Refractory Vasodilatory Shock

Key Article

Jentzer JC, et al. Management of refractory vosodilatory shock. Chest. 2018; 154:416-426.

Background

- Shock is characterized by tissue hypoperfusion and inadequate cellular oxygen utilization. This leads to organ failure and death.
- Currently, 33% of critically ill patients worldwide develop circulatory shock.
- Vasodilatory (distributive) shock is the most common form of shock.
- Despite recent advances in critical care, the mortality of patients with shock can reach 50%.
- Most often, patients with circulatory shock require vasopressor therapy
    - Vasopressor dose is one of the strongest predictors of short-term mortality in critically ill patients.
    - High doses of catecholamines have numerous adverse effects, which may also contribute to the high mortality.
    - Increased mortality with high dose vasopressors may simply reflect a greater severity of illness.

Definition of Refractory Shock

- No universal definition of refractory shock.
- Proposed definitions:
    - Failure to achieve BP goal despite pressors.
    - Need for rescue pressor therapy.
    - Need for high pressor doses.
- Currently, vasopressors are compared to norepinephrine (NE) at equivalent doses.
- NE doses greater than 0.5 mcg/kg/min have been proposed as a threshold to define high-dose vasopressors and refractory shock.
- The authors of the current article state that a reasonable definition is “an inadequate response to high-dose vasopressor therapy (>= 0.5 mcg/kg/min NE-equivalent dose)”
    - Using this definition, 6% to7% of critically ill patients may develop refractory shock

Pathophysiology

- Central feature is the impairment of vascular response to catecholamine stimulation and uncontrolled pathologic vasodilation.
- This can occur due to:
    - Changes in receptor signaling
    - Metabolic derangements
    - Depletion of endogenous vasoactive hormones
- Inappropriate vasodilation usually occurs due to inducible nitric oxide synthase (iNOS) – produces excessive amounts of nitric oxide (NO) – increases vascular levels of cAMP and cGMP to vasodilation.

- Absolute or relative deficiencies of endogenous vasoactive hormones (cortisol, vasopressin, angiotensin II) can further decrease vasopressor responsiveness.
- Not all vascular beds are equally affected – heterogeneous effects on different vascular beds leads to maldistribution of blood flow despite seemingly normal hemodynamics – it's all about the microcirculation.

Evaluation

- First step – make sure that BP/MAP readings are actually accurate.
- Identify the primary cause of shock – uncontrolled vasodilation or is it hypovolemia, obstructive causes, or cardiogenic.
- Vasodilatory shock usually characterized by high cardiac output and elevated ScvO2/SvO2.
- For those with low/inadequate cardiac output, assess fluid responsiveness using methods we've previously discussed on other podcast episodes.
- After fluid responsiveness, initiate and optimize vasopressor therapy.

Vasopressor Therapy

- Vasopressors added when MAP < 65 mm Hg despite fluids and other measures.
- Achieving and maintaining adequate MAP is central to treating refractory shock. MAP goal of 65 mm Hg reasonable for most, though some patients with HTN may need a higher MAP.
- No vasopressor has been conclusively shown to be superior as first-line therapy for vasodilatory shock. No other vasopressor has been found superior to NE to prevent mortality. Vasopressin also studied and not fount to have mortality benefit.
- Consensus view is that NE is the recommended first-line vasopressor for most critically ill patients. Maximum dose of NE remains uncertain, though responsiveness declines at doses > 0.5 mcg/kg/min.
- Use of multiple vasopressors at moderate doses may avoid the toxicity of high doses of a single agent.
- Authors of this article advocate for a rationale use of combination vasopressors.
- Vasopressin has been studied in the management of refractory vasodilatory shock
    - Relative or absolute deficiency and pathologic vasodilation in shock
    - Vasopressin effectively increases vascular tone and does not exacerbate tachycardia or arrhythmias; can reduce cardiac output
    - May have a role in acidemic conditions
    - Shown to increase MAP and decrease catecholamine requirements but not show to reduce mortality
    - Usually dose is 0.04 U/min
- Epinephrine
    - Produces substantial beta-adrenergic stimulation
    - Can obviate the need for additional inotropic support when cardiac output is low
    - Known to exacerbate hyperglycemia and lactic acidosis; predisposes to arrhythmias
- Dopamine and phenylephrine are weak vasopressors and usually not effective in refractory vasodilatory shock

Rescue Therapies

- None of following therapies conclusively shown to reduce mortality at the onset of refractory shock.
- Steroids

    - Augment vascular alpha-adrenergic responsiveness and reduce inflammation-mediated vasodilation
    - Patients with shock may have a relative or functional adrenal insufficiency
    - Conflicting evidence and remains controversial
    - Hydrocortisone (200-300 mg/day) may reduce vasopressor requirements and decreased duration of shock but mortality benefit remains uncertain.
    - Optimal timing of hydrocortisone remains uncertain, but should be considered in patients requiring multiple vasopressors.
    - Dose can be either 100 mg q8H or 50 mg q6h.
- Bicarbonate
    - Systemic acidemia may worsen tissue perfusion; vasopressor responsiveness declines when arterial pH < 7.15 due to impaired catecholamine signaling
    - Sodium bicarbonate may have harmful effects of intracellular acidosis, respiratory acidosis, hypocalcemia, hypernatremia, and increased lactate levels
    - Correction of metabolic abnormalities never shown to improve outcomes in patients with shock.
    - RRT
        - AKI may limit clearance of acidemia
        - CRRT may improve vasopressor responsiveness in patients with AKI
        - Observational studies on high-volume hemofiltration in sepsis have shown favorable hemodynamic effects – reduced vasopressor requirements and improved microcirculatory flow.
- Calcium
    - Calcium essential for cardiovascular function
    - Hypocalcemia commonly observed in critically ill patients
    - Severe hypocalcemia may depress CV function and produce hypotension
    - Bolus administration of CaCl can improve MAP by increasing vascular tone w/o augmenting cardiac output
    - Though no evidence to demonstrate improved patient-centered outcomes
- NO inhibitors
    - Overproduction of NO an important component to vasodilatory shock
    - Substantial interest in medications that inhibit inducible NO synthase
    - NOS inhibitors shown to increase vascular tone and MAP, but associated with increased mortality
    - Methylene Blue
        - Inhibits NOS and has been evaluated for refractory vasodilatory shock
        - Reverses vasodilation caused by excessive NO signaling and may be effective for increasing vascular tone in septic shock
        - May also inhibit MAO and cause serotonin syndrome in select patients
        - Effect is short and requires repeated dosing/infusion
        - Can increase pulmonary vascular resistance
- Hydroxycobalamin
    - Acts as an NO scavenger that can reverse NO-mediated vasodilation
    - Has been used as off-label in refractory shock
    - Limited evidence but in available studies has reversed vasodilatory shock
    - Remains in bloodstream and interferes with heme sensors on HD machines, so avoid or use with caution in those with AKI and possible HD
- Vitamins

- Endogenous NE and vasopressin synthesis require vitamin C. Absolute or relative vitamin C deficiency in critically ill patients may contribute to shock by reducing endogenous vasopressors
- Administration of high-dose vitamin C may improve hemodynamic variables
- Thiamine an essential cofactor in oxidative energy metabolism; thiamine deficiency can cause CV compromise and exacerbate lactic acidosis
- In patients with thiamine deficiency, there may be benefit to administering thiamine.
- Vitamin C, thiamine, and hydrocortisone??? Observational study by Marik et al demonstrated improved shock reversal and decreased severity of organ failure. Current VICTAS trial to investigate this combination

Future Therapies?

- Angiotensin II
  - Angiotensin II works with catecholamines and vasopressin to maintain BP.
  - Patients with sepsis have a functional ACE or angiotensin II deficiency and may lead to refractory shock.
  - ATHOS-3 trial compared angiotensin II with placebo in 321 patients with refractory vasodilatory shock; Angiotensin II increased MAP in 70% of patients by 3 hours; more favorable outcomes but a secondary outcome.
  - Currently available to administration but really need more data