NARRATIVE REVIEW ARTICLE

Vasopressors in Trauma: A Never Event?

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Vasopressor use in severely injured trauma patients is discouraged due to concerns that vasoconstriction will worsen organ perfusion and result in increased mortality and organ failure in hypotensive trauma patients. Hypotensive resuscitation is advocated based on limited data that lower systolic blood pressure and mean arterial pressure will result in improved mortality. It is classically taught that hypotension and hypovolemia in trauma are associated with peripheral vasoconstriction. However, the pathophysiology of traumatic shock is complex and involves multiple neurohormonal interactions that are ultimately manifested by an initial sympathoexcitatory phase that attempts to compensate for acute blood loss and is characterized by vasoconstriction, tachycardia, and preserved mean arterial blood pressure. The subsequent hypotension observed in hemorrhagic shock reflects a sympatholytic vasodilation phase. The objectives of hemodynamic resuscitation in hypotensive trauma patients are restoring adequate intravascular volume with a balanced ratio of blood products, correcting pathologic coagulopathy, and maintaining organ perfusion. Persistent hypotension and hypoperfusion are associated with worse coagulopathy and organ function. The practice of hypotensive resuscitation would appear counterintuitive to the goals of traumatic shock resuscitation and is not supported by consistent clinical data. In addition, excessive volume resuscitation is associated with adverse clinical outcomes. Therefore, in the resuscitation of traumatic shock, it is necessary to target an appropriate balance with intravascular volume and vascular tone. It would appear logical that vasopressors may be useful in traumatic shock resuscitation to counteract vasodilation in hemorrhage as well as other clinical conditions such as traumatic brain injury, spinal cord injury, multiple organ dysfunction syndrome, and vasodilation of general anesthetics. The purpose of this article is to discuss the controversy of vasopressors in hypotensive trauma patients and advocate for a nuanced approach to vasopressor administration in the resuscitation of traumatic shock. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

Ang II = angiotensin II; **AVP** = arginine vasopressin; **BP** = blood pressure; **CPP** = cerebral perfusion pressure; **DAMPs** = damage associated molecular patterns; **EPI** = epinephrine; **HR** = heart rate; **K_{ATP}** = adenosine-triphosphate sensitive potassium channels; **MAP** = mean arterial pressure; **MODS** = multiple organ dysfunction syndrome; **mRNA** = messenger ribonucleic acid; **NOREPI** = norepinephrine; **RAS** = renin-angiotensin system; **RCT** = randomized controlled trial; **SBP** = systolic blood pressure; **SCI** = spinal cord injury; **TBI** = traumatic brain injury; **TXA** = tranexamic acid; **SVR** = systemic vascular resistance

Trauma is the leading cause of death in adults <40 years old and uncontrolled blood loss is the most common cause of preventable fatalities.[1]

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Traumatic hemorrhagic shock is responsible for an estimated 49,000 deaths in the United States and 1.4 million patients worldwide each year.[1,2] By definition, shock is the inadequate delivery of oxygen necessary to maintain appropriate physiologic organ function.[1,3] The immediate goals in hemorrhagic shock are control of mechanical bleeding, treatment of trauma-induced coagulopathy, and restoration of intravascular volume. If hemorrhage cannot be controlled immediately, management goals are to minimize further blood loss until hemorrhage control can be achieved.[2,4,5]

Recent advances in hemorrhagic shock resuscitation are the early targeted administration of tranexamic acid (TXA)[5–8] and the individualization of blood product transfusion based on viscoelastic testing.[9] Strategies of permissive hypotension[10,11] and concerns of adverse effects have discouraged the use of vasopressors as part of the resuscitation strategy. The use of vasopressors in patients sustaining traumatic injuries was considered deleterious and thought to

worsen clinical outcomes.[12] Vasopressor use is currently reserved for the postresuscitation period in selected pathologies, such as maintaining cerebral perfusion pressure (CPP) in patients with central nervous system injury[13] or septic shock.[14] The administration of vasopressors to patients in hemorrhagic shock is included in recent European guidelines[15]; however, this was not commonly recommended in the United Kingdom and United States.

In this narrative review, we describe the impact of arterial hypotension and different forms of shock in the acute resuscitation phase after traumatic injury and discuss the controversy of vasopressor use in trauma patients. There were no systematic a priori inclusion criteria and no meta-analysis. To offer a balanced overview for a diverse topic including a summary of the pathophysiology of shock, each author performed their own literature search and papers discussed were included by consensus. We did not set out to formally appraise, score, and quality assess included papers. Specifically, for the selection of studies included in the Clinical Data on Vasopressors in Trauma section, a single PubMed search was performed for "vasopressors" and "trauma." There were 284 results, of which 23 were peer-reviewed, clinical studies evaluating the administration of vasopressors involving human subjects with traumatic injuries. These were reviewed and included in the discussion on vasopressor use in acutely injured trauma patients. Based on the findings, we also specifically address the impact of norepinephrine (NOREPI) and arginine vasopressin (AVP) in the trauma population.

PATHOPHYSIOLOGY OF HEMORRHAGE AND SHOCK IN TRAUMA

Sympathoexcitatory Response to Hemorrhagic Shock

Hemorrhage is the most common cause of preventable death after traumatic injury and is characterized by acute blood loss, coagulopathy, and arterial hypotension.[1] Perhaps most intriguing from a pathophysiologic standpoint is the impact of cardiovascular mechanisms involved in patients with hypovolemia due to hemorrhage. Comprehensive discussion of the pathophysiology of hemorrhagic shock is beyond the scope of this review and has previously been described.[16] Signs of hemorrhagic shock are classically taught as initial increasing heart rate, decreasing pulse pressure, and increasing respiratory rate with a later (monophasic) decrease in systolic blood pressure (SBP) and mean arterial pressure (MAP). Early MAP and cardiac output are maintained by tachycardia compensating for reduced stroke volume due to decreased venous return. However, hemorrhagic shock presents with variable changes in arterial blood pressure. Even in stages III and IV of shock (ie, >30%–40% circulating volume lost), observational data suggest that some patients may still maintain SBP >90 mm Hg.[17]

Schadt and Ludbrook[16] summarize the pathophysiology of acute blood loss in conscious mammals in 2 phases: (1) initial vasoconstriction (sympathoexcitatory) phase and (2) later vasodilatory (sympathoinhibitory) phase. During the sympathoexcitatory phase, arterial blood pressure is maintained by an increase in systemic vascular resistance (SVR). It is also during this nonhypotensive phase that heart rate increases, in part due to loss of resting cardiac vagal stimulation and an increased cardiac sympathetic drive.[18] The early response is largely driven by the sympathetic nervous system (Figure 1). The endocrine response to the early phase of acute hypovolemia includes an increase in plasma concentrations of angiotensin-II as a consequence of the renin-angiotensin system (RAS) and a lesser relative increase in AVP, epinephrine (EPI), and NOREPI.[18] In summary, the sympathoexcitatory phase represents a classic description of the signs and symptoms of early hemorrhagic shock and vasoconstriction.

Sympathoinhibitory Response to Hemorrhagic Shock

The initial vasoconstrictive and sympathoexcitatory response to acute blood loss evolves into a sympathoinhibitory phase characterized by distributive shock as a consequence of vascular hyporeactivity (Figure 2). Studies in animals and human subjects demonstrate that the occurrence of late arterial hypotension after hypovolemia is the result of a decrease in sympathetic nervous system activity and subsequent arterial vasodilation and bradycardia.[16,18,19] The exact mechanistic input from the autonomic nervous system that contributes to the sympathoinhibitory phase is incompletely understood in humans; however, it is theorized to involve cardiopulmonary vagal nerve reflexes.[16]

During the later phases of hemorrhage, the adrenal medulla increases production of both EPI and NOREPI in response to hypotension; however, this does not appear to offset the vasodilation of the sympathoinhibitory phase.[18] The physiologic effect of these neurohormones during this phase is not clear, and the hemodynamic response to blood loss is not altered by adrenal denervation in animal studies.[16] There are also contributions from other neurohormones during the sympathoinhibitory phase of hemorrhage. Angiotensin II and AVP both increase in response to ongoing blood loss and are involved in the restoration of arterial blood pressure after hemorrhage.[18] However, if blood loss continues precipitously, there is a physiologic exhaustion of these neurohormones, even to subphysiologic levels.[20] The depletion of AVP

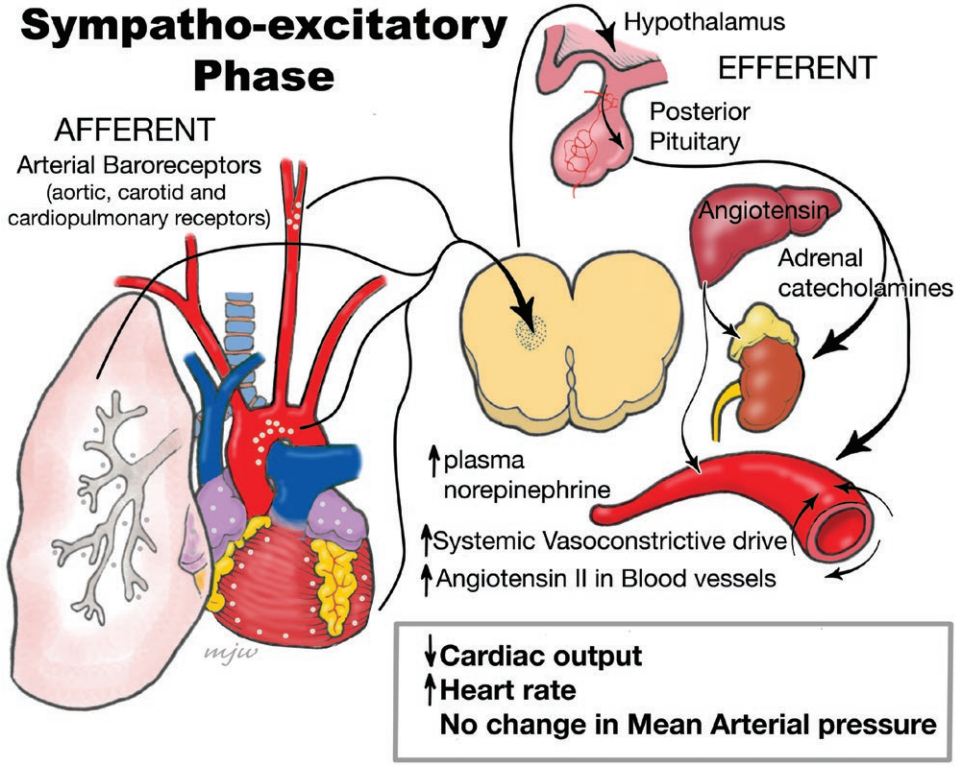


Figure 1. Sympathoexcitatory phase of hemorrhagic shock.

stores (and likely NOREPI) contributes to a deficiency syndrome characterized by a loss of vascular tone. In the decompensated sympathoinhibition phase, even blood transfusion may not restore arterial blood pressure.[21]

Shock-Induced Endotheliopathy

Endothelial dysfunction after injury is recognized as a significant contributing factor to the pathophysiology of posttraumatic hemorrhagic shock.[22,23] Representing one of the largest organs in the body, the endothelium is composed of the inner cellular lining of blood and lymphatic vessels.[24] The intact endothelium maintains vascular patency, regulates fluid permeability, and controls vasomotor tone. In addition, the endothelium participates in natural anticoagulation via heparinoids and antithrombin in the endothelial glycocalyx that allows the passage of oxygen and nutrients carrying blood through the vasculature.[24] Damage to the endothelium via either direct tissue injury or subsequent inflammatory products compromises both the mechanical and chemical integrities of the endothelial layer. Traumatic shock results in endothelial glycocalyx damage that contributes to trauma-induced coagulopathy, microvascular dysfunction, and multiple organ dysfunction syndrome (MODS).[22] A feature of posttraumatic endotheliopathy is the increase in vascular permeability, tissue edema, and loss of vascular vasomotor tone.[23,25] The ensuing vasodilatation appears similar in homology to that of septic shock.[22] The relationships among endothelial damage, injury severity, coagulopathy, and organ dysfunction are an association, and therapeutic targets have not yet been proven.

Pathophysiology of TBI and SCI

Traumatic brain injury (TBI) is the most common cause of death and disability after injury.[26,27] The 2 components of TBI are as follows: primary (ie, at the time of impact) injury and secondary injury for derangements that follow (ie, hypoxia, arterial hypotension, hyperthermia, etc).[27] Therapies can, therefore, impact only the latter. After TBI, the cerebrovascular tone becomes more sensitive to changes in acid-base balance and cerebral blood flow attempts to meet the demands of the cerebral metabolic rate even at the expense of increasing intracranial pressure.[27] Cerebral autoregulation becomes impaired such that the brain is unable to maintain constant cerebral perfusion over a range of MAPs. Consequently, arterial hypotension may cause cerebral hypoxia and observational studies have associated arterial hypotension with increased mortality in TBI patients.[28,29]

Similar to TBI, spinal cord injury (SCI) is associated with significant morbidity and health-related costs in survivors.[13] Injuries to the cervical and upper thoracic spinal column are at particular risk of cardiovascular decompensation due to loss of sympathetic tone and unopposed vagal stimulation below the level of injury resulting in vasodilatation, bradycardia, and impaired

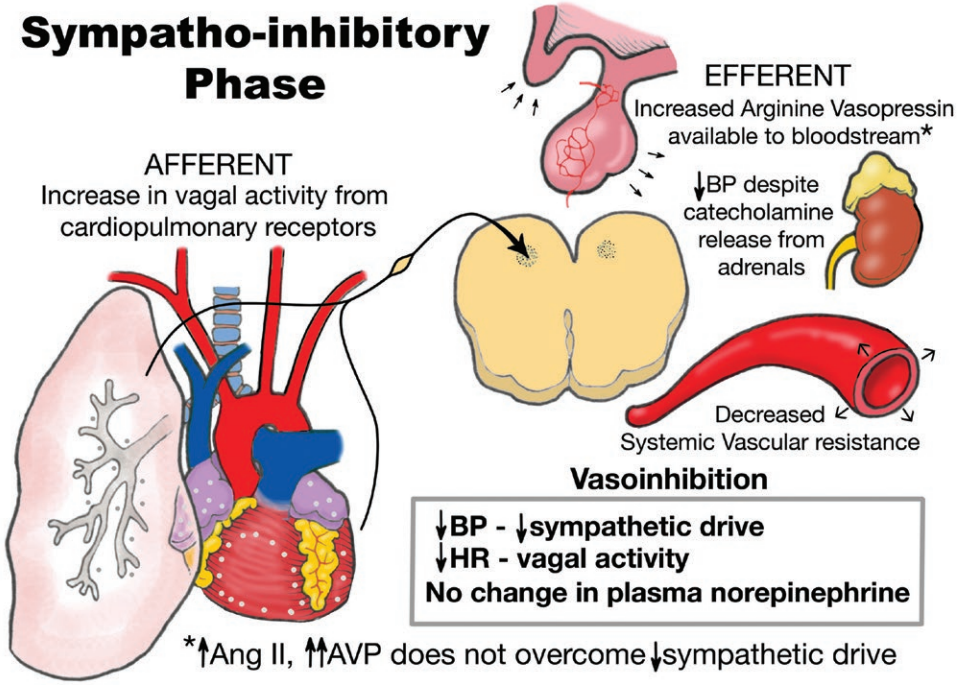


Figure 2. Sympathoinhibitory phase of hemorrhagic shock. Ang II indicates angiotensin II; AVP, arginine vasopressin; BP, blood pressure; HR, heart rate.

cardiac pump function, all leading to tissue hypoperfusion and shock (ie, neurogenic shock). Cardiovascular complications represent one of the leading causes of mortality in patients with SCI.[30] Arterial hypotension has been associated with worse functional outcomes, likely attributed to inadequate spinal cord perfusion.[31,32] Recent guidelines from the American Association of Neurological Surgeons and the Congress of Neurological Surgeons' Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries recommend an MAP of 85 to 90 mm Hg after traumatic SCI.[33]

Pathophysiology of Multiple Organ Dysfunction Syndrome

Historically MODS was noted to occur in nearly 50% of severely injured patients.[34] However, these originate from an era of large volume crystalloid administration and uneven ratios of red blood cells, plasma, and platelet transfusion. Both trauma-associated mortality and the incidence of posttraumatic MODS have decreased during the past 20 years.[35] Increasing injury severity, shock severity, large volume blood product resuscitation, and arterial hypotension are all independently associated with posttraumatic MODS.[36] In addition, vasodilatory complications associated with endotheliopathy and the inflammatory response further contribute to hypotension, hypoperfusion, and the development of MODS in the trauma population.[22,37]

The pathophysiologic mechanisms underlying the development of MODS after traumatic injury are related to the immunologic response to tissue injury and blood loss, dysregulation of coagulation, hemostasis, and endothelial function, neuroinflammation, endocrine dysfunction, and baseline demographic differences, such as age, sex, and premorbid medical conditions.[37] Tissue injury results in the release of biomolecular mitochondrial deoxyribonucleic acid and damage-associated molecular patterns from necrotic cells that stimulate the production of complement and activity of immunologic cells, such as monocytes and T-cells.[37,38] Acute hemorrhage contributes to hypotension, hypoperfusion, and acidemia which lead to further cell death. In addition, severe hemorrhage is associated with an acute traumatic coagulopathy that contributes to further blood loss and inability to achieve adequate hemostasis. Tissue injury and blood loss also impact the function and integrity of the vascular endothelium.[22,23] Despite initial robust productivity, endocrine functions are dramatically altered, as demonstrated by changes in cortisol, insulin, and vasopressin levels. Finally, older age is significantly associated with increased risk of organ dysfunction and multiple organ failure after traumatic injury, potentially due to age-related changes in the postinjury inflammatory response.[36,37]

Similar to septic shock, a solidifying theme in posttraumatic MODS is the relationship of prolonged hypotension and hypoperfusion that is associated with clinical shock, vascular dysfunction, and vasodilation.[14] The patterns of tissue damage, hypotension,

hypoperfusion, cellular dysfunction, and death are repeated with ongoing hemorrhage after significant injury.[22] Certain resuscitation measures, such as administration of large intravascular volume, further exacerbate organ dysfunction and increase the risk of MODS.[36] Additionally, the immunologic ramifications of organ failure contribute to greater susceptibility to infectious pathogens, development of septic shock, vasodilation, and further organ dysfunction.[37]

Blunt Versus Penetrating Trauma

The mechanism of traumatic injury along with the transfer and dispersal of energy is associated with patterns of tissue damage and inflammation. For example, trauma patients with a high-energy blunt mechanism often sustain multisystem injuries, including TBI and pelvic or long-bone fractures. The degree of soft tissue injury is associated with systemic inflammation and organ dysfunction in severely injured blunt trauma patients.[39] Quantification of the volume of clinical shock is valuable in predicting the response to severe injury and subsequent MODS.[40] However, the systemic and microcirculatory effects of severe clinical shock are likely different and, in part, based on the underlying mechanism of injury.[41,42]

Recent evidence from 2 a priori harmonized, prospective randomized controlled trial (RCTs) demonstrate the benefit of a targeted prehospital resuscitation therapy in blunt trauma patients, whereas a significant difference in mortality was not observed among patients with a penetrating injury.[41] Possible explanations for these observations among blunt and penetrating mechanisms are related to basic characteristics of the injured population and nature of the injuries. In addition, literature suggests that blunt mechanisms of injury, such as that occur after motor-vehicle and motorcycle collisions, are associated with overall longer prehospital transport times compared to penetrating injuries that tend to occur in urban environments.[41,43,44] Finally, the volume of shock after severe injury, along with subsequent alterations and derangements in coagulation, is associated with clinical outcomes, such as organ failure[36,40,45] and mortality,[3] and likely influenced by mechanism of injury.

Vasodilation

Vasodilation is a common manifestation in the various forms of shock after traumatic injury. While initial vasoconstriction is an early characteristic of hemorrhage (ie, sympathoexcitatory phase), continued blood loss with subsequent hypotension reflects a state of vasodilation. Both neurogenic and septic shock are also characterized by a decrease in SVR and resultant hypotension.[13,46] Vasodilatory shock is the most common form of shock and represents the final common pathway for severe shock from any cause.[47] Persistent hypotension and hypoperfusion contribute to further vascular dysfunction from which resuscitation does not contribute to the recovery of vascular tone.[47] Therefore, ongoing shock results in organ dysfunction and exacerbates persistent vascular and hematologic failure.[3]

The pathophysiologic mechanisms behind vasodilation are related to vascular smooth muscle relaxation via the adenosine triphosphate-sensitive potassium (K_{ATP}) channels,[47] synthesis of nitric oxide,[48] and vasopressin deficiency.[16,49] Activation of the K_{ATP} channels results in cellular hyperpolarization, which prevents the influx of calcium ions and inhibits cycling of actin-myosin cross-linkages. Increased production of nitric oxide occurs in vascular smooth muscle cells as well as the vascular endothelium. Nitric oxide is a vasodilator that functions through activation of myosin light-chain phosphatase as well as potassium-sensitive calcium channels. Under physiologic conditions, activation of these channels limits the activity of vasoconstrictive agents.[47] However, a vasodilatory state is expressed after pathologic stimulation through nitric oxide. Finally, vasodilation is also represented by a vasopressin deficiency, which is well documented in septic shock,[50] postcardiopulmonary bypass,[51] and hemorrhagic shock.[20]

CLINICAL DATA ON VASOPRESSORS IN TRAUMA

Despite vasodilation representing the final common and unifying pathway in different forms of shock after traumatic injury, clinical studies have demonstrated the disadvantages of vasoconstrictive agents in the trauma population. The concerns about vasopressor use in trauma patients include rapid increases in arterial blood pressure, increased cardiac afterload, arrhythmias, and reduced tissue perfusion with subsequent organ dysfunction.[12,52]

Initial clinical reports were that early vasopressor use (ie, phenylephrine, NOREPI, or AVP), within the first 12 hours after injury, was associated with increased mortality even after adjusting for the volume of crystalloid resuscitation.[12] In a retrospective study, Collier et al[53] reported an increased risk of mortality in trauma patients who received AVP within 72 hours of hospital admission. Another retrospective investigation compared 1349 trauma patients from a single center exposed to any vasoactive drug within 24 hours of admission and showed mortality rates of 43.6% vs 4.2%.[54] Further single-center, retrospective studies demonstrated similar findings.[55–57] A systematic review on vasopressor use in trauma patients identified a significant association between vasopressor use and increased short-term mortality,[52] and administration of vasopressors after initial damage control laparotomy quadrupled the rate of anastomosis failure.[58] A more recent Japanese database study

included 298 patients who received vasopressors and were propensity score-matched to subjects who did not receive vasopressors.[59] Vasopressor use within 24 hours after hospital admission was associated with greater inhospital mortality. These findings are similar to a retrospective study of 40 patients with hemorrhagic shock who were administered dopamine or NOREPI within 1 hour of hospital admission.[60]

Specifically, in patients with acute SCI, vasopressor administration, reported most commonly in the form of dopamine and phenylephrine, was associated with an increased risk of complications, such as tachyarrhythmias and troponin elevation.[61] These results were corroborated in a retrospective investigation of 556 patients with TBI.[62] Another investigation evaluated the Nationwide Inpatient Sample for patients who received a craniotomy for significant trauma. Patients who received vasopressors had an increased risk of death; however, the results were not adjusted for injury severity, admission Glasgow Coma Scale, or metabolic markers associated with secondary brain injury.[63] Ultimately, vasopressors are associated with higher MAP and CPP but also an increased risk of complications.[64] A previous retrospective study reported in patients with central cord syndrome reported an association with improved neurologic function and exposure to any vasopressor.[65] A more recent investigation of traumatic SCI observed that patients who achieved more frequent MAP measurements ≥85 mm Hg were more commonly exposed to vasopressors and were significantly more likely to have an improvement in neurologic outcome.[32] Based on the available human clinical data in nonrandomized studies, there are limited high-quality data demonstrating an association with improved survival or neurologic outcome and vasopressor administration in patients with neurologic injury,[66–68] which is an important consideration when administering vasopressors to patients with severe TBI or SCI.

The optimal arterial blood pressure target for resuscitation of patients with hemorrhagic shock is unknown. Prolonged hypotension and hypoperfusion are associated with an increased risk of organ failure and death. Registry data suggest an association between arterial blood pressures <110 mm Hg and mortality.[69] However, this finding does not necessarily imply that normalizing arterial blood pressure improves outcomes or organ perfusion. A clinical concern is the reported harm of vasopressors when administered with the goal to increase blood pressure. Ultimately, an important clinical question is "Does early vasopressor administration increase mortality and complications in severely injured trauma patients?"

A retrospective, propensity score–matched cohort study observed no significant increase with inhospital mortality in patients who received prehospital NOREPI.[70] In addition, a retrospective study of 746 trauma patients requiring emergent operations observed no significant increase in mortality in patients who received vasopressors, exclusive of EPI.[71] In the study that found AVP use was associated with increased mortality risk, when patients were stratified by whether they received only AVP or AVP in combination with another vasoactive, there was no difference in the risk of mortality in patients who received only AVP.[53] A further investigation noted that severely injured patients with TBI were significantly more likely to receive vasopressors. Although no difference was found in the volume of crystalloid or blood product transfusion, clinical outcome data with regard to vasopressors were not specifically reported.[56]

Two RCTs suggest that AVP administration may improve blood pressure while not worsening blood loss or increasing mortality in patients with hemorrhagic shock.[72,73] A prospective randomized trial of early infusion of low-dose AVP (ie, 2.4 IU/h for 5 hours on arrival at the emergency department) versus placebo in trauma patients resulted in the lower requirement of total fluids at 24 hours.[72] The study was underpowered to show a significant difference in death. Among the AVP and control groups, respectively, there was no difference in mortality at 24 hours (13% vs 23%, P =.28), 5 days (13% vs 25%, P = .19), or the primary outcome of 30-day mortality (34% vs 28%, P = .52). Most recently, a single-center, prospective RCT demonstrated that a continuous AVP infusion did not increase mortality but was associated with a lower need for blood product transfusion in trauma patients who required massive transfusion. Included patients were at risk for hemorrhagic shock and received 6 units of blood product within 12 hours of admission.[73] The authors hypothesized that an exogenous supply of AVP may not only increase vascular tone but also support hemostasis. Further studies in patients with TBI demonstrate that AVP was associated with less administration of hyperosmolar therapy and is a potential option and alternative to catecholamines for CPP management.[74,75]

PHARMACODYNAMICS OF NOREPI AND ARGININE VASOPRESSIN

Numerous retrospective studies in the trauma literature have investigated multiple vasopressors (ie, NOREPI, phenylephrine, dopamine, and AVP).[12,52,54,59] This discussion focuses on the 2 most common and clinically important vasopressors in this population: NOREPI and AVP (Table). Administration of EPI to patients in hemorrhagic shock has been studied in the setting of prehospital cardiac arrest[76] but it has not been specifically examined as a vasopressor in isolation with trauma patients. NOREPI is a neurohormone released from sympathetic, postganglionic

Table. Common Vasopressors Administered in Traumatic Shock

Vasopressor	Mechanism	Physiologic response
Norepinephrine	α-1-receptor agonist with modest β-1-agonist activity	Augment venous return and central systemic vascular volume increase coronary perfusion via α-1 and support cardiac contractility through β-1 activity
Vasopressin	V_1, V_2 receptors	Activation of V_1 receptors and increasing vascular tone with vasoconstriction via multiple G-proteins and regulation of intravascular volume resorption via V_2 receptors in collecting tubules

nerve fibers and is a product of the decarboxylation of dopamine. It is stored in presynaptic granules that release their content in the synaptic space on depolarization. After release, NOREPI acts on postsynaptic α- and (to a lesser extent) β-receptors.[46,77] The effects on both receptors are dose-dependent; with increasing doses, the α-receptor effect dominates. This results in: (1) contraction of smooth muscles fibers in venous and arterial vessels inducing venoconstriction and an increase in venous return (ie, recruitment of unstressed volume) as well as arteriolar vasoconstriction and (2) myocardial inotropic and chronotropic stimulation.[77–79]

The physiology of AVP has been described in detail.[49,80] AVP is a neuroendocrine nonapeptide, produced in the neurons of the paraventricular and supraoptic nuclei in the posterior hypothalamus.[46] AVP acts on multiple G-protein–coupled receptors and uses the phosphatidylinositol pathway to increase Ca^{2+} influx.[49] AVP-1 receptors are densely situated on vascular smooth muscles of the systemic, splanchnic, renal, and coronary circulation; their stimulation leads to potent vasoconstriction,[49] concomitant increase in cardiac output, and centralization of blood volume.[81] In renal efferent arterioles, this vasoconstriction increases glomerular filtration rate. In the pulmonary vasculature, AVP induces less vasoconstriction than NOREPI.[46,77] Platelet AVP-1 receptor stimulation facilitates thrombocyte aggregation.[82] AVP-2 receptors located in the renal collecting system induce antidiuresis by shuttling aquaporin-2 containing vesicles to the cell surface and stimulation of synthesis of aquaporin-2 messenger ribonucleic acid (mRNA). There is also a complex physiologic interaction of AVP on oxytocin and purinergic receptors. Purinergic receptors on the cardiac endothelium seem to exert a positive inotropic effect without associated positive chronotropy and without a resultant increase in oxygen demand.[83] In some vascular beds, such as the lung, AVP binding to oxytocin receptors leads to pulmonary vasodilation.[77]

CURRENT GUIDELINES FOR HEMORRHAGIC SHOCK AND GAPS IN CLINICAL KNOWLEDGE

The current paradigm for trauma resuscitation balances restoring organ perfusion, providing hemostatic resuscitation,[84] and minimizing coagulopathy.[4] Therapy components include blood products,[85] a period of permissive hypotension, rapid imaging, and damage control surgical techniques.[86] Multiple organizational guidelines exist for the management of hemorrhagic shock, such as the European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma,[15] Advanced Resuscitative Care in Tactical Combat Casualty Care,[8] and the Eastern Association for the Surgery of Trauma Clinical Practice Guidelines for Damage Control Resuscitation in Patients with Severe Traumatic Hemorrhage.[5] Common principal themes in each guideline are the minimization of crystalloid administration, early transfusion of blood products in prespecified ratios, and administration of hemostasis adjuncts, such as TXA. Aggressive resuscitation with excessive crystalloid volumes is associated with increased rates of MODS and mortality.[36] In addition, limited prehospital crystalloid resulted in decreased mortality in patients with penetrating torso trauma.[87] Furthermore, development of resuscitation protocols and established ratios of blood product administration is associated with improved clinical outcomes.[4,85] Early plasma-based resuscitation contributes a significant mortality benefit in trauma patients.[43,44] Administration of TXA within 3 hours of injury has also demonstrated a significant improvement in mortality for trauma patients at risk for blood product transfusion[6]; however, more recent evidence from mature and developed trauma systems is generating continued controversy on this topic.[88–90] The practice of permissive hypotension is also advocated by some organizations[5]; however, vasopressor administration is only recommended in the European guidelines.[15]

Resuscitation with permissive hypotension has long been a component of early hemorrhagic shock resuscitation. This strategy aims to tolerate lower arterial blood pressures to minimize further blood loss from the bleeding site due to lower hydrostatic pressures and reduce resuscitation volumes, most importantly crystalloid fluid administration.[10] Multiple RCTs[87,91–93] and a meta-analysis[11] advocate that permissive hypotension is associated with decreased mortality. However, there are numerous methodologic problems. In the recent meta-analysis, the included studies were of poor to moderate quality due to lack of blinding and incomplete protocol reporting.[11] In addition,

individual RCTs report heterogeneous SBP and MAP targets with inconsistent effects. A majority of studies also excluded patients with TBI. Furthermore, despite tolerating lower blood pressures, the MAPs were normal and there were no statistical differences in the end point blood pressures between intervention and control groups in several clinical trials[91–93] that raise the question on whether permissive hypotension was achieved.

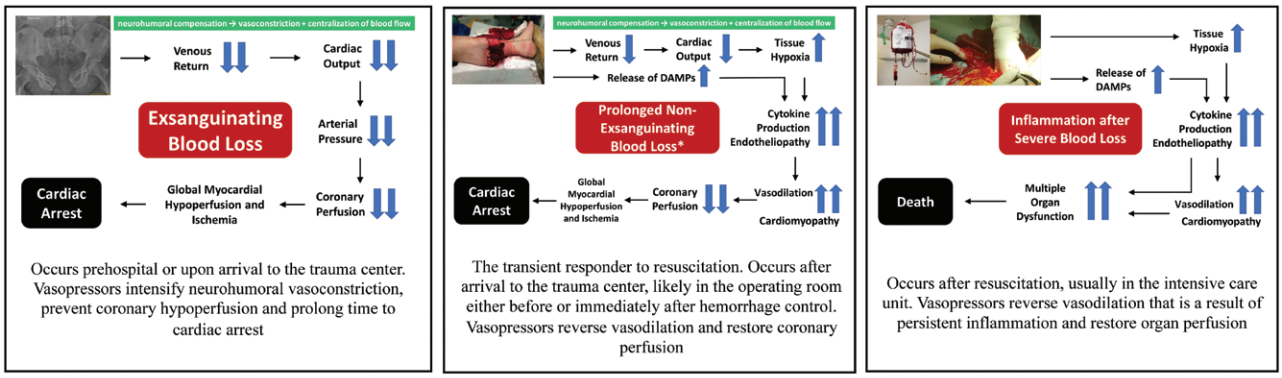
The only RCT in the meta-analysis, which demonstrated a primary difference in mortality and contributed >50% of patients to the meta-analysis, was performed in patients with penetrating torso trauma who were randomized to either a restrictive or a liberal crystalloid resuscitation strategy.[87] The SBP in the restrictive group was lower than in the liberal crystalloid group (72 vs 79 mm Hg, P = .02); however, the clinical implications of this difference are likely minimal. The role of permissive hypotension in the era of whole blood resuscitation is also unexplored and the period of organ hypoperfusion may contribute to subsequent MODS. Prolonged periods of arterial hypotension and hypoperfusion in nontrauma surgery are associated with increased rates of myocardial injury,[94] acute kidney injury,[94,95] and severe coagulopathy.[3,96] A review of the literature would seemingly advocate for permissive hypotension in bleeding trauma patients. Although this lower level of evidence appears to support use of lower arterial blood pressure, avoidance of vasopressors in trauma patients to achieve permissive hypotension represents a significant gap in clinical knowledge and practice.

RECOMMENDATIONS FOR A NUANCED APPROACH TO HEMORRHAGIC SHOCK AND VASOPRESSORS

Acute hemorrhage is a common cause of hemodynamic decompensation and death[85,97]; however, trauma patients and their injury profiles are often heterogeneous.[98] Moreover, circulatory instability after hemorrhage in trauma patients may occur at different temporal periods and have several, often overlapping causes (Figure 3). Different injury patterns and disease processes contribute to multiple causes of posttraumatic shock. TBI may induce persistent shock,[99] and TBI patients seem to be at particular risk for prolonged arterial hypotension.[29] Prior studies that determined vasopressors are associated with increased mortality in trauma patients excluding patients with TBI. Therefore, the full impact of hypotension and vasopressor administration in a large portion of the trauma population is not defined.

Vasopressors have a sound mechanism to improve oxygen delivery by decreasing venous system compliance, augmenting the mean systemic filling pressure, and thereby increasing the stressed blood volume and cardiac output within the circulation.[79,100,101] Regardless of whether vasopressors contribute to an improvement in the repayment of oxygen debt after hemorrhagic shock in humans must be critically examined by further clinical studies. The use of vasopressors in hemorrhagic shock is supported by European guidelines,[15] and an argument for the therapeutic use of NOREPI or AVP in traumatic shock resuscitation is to augment the body's physiological response and maintain homeostasis.[80] To date, AVP is the only agent evaluated in trauma patients via RCTs, albeit small population size.

There are certain clinical scenarios in which early vasopressor use with NOREPI or AVP would be recommended in trauma patients[102] (Figure 3). For example, severe brain injury is frequently encountered after blunt mechanisms of injury.[103] Guidelines from the Brain Trauma Foundation suggest achieving specific blood pressure targets to achieve a CPP of 60 to 70 mm Hg, with vasoactive agents as necessary, to minimize the insult of secondary injury. The detrimental effects of permissive hypotension in severely injured patients with TBI are a significant concern.[104,105] Administration of NOREPI or AVP has been successfully utilized in this population to maintain CPP and without increases in morbidity.[32,71,74] Moreover, in acute, massive



DAMPs: damage-associated molecular patterns.

Figure 3. Pathophysiology, temporal evolution, and patterns of traumatic hemorrhagic shock. DAMPs indicates damage associated molecular patterns.

exsanguination, there is decreased venous return, consequent reduced cardiac output, loss of coronary perfusion pressure, and ultimately prehospital cardiac arrest. Vasopressin or NOREPI administration maintain venous return, cardiac output, and coronary perfusion pressure until surgical hemorrhagic control.[106,107] In addition, persistent hemorrhage and arterial hypotension unresponsive to continued blood product transfusion would benefit from vasopressor administration to maintain organ perfusion. It is likely that this situation may already be encountered in the operating room when the sympathoinhibitory phase of hemorrhagic shock occurs before hemorrhage control.[16,102,108] In addition, vasopressors may be necessary due to effects of intravenous and inhalational anesthetic agents that blunt the physiologic, sympathetic vasoconstrictive response and further enhance vasodilatation.[108] Persistent and prolonged shock with severe tissue damage and release of proinflammatory mediators also aggravates vasodilation and necessitates vasopressor administration even after definitive hemorrhage control.[37,102] Finally, NOREPI may be beneficial after hemorrhage control (ie, in the intensive care unit) in patients demonstrating early organ dysfunction as a result of persistent inflammation, vasodilation, and MODS in the postresuscitation period[78] (Figure 3), as determined by bedside echocardiography[109–111] or invasive hemodynamic indices.

The administration of vasopressors to patients in hemorrhagic shock appears counterintuitive to the paradigm practice of hypotensive resuscitation and permissive hypotension. However, limited high-quality evidence supports permissive hypotension, particularly in the era of balanced blood product-based resuscitation and the reemergence of whole blood transfusion.[112] Furthermore, the pathophysiologic stages of hemorrhage demonstrate that vasodilation likely occurs in a proportion of hypotensive patients with acute blood loss.[16,102] In these clinical situations, we advocate for vasopressor therapy with NOREPI or AVP. This is consistent with European guidelines on the management of blood loss after traumatic injury.[15] However, vasopressor administration in the bleeding trauma patient must be exercised with caution and in concert with appropriate intravascular resuscitation (ie, early blood product transfusion). The decision to decrease vasopressor support must also be made in the clinical context of an improving metabolic acid-base status[113–116] and appropriate echocardiographic parameters and cardiac function.[109–111] Further investigations are necessary to more clearly delineate the temporal course of vasodilation and vascular dysfunction after hemorrhagic shock. Additional work is also necessary to determine optimal blood pressure targets and organ perfusion markers in specific trauma populations, such as blunt mechanisms of injury and TBI, and in patients resuscitated with whole blood.

CONCLUSIONS

The use of vasopressors is traditionally cautioned against in the management of traumatic hemorrhagic shock. However, the pathophysiology of shock in trauma patients is complex. Multiple clinical scenarios exist, which may warrant early administration of AVP or NOREPI, along with appropriately titrated volume administration and resuscitation. Further scientific work is necessary to better define specific vasopressor medications, optimal arterial blood pressure goals, and resuscitation strategies that are most beneficial to the critically injured trauma patient. Based on the current literature, we conclude that clinical equipoise exists and will only be solved by adequately powered, multicenter, prospectively randomized trials.

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