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CASE STUDY

12 years of recurrent distributive shock episodes – Where to look when a search for common causes comes up short?

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ABSTRACT

Shock is a state of circulatory failure with common etiologies to include sepsis, cardiac dysfunction, hemorrhage, and vascular flow obstruction. Accurate and timely identification of the etiology of shock is essential to prevent multi-organ dysfunction and death. This is a case of a 69-year-old female who presented with 12 years of recurrent shock episodes thought to be due to recurrent sepsis of unknown source. Despite an exhaustive review of infectious sources and other common shock etiologies, a durable explanation for shock was not found. A review of chronic medications demonstrated concurrent chronic use of lisinopril and verapamil; with discontinuation of lisinopril her episodes of recurrent shock ceased. Concurrent use of ACE-I and CCB can suppress native sympathetic cardiovascular responses to insignificant hemodynamic insults. Therefore, going back to the basics with a review of exogenous variables (i.e. medications) is an essential first step in identifying the cause of recurrent episodes of shock when no other common unifying etiology can be identified.

Introduction

Shock is defined as a state of circulatory failure in which cellular hypoxia is the outcome of inadequate oxygen delivery to meet cellular metabolic requirements. Timely optimization of hemodynamic parameters to deliver oxygen to the tissue is essential to prevent clinical deterioration and death. Identification of shock-etiology and shock-type helps to guide diagnostic and management strategies to allow for optimization of hemodynamic parameters to deliver oxygen to the tissues. Yet, even despite this, refractory shock can lead to irreversible tissue damage and subsequent multi-organ dysfunction and death.

Accurate classification of shock-type is important in guiding appropriate diagnostic and management strategies. The four main classifications of shock include distributive (i.e. commonly due to sepsis), hypovolemic (i.e. volume loss such as hemorrhage), obstructive (i.e. pulmonary embolus), and cardiogenic (i.e. primary myocardium failure, valvular dysfunction, or arrhythmia). The most common shock presentation is that of distributive shock. Therefore, distributive shock carries the broadest etiology differential including infectious/sepsis, systemic inflammatory response syndrome (SIRS), neurogenic (i.e. traumatic brain injury), and undifferentiated vasoplegia.

Type of Shock	Physiological Manifestation	Common Causes	Common Management Strategies
Distributive	Vasodilation • Cardiac output: Normal to decreased • Preload: Normal to decreased • SVR: Low • ScVO2: >65%	Sepsis, traumatic brain injury, systemic inflammatory response syndrome (SIRS)	• Vasopressor therapy (i.e. norepinephrine, vasopressin, epinephrine). • Systemic steroids • Inotropes (sometimes) • Volume resuscitation • If septic, source control and antimicrobial therapy
Hypovolemic	Decreased intravascular volume • Cardiac output: Initially increases to try and compensate for low volume; then Normal to low. • Preload: low • SVR: high • ScVO2: >65% then decreases	Hemorrhage	• Volume resuscitation including massive transfusion as indicated • Vasopressor therapy
Obstructive	Obstruction to forward blood flow through heart/lungs. • Cardiac output: Low • Preload: High • SVR: High • ScVO2: >/< 65%	Pulmonary embolus, tension pneumothorax, pericardial effusion, pulmonary hypertension	• Treat the obstructive process (i.e. embolectomy if pulmonary embolus, pericardiocentesis, thoracocentesis)

Cardiogenic	Cardiac pump failure • Cardiac output: low • Preload: high • SVR: high • ScVO2: <65%	Heart failure, arrhythmia, valvular dysfunction	• Inotropic therapy (i.e. dobutamine, dopamine) • Volume resuscitation vs. diuretics • Vasopressors (sometimes) • Ventricular assist devices
SVR: Systemic vascular resistance; ScVO2: Central venous/mixed oxygen saturation			

This case report aims to address the importance of timely shock-type identification to allow for appropriate diagnostic evaluation and management strategies.

Case Presentation

This is a case of a 69 y.o. female who presented to the pulmonary clinic in 2021 for evaluation of an indeterminate left upper lobe pulmonary opacity. Of note, this opacity was subsequently resected via video assisted thorascopic wedge resection and found to be stage 1 non-small cell lung adenocarcinoma.

During her initial evaluation she reported multiple episodes of shock after splenectomy secondary to splenomegaly. Each episode of shock was defined by hypotension with hemodynamic instability and systemic manifestations thereof. Episodes presented with feelings of warmth, prickling on the chest, loose stools, weakness, and nausea; she was afebrile. She was found to have leukocytosis but no positive cultures, and no identifiable infectious source. There was initially the question of a colonic diverticular infectious source due to hematochezia and some colonic thickening on CT angiogram, however colonoscopy and indium-labeled white blood cell scan was unrevealing. There was no evidence of colitis, and the mesenteric vasculature was normal. She was treated with volume resuscitation and antibiotic therapy with improvement. She subsequently presented with at least two similar episodes per year over the next 12 years; each episode had a similar symptomatic presentation and treatment provided requiring hospitalization and, on some occasions, admission to the intensive care unit.

Given no identifiable infectious etiology to shock, alternate etiologies of shock were evaluated. Such evaluations looked for autonomic dysfunction (only mild adrenergic findings with possible autonomic diabetic neuropathy), vasovagal physiology from bowel habit abnormalities, cardiogenic (echocardiographic studies), arrhythmia (despite premature atrial contractions managed with verapamil), atypical infectious processes (i.e. Q fever or Tropheryma whipplei, tick-born parasites), recurrent/ischemic colitis yet none yielded a durable explanation for her recurrent symptomatic shock episodes. Of note, lung cancer in 2021 was not thought to be an etiology for 12 previous years of recurrent shock episodes.

Despite not being able to identify a pathologic etiology of her shock-presentations, she had been found to be on the low-end of normotension (systolic 100-115 at baseline). She was chronically managed with calcium channel blocker verapamil (120 mg daily since 2011 for symptomatic premature atrial contractions with subsequent symptomatic improvement), lisinopril (10mg daily since 2011 for hypertension). She was subsequently counselled to discontinue lisinopril in 2022 and remain on single agent verapamil. Since that time, she has not had a recurrence of shock episode.

What does literature say?

Co-ingestion of angiotensin converting enzyme inhibitors (ACE-I) and calcium channel blockers (CCB) have been reported (though rare) to lead to the development of shock. ACE-I prevents the conversion of angiotensin 1 to angiotensin 2 which therefore limits activation of the renin-angiotensin-

aldosterone system (RAAS) subsequently leading to arteriolar vasodilation and decreased central nervous system sympathetic outflow. While hemodynamic compromise can happen with ACE-I or CCB independently, the combination of these medications can lead to worsening hypotension. This is thought to be due to a synergistic effect of ACE-I and CCB where the RAAS's normal ability to respond to shock is inhibited leading to worsening vasodilation (lack of angiotensin 2 mediated vasoconstriction) and less endogenous catecholamine release. Additionally, ACE-I leads to increased bradykinin peptides which promotes further vasodilation.

Discussion

This patient initially presented with, what appeared to be, distributive shock secondary to sepsis possibly from a colonic source (i.e. such as possible low-grade transient bacteremia). Given her clinical presentation it was clinically appropriate and prudent to pursue an exhaustive workup for an infectious source of any site including gastrointestinal. No infectious source was identified over multiple similar presentations nor evidence to support that consideration (i.e. no evidence of colitis). A lack of septic source mandated that other etiologies of recurrent distributive shock be evaluated.

Concurrent use of ACE-I and CCB, with concurrent but less nefarious intermittent precursor events, likely led to recurrent episodes of distributive shock. Yet, with the concurrent use of ACE-I and CCB limiting native cardiovascular response to hemodynamic insults this likely led to the exaggerated repeated symptomatic presentations. Note, there was no concern for unintentional or intentional overdose of ACE-I or CCB in this case; dosing was appropriate.

With discontinuation of lisinopril, and maintenance of CCB for premature atrial contraction management, she has not had any recurrent episodes of shock. Given the repeated unrevealing search for an infectious source, it would be appropriate to conclude that she was not experiencing recurrent shock secondary to sepsis but rather episodes of distributive shock secondary to vasoplegia in setting of oversuppression of her native sympathetic cardiovascular response system. Throughout the course of her shock episodes, there was no augmentation to any possible infectious source (i.e. no colonic resection or intervention) that would be limiting or eliminating the likelihood the possible low-grade insulting events; the only intervention was elimination of lisinopril to unhamper her native sympathetic response.

Conclusion

It would be appropriate to initially suspect septic shock as the cause of this patient's presentation with hypotension, leukocytosis, and intermittent colonic symptoms. Yet, without an identifiable source and with recurrent similar presentations, the search for an alternate etiology of shock must be considered. Going back to the basics of medication review to evaluate the impact of exogenous sources on her presentation must be undertaken to uncover the true cause of shock. Less common drug-drug interactions (i.e. ACE-I and CCB) must be considered as probable causes of recurrent symptomatic shock presentations. This case serves as a reminder to all healthcare providers to review the patient's medication list first so that an appreciation of all variables can be considered when developing a differential diagnosis.

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