Integrative human cardiovascular control

Danish Cardiovascular Research Academy

Ph.D. course

The Panum Institute, University of Copenhagen

Rigshospitalet

May 15 – 20, 2017

BACKGROUND MATERIAL

FOR FRIDAY 19TH MAY
Mesenteric hemodynamic response to circulatory shock  
Eugene P. Ceppa, BA, Katherine C. Fuh, MS, and Gregory B. Bulkley, MD

Purpose of review  
The mesenteric hemodynamic response to circulatory shock is substantial and asymmetrical; the vasoconstrictive response disproportionately affects the mesenteric organs. The cardiac output is sustained partially, at no cost in nutrient flow to the mesenteric organs, by vasoconstriction of the mesenteric veins, resulting in the "autotransfusion" of up to 30% of the circulating blood volume into the systemic circulation.

Recent findings  
Hemorrhagic or cardiogenic shock also results in decreased perfusion pressure, prompting selective vasoconstriction of the mesenteric arterioles to maintain perfusion pressure of the vital organs, here at the selective expense of the mesenteric organs. Septic shock may be associated with increased or decreased mesenteric blood flow but is characterized by increased oxygen consumption, exceeding the capability of mesenteric oxygen delivery.

Summary  
The response to any of these conditions can, variably and unpredictably, cause hemorrhagic gastric stress erosions, nonocclusive mesenteric ischemia of the small bowel, ischemic colitis, ischemic hepatitis, acalculous cholecystitis, and/or ischemic pancreatitis. Injury to the mesenteric organs can also initiate the systemic inflammatory response syndrome and, consequently, multiple organ failure.

Keywords  
free radicals, renin–angiotensin axis, multiple organ failure, shock, splanchnic vasoconstriction, systemic inflammatory response syndrome

The mesenteric hemodynamic response to circulatory shock is complex, asymmetric, and substantial. This asymmetry was recognized by Cannon [1], who described the “fight or flight response,” whereby perfusion of the skin and mesenteric organs was disproportionately curtailed in deference to the perfusion of organs more vital for fight or flight (skeletal muscle) or survival (brain, heart, lungs, kidneys). The magnitude of this response is, indeed, substantial, with profound consequences for the organs served by both the mesenteric and nonmesenteric circulations. It seems obvious that the short-term impact of such a redistribution of the diminished cardiac output would provide a survival benefit that would cause this response to have been naturally selected over time. On the other hand, in patients resuscitated and sustained by modern cardiovascular life support technology, the negative impact of this redistribution away from the organs served by the mesenteric vasculature can cause detrimental and even lethal consequences over the longer term.

Normal mesenteric hemodynamics  
Anatomy  
Much of the mechanism for the selective control of mesenteric hemodynamics is based on a unique configuration of parallel- and series-coupled circuits [2]. Initially, the mesenteric blood flow is divided into two parallel circuits that serve the muscularis propria and submucosa/mucosa, respectively. The perfusion of the mucosa is, in series, downstream from that of the submucosa [2]. Each of these circuits consists of five series-coupled components (Fig. 1).

(1) The resistance arterioles are the dominant determinant of vascular resistance, regulating blood flow through the mesenteric bed and more specifically through each individual circuit. This is based on the notion that flow is inversely proportional to vascular resistance and proportional to arterial pressure (the cardiovascular version of Ohm’s Law).
(2) Precapillary sphincters control perfused capillary density by altering capillary bed patency.
(3) Capillary exchange vessels allow the tissues to exchange fluids, metabolites, and other solutes with the blood.
(4) Postcapillary sphincters affect the postcapillary-to-precapillary resistance ratio, which directly correlates with mean intravascular hydrostatic pressure, which determines the net fluid filtration from the capillary exchange vessels into the tissue.
Distal venules are high capacitance vessels, which, in combination with the mesenteric collecting veins (portal tributaries), contain up to 30% of the body’s total blood volume [3].

The intestinal villus has a characteristic vascular anatomy (Fig. 2): a single unbranched arteriole travels to the tip of the villus and then arborizes into a network of capillaries that converge to ultimately form a central venule at the base of the villus. This arrangement allows countercurrent exchange to take place [4], whereby small molecules (oxygen) may diffuse rapidly from the arteriole directly into the venule, bypassing the distal exchange capillaries. Although the role of this countercurrent exchange of oxygen under normal flow conditions is unclear [4], during ischemia it creates a hypoxic gradient at the villus tip [5]. This partially explains the increased susceptibility of the villus tip to ischemic injury.

Physiology

The organs served by the mesenteric circulation account for only 5% of the total body weight yet command a substantial proportion (20–30%) of the total cardiac output under normal hemodynamic conditions [3]. This provides a large reserve, which may be tapped to support the systemic circulation during shock. The mucosa and submucosa receive approximately 70% of this gut blood flow, with the primary site of absorption—the superficial villus region—receiving half of this allotment [6]. In response to feeding, the mesenteric organs undergo a functional hyperemia characterized by increased local blood flow, oxygen uptake, and oxygen consumption. This response is most marked within the mucosa, where most of the metabolic activity takes place.

Autoregulation of blood flow is traditionally described in organs such as the brain, kidney, or heart, but this phenomenon has been reported in the mesenteric organs as well [7,8]. It is defined as a disproportionately smaller decrease in tissue perfusion (blood flow) in response to a corresponding decrease in perfusion pressure. Autoregulation is also manifested as posts ischemic reactive hyperemia which is the attenuation of the decrease in blood flow immediately after a fixed decrease in perfusion pressure and by autoregulatory escape [2]. These autoregulatory compensatory responses are mediated by arteriolar vasodilation. There are two categories of stimuli that trigger this response: the myogenic response is a direct reflex response to the decrease in perfusion pressure itself. Its mechanism is believed to be dependent on the endothelial generation of nitric oxide [9,10]. The metabolic response is to increased levels of adenosine in response to decreased pH and oxygen tension [11,12]. During mesenteric ischemia, the perfusion of the different layers of the intestine is redistributed disproportionately, favoring the more metabolically active areas, evident by relatively smaller decreases in flow in the superficial villus region [2]. However, because of increased metabolic demand at the villus tip, and the countercurrent shunting of oxygen at the villus base, the villus tip remains preferentially susceptible to ischemic injury; indeed, under ischemic conditions, the gut dies progressively from the inside outward.
As mesenteric organs are perfused less, the tissues respond by reciprocally increasing oxygen extraction, thereby maintaining oxygen consumption relatively constant over a substantial range of blood flows [13]. This response is due to the opening of the precapillary sphincters, providing an increased perfused capillary density, thereby increasing the surface area for nutrient exchange and correspondingly decreasing the distance for nutrient diffusion (Fig. 1) [14,15]. This function is protective, especially in times of hypoperfusion, and does not compromise the systemic circulation’s ability to perfuse the rest of the body. However, the oxygen tension of portal venous blood is reduced proportionately but probably without consequence for the liver. Although this autoregulation of oxygen consumption is protective for the gut under conditions of mild to moderate ischemia, severe ischemia exceeds the compensatory capability of increasing oxygen extraction, and tissue injury may then occur [15].

Mesenteric hemodynamic response to shock
Cardiogenic and hemorrhagic shock
Under conditions of hemorrhagic or cardiogenic shock, there is systemic vasoconstriction of the arteriolar resistance vessels throughout the body, but this response is disproportionately larger within the mesenteric circulation. Consequently, the perfusion of the mesenteric organs is compromised preferentially [16–18]. For example, during cardiogenic shock, 40% of the increase in total systemic vascular resistance is due solely to mesenteric vasoconstriction [18,19,20•]. This vasoconstriction functionally overrides blood flow autoregulation, leaving the capability of the gut to increase oxygen extraction as the only remaining defense against ischemic injury [2].

Both the sympathetic nervous system (norepinephrine released locally by nerve terminals and circulating epinephrine) and other circulating vasoactive mediators (renin–angiotensin axis, vasopressin, and others) mediate the vasoconstriction of the mesenteric resistance vessels under these circumstances. (The parasympathetic nervous system also supplies the mesenteric organs but does not innervate the splanchnic vasculature.) However, the α-adrenergic vasoconstrictive response of the mesenteric resistance vessels to stimulation of the sympathetic nervous system is proportionate to that of the systemic vasculature. Therefore, although the sympathetic nervous system contributes to mesenteric ischemia during shock, it does not account for the disproportionate mesenteric ischemia [15,16,21]. The predominant and disproportionate response of the mesenteric circulation to shock is mediated largely by the renin–angiotensin axis [16,19,22–24]. Whereas mesenteric levels of circulating renin do not differ from systemic levels during shock, the angiotensin II receptors of the mesenteric vascular resistance smooth muscle have a five-fold affinity for angiotensin II and therefore respond disproportionately [25]. Experimentally, prior ablation of the renin–angiotensin axis completely blocks this disproportionate mesenteric vasoconstriction seen in circulatory shock and improves survival, whereas ablation of the sympathetic nervous system fails to do so [26].

Other vasoactive mediators, including vasopressin, endothelin, and (the decreased generation of) nitric oxide, have been considered to be contributors to mesenteric vasoconstriction of hemorrhagic shock as well [16,27–30,31•]. Vasopressin, in particular, affects the mesenteric vasculature disproportionately but appears to play a secondary role to the renin–angiotensin axis in the redistribution of arterial blood flow away from the gut during shock [16,18].

On the venous side of the mesenteric circulation, the mesenteric venous capacitance vessels contain a substantial volume of blood that is redistributed into the systemic circulation during shock. This mesenteric vasoconstriction effects what is essentially an “autotransfusion” of up to a third of the total circulating blood volume. This increased venous return supports cardiac filling pressure (preload), thereby supporting cardiac output via the Starling cardiac relationship. This occurs without negatively affecting the nutrient perfusion of the mesenteric bed and is mediated almost exclusively by the sympathetic nervous system.

Septic shock
The mesenteric hemodynamic response to septic shock is more variable and less clearly defined than that to hemorrhagic or cardiogenic shock. Clinically, the mesenteric blood flow may be increased or decreased depending on the situation. Experimentally, either can be seen, depending on the model used to induce sepsis and the timing of the measurement [32,33•,34]. A decrease in mesenteric blood flow can be caused by decreased perfusion pressure, mesenteric vasoconstriction, or both. An increase in mesenteric blood flow can be mediated by a direct vasodilatory effect of bacterial endotoxin on the smooth vascular muscle. However, this increase in blood flow, when present, does not benefit the mesenteric organs for two reasons: (1) an increased level of metabolic activity increases the demand of oxygen above the levels of increased oxygen delivery, and (2) the uncoupling of ATP-generating oxidative phosphorylation from the reduction of oxygen to water greatly diminishes the metabolic efficiency of oxygen consumption [35,36]. More recently, investigators have suggested that this uncoupled reduction of oxygen also generates reactive oxygen metabolites (free radicals), thereby not only consuming needed oxygen but also effecting microvascular injury and inflammation directly via the generation of reactive oxygen species (ROS). The generation of ROS may itself account for a 30% increase in oxygen con-

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
ischemic hepatitis, including synthetic and catabolic dysfunction associated with centrilobular necrosis [51–54]. This is a result of simultaneous reduction of hepatic blood flow via both the hepatic arterial and portal venous circulations, the former of which is mediated by hepatic arteriolar vasoconstriction, and the latter of which is mediated by intestinal vasoconstriction upstream of the portal venous inflow. This is because both of these vascular beds are hyperresponsive to angiotensin II; consequently, the normally protective hepatic arterial buffer response (hepatic arterial bed vasodilation in response to portal venous occlusion) is obviated [55,56•]. Ischemic cholecystitis (one form of acalculous cholecystitis) and ischemic pancreatitis are also well described following shock [52,57]. In each case, the major cause is disproportionate ischemia resulting from selective mesenteric organ arteriolar vasoconstriction in response to the renin–angiotensin axis [22–24,51].

The actual mechanisms of shock-induced injury to the mesenteric organs are numerous and include hypoxia, reperfusion, gastric acid, luminal proteases, bacterial toxins, and others. Hypoxia remains the predominant cause of tissue destruction and is exacerbated by the tissue’s inefficient utilization of oxygen in shock. However, other causes contribute substantially. Ischemia followed by reperfusion of tissue results in oxygen-dependent, xanthine oxidase–generated superoxide free radical (O$_2^−$) formation, triggering a free radical chain reaction. These free radicals induce endothelial cells to upregulate surface adhesion molecules, causing neutrophil arrest, adhesion, and diapedesis (i.e., microvascular inflammation with consequent tissue injury). Gastric acid and intraluminal proteases function normally within the stomach and intestine, respectively, but many cause tissue injury after an ischemic insult, resulting in a compromised mucosa that can no longer serve as an effective barrier. Ligation of the pancreatic duct [58], intestinal pancreatic protease inhibition [59•], or isolation of the bowel from its upstream luminal contents [60] have each been found to be protective against small intestinal mucosal damage after ischemia in experimental animals, whereas the inhibition of gastric acid secretion in high-risk patients has almost eliminated the clinical appearance of hemorrhagic gastritis.

Distant (nonmesenteric) organ injury may be another consequence of the mesenteric ischemia of shock. The systemic inflammatory response syndrome (SIRS) can occur in the critically ill, often when the cause of injury to the tissue is a result of trauma, infection, or hypoperfusion. This produces a large systemic inflammatory response, which progresses from a local tissue injury and a hypermetabolic state to acute respiratory distress syndrome and eventually multiple organ failure syndrome. This response has been attributed to many etiologies [61–63], but ischemia/reperfusion injury to the superfi-
Evolution of the genome. Modern medical care providers failed to survive to put a natural selective pressure on the medics, blood banks, and intensive care facilities, an selective pressure for it to evolve: in the absence of parasite mechanism is probably explained by a lack of natural restraint on this pathologic extreme of a homeostatic responsiveness but can be paradoxically lethal after resuscitation from severe shock. The lack of a negative feedback re-emphasis on mesenteric perfusion in young pigs. Am J Physiol 1997, 272: G612–G616.

Conclusions
Shock directly stresses the hemodynamic homeostasis of the afflicted organism and triggers hemodynamic compensation. To allow survival from the initial catastrophic insult of shock, the physiologic hemodynamic response prioritizes systemic blood flow at the expense of mesenteric blood flow. As a result, mesenteric organ ischemic syndromes may appear in modern medical patients well after successful initial resuscitation from shock. These injuries result not only from tissue ischemia itself (metabolic demand exceeding oxygen delivery) but also from an inflammatory response triggered by the generation of ROS at reperfusion and by luminal contents. This microvascular inflammatory response can trigger SIRS and multiple organ dysfunction syndrome. Consequently, the mesenteric response to circulatory shock is homeostatic and protective under mild to moderate shock conditions but can be paradoxically lethal after resuscitation from severe shock. The lack of a negative feedback restraint on this pathologic extreme of a homeostatic mechanism is probably explained by a lack of natural selective pressure for it to evolve: in the absence of parmedics, blood banks, and intensive care facilities, animals and humans so severely injured initially would have failed to survive to put a natural selective pressure on the evolution of the genome. Modern medical care providers must therefore take the pathologic extreme of this response, and its potentially lethal consequence, into account in the care of the modern patient with shock. The circulation of the gut remains an important key to the understanding and treatment of these patients.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
•• Of outstanding interest


The authors investigated intestinal mucosal nitric oxide formation after either hypovolemic shock or severe hypovolemia and sepsis in rats [abstract]. FASEB J 1990, 4:A456.


