Medical Direction and Practices Board

WHITE PAPER

Use of Pressors in Pre-Hospital Medicine: Proper Indication and State of the Science Regarding Proper Choice of Pressor

BACKGROUND

Shock is caused by a reduction of cardiac output that leads to poor perfusion. There are multiple causes of shock. Some examples include:

- Sepsis
- Anaphylaxis
- Cardiogenic
- Hypovolemia (trauma, GI bleed)
- Adrenal crisis

The key to "best practice" rests in understanding that low blood pressure is merely one manifestation of poor perfusion, but it is not the sole finding in shock. Some patients are in shock, despite what appears to be normal blood pressure. Children and young adults are classic examples of patients who do not initially drop their blood pressure when they first fall into shock. Hypotension in adults is defined as a systolic blood pressure less than 90mm Hg. But it is also defined as a systolic blood pressure more than 30 mm Hg below a patient's baseline. Because a patient's baseline is often unknown, EMS providers must rely on other findings that define poor perfusion. For example, cool hands and feet are a result of poor perfusion to the extremities. Subtle altered mental status is a result of poor perfusion to the brain. Chest discomfort and shortness of breath are the result of poor perfusion to the heart and lungs.

WHAT ARE PRESSORS?

The term "pressors" refer to medications that raise the blood pressure and increase cardiac output in an effort to increase perfusion. There are several different pressors and each works by a different mechanism of action.

Table 7
Distribution of adrenoceptor subtypes and physiologic response

Adrenoceptor Type	Primary Location	Physiologic Response to Agonist Activity
α_1	Arteries, arterioles, veins	Arterial and venous constriction
α_2	Arteries, arterioles, veins CNS	Arterial and venous constriction Decreased BP
β_1	Heart	Increased contractility and heart rate (positive inotropic and chronotropic effects)
β_2	Vascular smooth muscle (blood vessels) Bronchial smooth muscle	Vasodilation Bronchodilation
D_1	Renal, coronary, and cerebral smooth muscle	Vasodilation
D_2	Nerve endings	Modulates neurotransmitter release
V_{1a}	Vascular smooth muscle	Vasoconstriction
V_2	Renal collecting duct	Water reabsorption

Data from Biaggioni I RD. Adrenoceptor agonists & sympathmimetic drugs. In: Katzung BM, S Trevor A, ed. Basic & clinical pharmacology. 11th edition. Ipswich (MA): McCraw-Hill Professional; 2009.p. 127–48; and Goodman LS. GA, Brunton LL. Adrenergic agnoists and antagonists. Goodman & Gillman's manual of pharmacology and therpeutics. Ipswich (MA): McGraw-Hill Professional; 2008.p. 148–87.

Table 8
Adrenoceptor affinity and clinical effects of vasopressors and inotropes

	Receptors							Clinical Effects			
Medication	α_1	α_2	β	β_2	D_1	D_2	V_{1a}	CO	SVR	HR	BP
Phenylephrine	+++	+	0	0	0	0	0	↔/↑	↑↑	↔/↓	↑
Epinephrine[a]	+++	++	+++	++	0	0	0	↑↑	↔/↑	↑	↑
Norepinephrine[a]	+++	++	++	0	0	0	0	↔/↑	↑↑	↔/↑	↑
Dopamine[a]	++	++	++	+	+++	+++	0	↑	↑	↑	↔/↑
Dobutamine	0/+	0	+++	+	0	0	0	↑	↓	↑	↑/↓
Vasopressin	0	0	0	0	0	0	++	↔/↓	↑	↔/↓	↑

Abbreviations: 0, no effect; +, mild agonist effect; ++, moderate agonist effect; +++, marked agonist effect; ↔, no change; ↑, increased; ↓, decrease; HR, heart rate.
[a] The α_1 effects of epinephrine, norepinephrine, and dopamine are more prominent at high doses.
Data from Refs.[91,93,94,100]

HOW DO PRESSORS WORK?

All pressors target specific receptors in the peripheral blood vessels that cause them to squeeze tighter. The result is to push blood back from the extremities towards the core. This bolus of peripheral blood fills the heart and allows more blood to be circulated to the core organs. Other pressors target receptors in the heart as well causing the heart rate to increase and causing each heart beat to squeeze stronger. The result of these actions is to increase cardiac output and increase perfusion to core organs (brain, heart, kidneys.)

WHY CHANGE FROM DOPAMINE TO NOREPINEPHRINE?

Dopamine has been the choice pressor for EMS since these medicines were introduced to prehospital medicine. Since that time there has been a gradual shift in the hospital. Although there has not been a definitive study showing any difference in mortality between any of the pressors listed above, there has been rising concern that dopamine causes more side effects. Specifically, dopamine has been associated with more tachyarrhythmias[1]. Norepinephrine achieves the same effect as dopamine, but with less risk to your patient.

WHY IS A PUMP REQUIRED?

Although dopamine has been used for many years in prehospital medicine without a pump, this is no longer considered safe. Hospital practice transitioned years ago to mandate use of pumps in an effort to ensure accurate dosing and similar practice is beginning to become standard in EMS practice across the country. Accurate dosing of a pressor is critical both achieve both the desired effect, and to avoid dangerous side effects. A pump assures accurate dosing and facilitates accurate titration of the dose. If too little of a pressor is given, there is no improvement in perfusion. If too much is given, we risk cardiac arrhythmias and dangerous hypertension. It is worth the added logistics of setting up a pump in order to protect patients from inadvertent errors in dose. It is important to use the lowest dose possible to achieve the desired tissue perfusion. Most side effects (and increased mortality) occur at higher doses.

PERIPHERAL IVs

It is important to use the largest vein possible when giving a pressor. If this medicine leaks into the tissue (extravasates) it can cause sloughing and necrosis of the tissue. Larger veins are sturdier and less likely to "blow." If the situation allows a choice, always choose the IV site closest to the core. An IV in the AC is safer than one in the hand. Prior to initiating any pressor, confirm that the patient's vein is not blown by ensuring there is no evidence of IV crystalloid infiltrating the area and the patient has no pain or erythema at the IV site.

Recall however, these are critically ill patients in shock and we may not have the luxury to choose between different IV sites.

TREATMENT

1) SEPSIS

Sepsis decreases perfusion because the infectious process causes blood vessels to dilate. When all the blood vessels in the body dilate at once, there is a drop in blood pressure and less blood is delivered to core organs. NOTE: because of the vasodilator mechanism of this shock, they may have pounding pulses and warm extremities, but still be in shock. Remember, an elevation of lactic acid (>4 mmol/L) can be an early sign of septic shock. Sepsis responds best to large amounts of IV fluids (e.g. normal saline.) Although it seems

[1] De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362(9): 779-89

to make sense adding a pressor early would fix the underlying problem, studies have shown patients do better if large amounts of IV fluid is given first. **The recommended initial IV fluid bolus in sepsis is 30 mL/kg**[2]. (In a 100 kg adult this would be 3 liters of normal saline.) The MDPB does not recommend starting norepinephrine until at least this amount of fluid is given first.

2) ANAPHYLAXIS

Similar to sepsis, anaphylaxis causes a global dilation of peripheral blood vessels, but by a different mechanism. The chain reaction of mast cells releasing histamine and other vasoactive agents causes body-wide dilation of blood vessels and resulting hypotension. NOTE: because of the vasodilator mechanism in this form of shock, they may have pounding pulses and warm extremities, but still be in shock. In this process, it is recommended to give a pressor early to reverse the process. **The MDPB recommends epinephrine as the initial pressor in anaphylaxis.** Epinephrine targets both alpha and beta receptors (norepinephrine only targets alpha receptors.) [See chart above.] As a result, epinephrine will have the dual action of improving perfusion (increase blood pressure) by targeting alpha-receptors and cause bronchodilation by targeting beta-receptors. The MDPB recommends initially delivering this pressor as a 1:1000 IM injection in the lateral thigh. If repeat injections do not cause reversal of the anaphylaxis, it may be necessary to give epinephrine intravenously. To do this safely, you must use a pump.

4) CARDIOGENIC SHOCK

In cardiogenic shock, the heart as a pump is failing. Not only is it causing a back-up of fluid to the lungs (rales, shortness of breath, hypoxia) but it is also leading to poor perfusion and hypotension. The most common cause is left ventricular failure following STEMI or cardiac "stunning" after cardiac arrest. These are difficult cases because too much IV fluid may make the process worse. However, many of these patients need some IV fluid to improve. **It is best to give smaller IV fluid boluses (250 to 500 mL at a time) and reassess frequently. Watch for worsening dyspnea or shock. In contrast to sepsis, we recommend starting pressors early here. If you do not find improvement in perfusion after 1 to 2 liters of IV fluid or at any time your patient gets worse, start norepinephrine and titrate to systolic blood pressure of 90 mm HG (or to clinical improvement in perfusion.)**

5) ROSC (POST-ARREST HYPOTENSION)

Once you successfully resuscitate cardiac arrest, it is important to avoid any hypotension (systolic BP < 90 mm Hg), as this has been associated with worse neurologic outcomes.[3] The 2010 ACLS course recommends an initial IV fluid bolus of 1 to 2 liters once ROSC has been achieved. If this does not correct hypotension, we recommend starting norepinephrine.

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[2] Dellinger RP et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. 2012. Crit Care Med 2013 Feb; 41:580

[3] Stub D et al. Post cardiac arrest syndrome: a review of therapeutic strategies. 2011 Circulation. Apr 5; 123(13):1428-35.

6) TRAUMA/GI BLEEDS/HYPOVOLEMIC SHOCK

There is no role for pressors in hypovolemic shock. The solution is to stop the bleeding and replace lost blood with new blood. In the prehospital environment, there is often no access to blood, therefore, IV crystalloids (saline or Ringer's) are the chosen volume expanders. It is key for "best practice" to understand that IV fluids do not correct the underlying problem and may lead to worse outcomes. Too much IV fluid dilutes the blood and coagulation factors and decreases the effectiveness of its oxygenation carrying capacity. Too much blood pressure may dislodge early clots that have formed at the bleeding site. **The goal is just enough blood pressure to maintain perfusion, but no more**. We recommend a goal systolic blood pressure of just 90 mm Hg. You may find you achieve adequate perfusion (improved mental status, warmer extremities) at a lower blood pressure (systolic 70 or 80 mm Hg,) and that would be "best practice" for your patient. The exception to this guidance are patients with both shock and head injuries. Hypotension and hypoxia are proven to decrease mortality in patients with head injuries and therefore the MDPB recommends maintaining a blood pressure of at least 90 mm Hg in patients with head injuries, even if there is associated hypovolemic shock.

DOSAGE

Epinephrine and norepinephrine are vasoactive within 3 to 5 minutes. This means that desired effects will be observed within 3 to 5 minutes of medication initiation or increasing medication dose. It makes sense to increase the dose every 3 to 5 minutes until perfusion goals have been achieved.