts Shorter resuscitation time Similar outcome compared with Lower incidence of pulmonary or colloids interstitial edema May improve survival in patients with severe shock
Disadvantages	Two to four times more volume Expensive needed to achieve effective May leak from vascular space and expansion become trapped in the interstitium Longer resuscitation time in cases of increased vascular Increased incidence of pulmonary and permeability interstitial edema No difference in outcome	

X

Central Venous Access As a Hemodynamic Monitoring Tool

I (B).

II. Indications

A. Venous access

V. Monitoring Resuscitation

A. Central venous pressure monitoring

1. Volume in central veins
2. Right heart function
3. Intrathoracic pressures

B. Limitations of CVP monitoring

1. Inaccurate positioning
2. Right heart dysfunction
3. Pulmonary embolus
4. Cardiac tamponade
5. Pulmonary hypertension
6. Mechanical ventilation
7. Availability of equipment

C. Accurate measurements

1. End exhalatory
2. Level of right atrium
3. Good wave forms
4, Transmission of Peep is 1/2 - 1/3

VI. Fluid Bolus in Hypotensive Patients

A. Assessment of

1. Heart rate
2. Blood pressure
5. Respiratory rate
6. Urine output

3. Pulse pressure 7. CVP

4. Mental status 8. SA02

B. NS or RL fluid bolus 250 - 500 cc over 10 - 15 min with reassessment of above data

C. Discontinue fluid boluses for:

1. Decreasing blood pressure

2. Increasing respiratory rate

3. Decreasing oxygen saturation

D. Establishing a trend

1. Obtain data

2. Organize data

3. React to data

E. If no change following 2L crystalloid consider vasopressors

VII. Clinical Pearls for CVP Monitoring

• Beware the dilator

• Deep sulcus sign

• Cordis is ideal

Role of Vasopressors in Hemodynamic Support

I. Indications for Sympathomimetic Therapy

Table I
Indications for Sympathomimetic Therapy

Indication	*Objective*	Primary *Receptor Type*
Bradycardia	Increased heart rate	
Hypotension		

Hypovolemic*	Vasoconstriction	a
Cardiogenic	Increased contractility	B
Vasogenic	Vasoconstriction	a
Mixed	Vasoconstriction. and increased contractility	a and B
Selective organ hypoperfusion	Vasodilation or Vasoconstriction	Dopamine or a

*Used as temporizing measure until intravascular volume is replete.

II. Receptors

Table 2 Cardiovascular Actions and Signal Transduction Pathways **Initiated by Adrenergic Receptor Activation**		
Receptor Type	*Cardiovascular Actions*	*Signal Pathway*
a1	Vasoconstriction	Activation of phospholipase C
a2	Decreased central sympathetic outflow; feedback inhibition of norepinephrine release; vasoconstriction	Inhibition of adenyl cyclase
B1	Increased heart rate, contractility, and conduction velocity	Activation of adenyl cyclase
B2	Vasodilation	Activation of adenyl cyclase
Dopamine	Vasodilation	Activation of adenyl cyclase

III. Commonly Used Sympathomimetic Agents

Table 3 Ability of Commonly Used Sympathomimetic Agents to Stimulate Adrenergic Receptors				
	Receptor Type			
	a	B1	B2	Dopamine
Norepinephrine	++++	++++	+/++	
Epinephrine	+++	++++	+++	
Dopamine	++/+++	++++	++	++++
Dobutamine	+	++++	++	

IV. Considerations When Using Vasopressors

A. Caution in:

1. Right-sided myocardial infarction

2. Valvular heart disease

3. Myocardial ischemia

B. Side-effect potential

1. Tachyarrhythmias

2. Myocardial ischemia

3. Hypoperfusion

4. Hyperglycemia

V. Dosages of Common Agents

A. Norepinephrine - start at 2 mcg/min and titrate

B. Dobutamine - start at 2 mcg/kg/min and titrate

C. Epinephrine - start at 1 mcg/min and titrate

D. Dopamine - start at 2 mcg/kg/min

VI. Dose-Response Curves

A. Variability

1. Patient to patient

2. Drug to drug

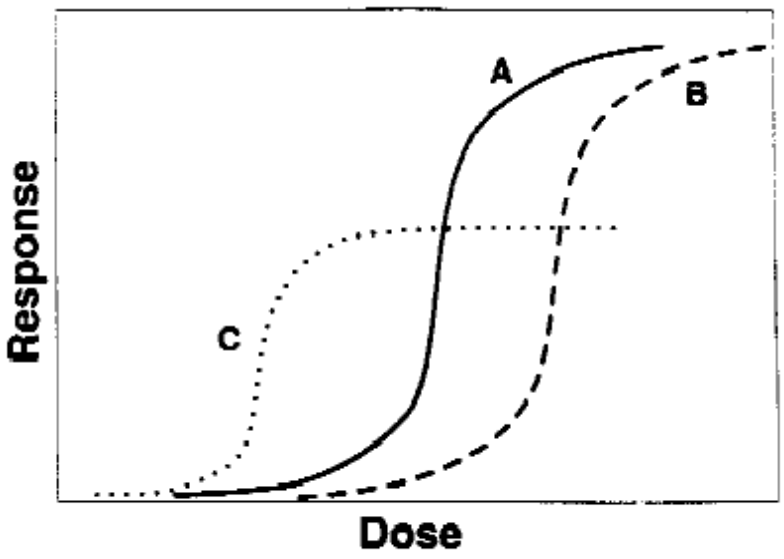


Figure 4 —Dose-response curves for three hypothetical sympathomimetic agents, all of which interact with the same adrenergic receptor, are shown here. Although both are full agonists, drug A (——) achieves a given response at a lower dose than does drug B (– – –). Drug C (.....) is only a partial agonist, and therefore it elicits a considerably lower maximum response, albeit at a lower dose.

B. Clinical response

1. Blood pressure

2. Heart rate

3. Urine output

4. Mental status

5. Oxygen saturation

C. Pulmonary artery catheter

1. Cardiac outputtindex

2. Systemic and pulmonary vascular resistance

3. Pulmonary capillary wedge pressure

4. Mixed venous oxygen saturation

D. Treatment plan

1. Each patient is unique

2. Avoid dogmatism, "fixed recipe"

3. Evaluate the need for ongoing therapy

4. Use minimum dose required

5. Identify finite end points

D. New technologies

1. Gastric intramucosal pH monitoring

2. Constant cardiac output monitoring

3. Constant mixed venous oxygenation

4. End tidal C02 monitoring

VIII. Clinical Pearls for Vasopressors

A. Norepinephrine

1 - Beats dopamine head to head

2. Improves renal blood flow

B. Dopamine

1. Most commonly used vasopressor

2. Dose response curve is unclear

3. Baldwin L, et al: Ann Intern Med, 1994.

. Duke GJ, et al: Crit *Care Med, 1994.*

5. No role in the emergency department as “renal dose”