

Current Concepts in Hemorrhagic Shock

Richard P. Dutton, MD, MBA^{a,b,*}

^aUniversity of Maryland School of Medicine,
22 South Greene Street, Baltimore, MD 21201, USA

^bDivision of Trauma Anesthesiology, R Adams Cowley Shock Trauma Center, University
of Maryland Medical System, 22 South Greene Street, Baltimore, MD 21201, USA

Pathophysiology of hemorrhagic shock

Loss of intravascular volume triggers a predictable systemic response, mediated by both local vascular signaling and the neuroendocrine system [1]. Decreased filling pressures in the heart result in a decrease in cardiac output, in accordance with Starling's Law. Vasoconstriction of ischemia-tolerant vascular beds (eg, skin, muscle, gut) allows preservation of flow to organs that depend on a continuous supply of oxygen, principally the heart and the brain. Vasoconstriction is triggered by reduced blood pressure, pain, and cortical perception of injury. In injured tissue, local mediators act to constrict blood flow and reduce bleeding. Central sympathetic outflow is increased and parasympathetic flow is decreased, leading to an increase in heart rate and contractility. Adrenal stimulation results in the "fight or flight" response, with increased levels of circulating epinephrine.

Persistent hypoperfusion leads to cellular death and organ system failure. Cells that lose nutrient blood flow undergo necrotic cell death. Other cells undergo apoptosis, or "programmed cell death," sacrificing themselves in the face of insufficient resources. Cells in many organ systems have the ability to hibernate. Cells in the renal cortex, for example, stop filtering fluid at a level of ischemia less than that which causes necrosis.

Shock is more than a transient failure in oxygen supply, but also the systemic disease that follows [2]. Cells in the liver and gut may remain ischemic after flow is reestablished in the macrocirculation, because of the occlusion of capillary networks caused by edema [3]. This "no-reflow" phenomenon

* Division of Trauma Anesthesiology, R Adams Cowley Shock Trauma Center, University of Maryland Medical System, 22 South Greene Street, Baltimore, MD 21201.

E-mail address: rdutton@umaryland.edu

persists even after cardiac output is normalized. Reperfusion following hemorrhagic shock releases toxic mediators into the circulation; these mediators are potent immune modulators. Even short periods of relatively minor ischemia can trigger a cascade of cellular signaling and response that results in organ system failure (Fig. 1).

The consequences of ischemia first become apparent in the less critical organs. Skin and muscle cells become anaerobic, producing lactic acid. Organs of the splanchnic circulation hibernate (peristalsis and renal filtering cease) and then suffer cellular damage, progressing to organ system failure. Hypoperfusion of the liver results in decreased glucose availability, loss of clotting factors, and, eventually, cell death [4]. Intestinal mucosal cells lose the ability to transport nutrients; if ischemia persists, the barrier function of the gut is lost, and translocation of bacteria occurs from the intestinal lumen into the portal circulation.

The lungs are the downstream filter for toxic metabolites, inflammatory mediators released by ischemic cells, and translocated bacteria from the gut. The lungs are also the sentinel organ for the development of multiple organ system failure. The acute respiratory distress syndrome, occurring after hemorrhagic shock, was first described in the 1960s as “Da Nang lung” [5]. Pulmonary failure develops over 1 to 3 days following severe trauma, is exacerbated by ventilator-associated pneumonia, and may require weeks of supportive care to resolve. Increased pulmonary resistance may lead to right-heart failure, even in young patients.

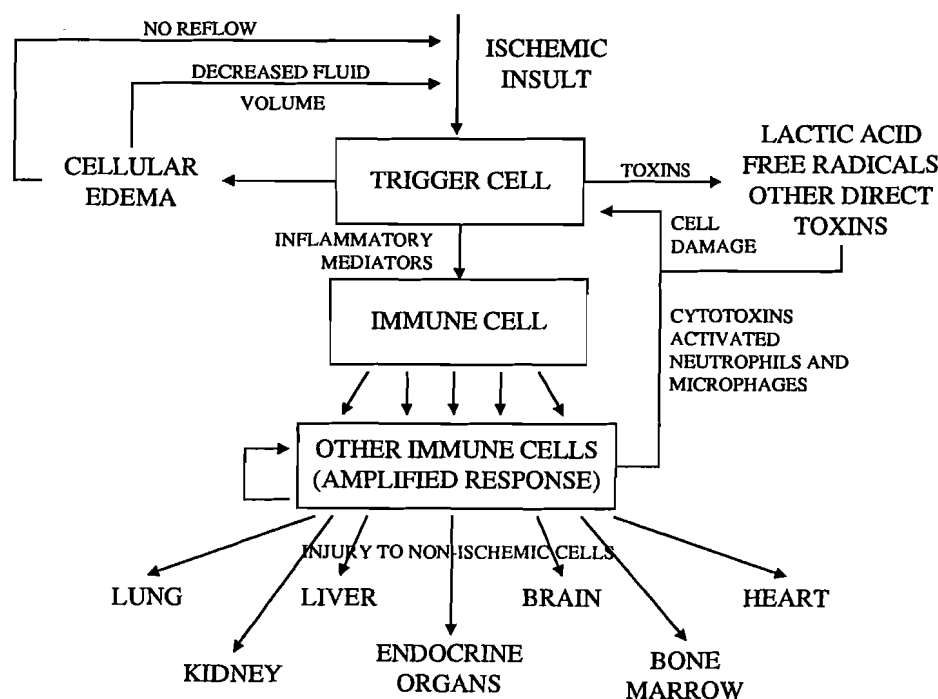


Fig. 1. The shock "cascade."

Symptoms of shock

Symptoms of shock are shown in Box 1. Vital signs do not reflect the quantity of hemorrhage accurately! Fit, young patients may lose 40% of their blood volume before the systolic blood pressure (SBP) drops below 100 mmHg, whereas the elderly may become hypotensive with volume loss of as little as 10% [6]. Hemorrhaging trauma patients are intensely vasoconstricted, and may suffer from end-organ ischemia even with a normal SBP [7]. Metabolic acidosis revealed by arterial blood gas measurement is the gold standard diagnostic test. Noninvasive monitors to diagnose shock are under development, as shown in Table 1.

Acute, fatal hemorrhagic shock is characterized by progressive metabolic acidosis, coagulopathy, and hypothermia (the lethal triad), followed by circulatory system failure [8]. Inappropriate vasodilatation results from loss of energy reserves in the vascular endothelium. Shock is seldom reversible at

Box 1. Signs and symptoms of hemorrhagic shock

Appearance

Pale, diaphoretic

Injuries

Open wounds, bruising, or bony instability consistent with blood loss

Mental status

Progressive deterioration from normal to agitated to lethargic to comatose

Vital signs

Decreased SBP (<100 mmHg), narrow pulse pressure, tachycardia, tachypnea, nonfunctional pulse oximeter, progressive hypothermia

Pulses

Diminished or absent, poor capillary refill

Renal

Diminished urine output

Laboratory

Decreased pH, abnormal base deficit, elevated lactate, elevated osmolarity, elevated prothrombin time (PT)

Response

Increased SBP with fluid administration (fluid responsiveness), exaggerated decrease with analgesics or sedatives

Table 1
Noninvasive shock monitors currently under development

Monitoring technology	Description	Comment
Gastric tonometry	Gastric pH reflects mucosal perfusion	Requires long calibration time; approved, but not commonly used
Sublingual capnometry	Sublingual pH easier to access than gastric; same correlation with perfusion	Faster than gastric tonometry, but still somewhat cumbersome
Near-infrared tissue oximetry	Reflectance oximetry of deltoid or thenar muscle bed	Approved and used in some ICUs; not yet proven in early shock management
Beat-to-beat heart rate variability	Analysis of EKG signal processed to determine sympathetic/parasympathetic balance	Encouraging preliminary results; needs more study in early patients who have severe hemorrhage
Acoustic arterial flow analysis	Compares vascular acoustic "signature" to determine degree of vasoconstriction	Not yet commercially available

this stage, even with massive transfusion. If perfusion is restored before this point, the ultimate outcome will depend on the total "dose" of shock (the depth and duration of hypoperfusion), the patient's underlying physiologic reserve, and the details of medical management.

System-specific actions to control hemorrhage

Table 2 shows the five compartments of the body into which significant intravascular volume can be lost [9]. Successful resuscitation is unlikely in the absence of hemostasis. Anatomic control of bleeding is the single most important step in resuscitation from hemorrhagic shock. Exsanguination to the environment ("the street") is easiest to diagnose, and is treated by direct pressure on the bleeding wound. By itself, external bleeding is seldom life-threatening. In the presence of other injuries, however, "a little scalp bleeding" may be overlooked, especially if it occurs from rebleeding caused by increased blood pressure and clotting factor dilution.

Bleeding into long-bone compartments is substantial at the time of injury, but ongoing hemorrhage is rare. Vasoconstriction in the periphery and tamponade in closed fascial compartments limit blood loss. Exceptions are open fractures and direct injury to major arteries. Opening of the fascia, disruption of periosteal clot, and blood dilution with intravenous fluids contribute to rebleeding at the time of surgical repair. It is wise to complete resuscitation, secure vascular access, and ensure the availability of blood products before definitive repair is attempted.

Injury to the lung causes low-pressure bleeding that usually stops spontaneously. Management is by placement of a tube thoracostomy, which allows

Table 2
Potential sites of exsanguination in the unstable trauma patient

Site of bleeding	Diagnostic modality
Chest	Physical examination (breath sounds, bruises, or abrasions) Chest radiograph Thoracostomy tube output CT scan
Abdomen	Physical examination (distention, pain) Ultrasound (FAST) CT with contrast Peritoneal lavage
Retroperitoneum	Physical examination (unstable pelvic ring) Pelvic radiograph CT with contrast Angiography
Long bones	Physical examination Plain radiographs
Outside the body	Medic's or bystander's report Physical examination

Abbreviation: FAST, Focused Assessment by Sonography in Trauma.

for drainage and quantification of hemorrhage, underwater seal of the pleural space, and application of continuous suction. Fewer than 15% of patients will require emergent surgical exploration, typically as the result of bleeding from the hilum of the lung or from a lacerated intercostal artery [10]. Initial blood loss in excess of 1 L, or ongoing bleeding greater than 200 mL/hour, should prompt surgical exploration. Traumatic aortic rupture results from high-energy blunt trauma, and represents a spectrum of disease, from minor intimal disruption to complete transection. Tamponade by surrounding structures may prevent exsanguination into the left pleural space, allowing a window of opportunity for diagnosis and surgical therapy [11]. The use of angiographic stent grafting will soon become the standard of care for these injuries.

Hemorrhage in the mediastinum is a true emergency, and a successful outcome depends on rapid surgical management. Shock develops from cardiac tamponade, and patients require emergent pericardotomy; if the underlying cardiac or vascular injury can be controlled, and a perfusing blood pressure restored, the patient will often recover.

Abdominal hemorrhage is diagnosed by ultrasound: the Focused Assessment by Sonography for Trauma examination. Hemorrhage may also be diagnosed by CT or by diagnostic peritoneal lavage. In the stable patient, CT followed by angiographic embolization of liver or splenic bleeding may allow for successful, nonoperative management. Hemorrhage in an unstable patient indicates emergent laparotomy. "Damage control surgery" is the concept of a swift initial operation focused only on control of hemorrhage, followed by re-exploration and definitive surgery after 24 to 48 hours of ICU stabilization [12].

Life-threatening retroperitoneal hemorrhage arises from injury to the venous plexus that lies on the inner surface of the sacrum. Patients who have posterior venous plexus bleeding are transient responders to initial fluid therapy. Physical examination reveals instability of the pelvis, and plain film radiography shows the fracture. Pelvic venous bleeding is not accessible surgically. Abdominal exploration in this setting may be counterproductive, because it releases tamponade of the retroperitoneal hematoma. Treatment is by urgent pelvic compression with a pelvic binder or external fixator to facilitate tamponade, followed by angiographic embolization of pelvic vessels and orthopedic stabilization of the sacroiliac joint [13].

Fluid resuscitation: strategy

Minimizing hypoperfusion and tissue ischemia would seem to dictate rapid volume resuscitation in the actively bleeding patient. Unfortunately, there are competing priorities. Before definitive hemostasis, vigorous fluid administration increases the rate of bleeding from injured vessels. Fluid administration raises cardiac output and increases blood pressure. Increased blood pressure counters local vasoconstrictive mechanisms and exerts greater force on fragile clots [14]. When isotonic crystalloids are used, dilution of the blood is inevitable, which reduces hematocrit (lowering oxygen carrying capacity) and reduces the concentration of clotting factors and platelets. Hypothermia is a strong possibility, contributing to the development of coagulopathy. Typically, crystalloid administration leads to a transient rise in blood pressure, followed by an increase in the rate of hemorrhage and a subsequent deterioration, which, in turn, begets further fluid administration, leading to the "bloody vicious cycle" of hypotension, fluid bolus, rebleeding, and deeper hypotension [15]. The Advanced Trauma Life Support (ATLS) curriculum recommends rapid administration of up to 2 L of crystalloid, followed by continued blood and crystalloid targeted to a normal pulse and blood pressure, but includes the following statement: "Aggressive and continued volume resuscitation is not a substitute for manual or operative control of hemorrhage" [9].

Laboratory evidence supporting a lower blood pressure target during active bleeding is substantial. In 1965, Shaftan [16] demonstrated that blood loss from a femoral artery injury in dogs was greatest in quantity and most prolonged when fluids or vasopressors were given, and least and shortest when either resuscitation was withheld or vasodilators were administered. Swine [14] and rat [17] models of uncontrolled hemorrhage have demonstrated that optimal oxygen delivery and survival is achieved in animals resuscitated to a lower target blood pressure. A consensus conference in 1993 summarized the available animal data, and advocated human trials of deliberate hypotensive resuscitation for patients who have active hemorrhage [18].

Two such trials have been conducted. The first included 600 hypotensive victims of penetrating thoracoabdominal trauma [19]. Patients were

randomized to standard care (two large bore IVs, fluid administration to maintain SBP > 100) or to fluid restriction (no IV fluids), and this therapy was continued to the operating room. Patients in the no-fluids group received less fluid than those in the standard care group, but had a similar SBP. Survival in the no-fluids group was 60%, versus 54% in the standard care group ($P = .04$). Despite the positive result of this trial, it was criticized for its all-or-none approach, its restriction to penetrating trauma patients, and its failure to continue fluid restriction into the operative period.

The results of this trial are supported by other data. Patients receiving fluids by way of a rapid infusion system were found retrospectively to do poorly, compared with historical controls [20]. In a prospective trial, patients presenting in hemorrhagic shock were randomized to conventional treatment (SBP > 100) or restricted treatment (SBP > 80), and this therapy was continued until definitive control of hemorrhage [21]. The rate of mortality was not different (4 of 55 patients in each group), but hemorrhage was controlled more rapidly in the low-pressure group.

A consensus approach to early resuscitation is summarized in Box 2. The priority is to identify the patient who is bleeding actively. Intubation and mechanical ventilation allow for better analgesia and more rapid transition to CT, operating room, and angiography. Blood pressure is kept low, with an emphasis on preserving blood composition.

The hemostatic moment is easy to identify. Even without exogenous fluid administration, a hypovolemic patient will "auto-resuscitate" if there is no ongoing blood loss [21]. At this point, the targets for resuscitation shift to the more familiar list in Box 3, with the administration of fluids to achieve

Box 2. Goals for early resuscitation (prior to definitive control of hemorrhage)

Control of airway and ventilation

Expeditious control of hemorrhage

SBP 80–100 mmHg

Blood composition

- Limited use of crystalloid fluid
- Hematocrit 25%–30%, with early administration of red blood cells (RBCs) (including uncrossmatched Type O)
- Early use of plasma to maintain normal clotting studies
- Possible use of cryoprecipitate and/or Factor VIIa if patient is already coagulopathic
- Platelet count >50,000
- Ionized calcium monitored and treated

Maintained core temperature of >35°C

Gradual conversion to deep general anesthesia

Box 3. Goals for late resuscitation (after definitive control of hemorrhage)

Complete resuscitation is achieved by titrated administration of fluids until the following parameters are met

Normal or hyperdynamic vital signs

Hematocrit >20% (transfusion threshold determined by patient's age)

Normal serum electrolytes

Normal coagulation function, platelet count of at least 50,000

Restoration of adequate microvascular perfusion, as indicated by

- pH = 7.40 with normal base deficit
- Normalized serum lactate
- Normal mixed venous oxygenation
- Normal or high cardiac output

Normal urine output

normal vital signs and to restore perfusion in the microcirculation. Trauma patients may normalize their blood pressure while still hypovolemic. This "occult hypoperfusion" carries a high risk for subsequent organ system failure, sepsis, and death [22]. Although normal pH is a good indicator of adequate fluid volume, serum lactate level is a better indicator of the depth and duration of shock. The rate at which shock patients normalize lactate is correlated strongly with outcome [7]. Patients who do not clear lactate with post-hemorrhage fluid loading are suspicious for ongoing hemorrhage or occult myocardial dysfunction, and should be assessed further. Measurement of cardiac output is indicated, with judicious use of inotropic agents in patients who do not respond to adequate preload [23].

Fluid resuscitation: component therapy

Fluid resuscitation must restore intravascular volume, oxygen delivery, and hemostatic capability. Fresh whole blood is the ideal fluid for victims of serious hemorrhagic trauma, because it meets these goals with the least potential for side effects [24]. Except in certain military settings, this therapy is not available in the United States. "Component therapy" refers to the practice of fractionating units of donated whole blood into separate units of red cells, plasma, and platelets.

Many trauma patients do not need blood products at all. Isotonic crystalloid administration replaces the deficit in intravascular volume associated with acute hemorrhage, and produces an increase in cardiac output. In hemostatic patients this may be sufficient, but in actively bleeding patients the benefit is transient. It is important to identify the transient responder early.

Whether using deliberate hypotension or not, use of crystalloid as the primary resuscitative fluid causes a drop in hematocrit and clotting factor concentrate. Hypotension persisting or returning after an initial bolus of crystalloid is a strong indicator for RBC transfusion.

Colloid solutions are also used during resuscitation, especially in European trauma systems. Isotonic crystalloids equilibrate rapidly across all fluid compartments, leaving as little as 11% in the intravascular space 60 minutes after administration [25]; however, colloids are highly osmotic, and will draw free fluid into the circulation. The immediate effect of colloid on vascular volume, cardiac output, and blood pressure is greater than the effect of a similar dose of crystalloid. In some (nonbleeding) patients, the more rapid restoration of perfusion is a benefit, whereas in others, the rapid increase in blood pressure contributes to rebleeding.

Preservation of oxygen delivery is the goal of early resuscitation. Most severely injured patients requires transfusion of heterologous blood. RBC administration should begin as soon as severe hemorrhagic shock is diagnosed, without waiting for laboratory measures. Because the unresuscitated patient is losing whole blood, the hemoglobin concentration and hematocrit will not change until substantial fluid shifts have occurred. Systemic acidosis, indicated by decreased pH, elevated lactate, or abnormal base deficit, is a sensitive indicator of the need for transfusion, but even these tests take time. Waiting to begin transfusion until the patient is demonstrably anemic creates a perfusion deficit that makes later resuscitation more difficult. Early use of RBCs limits the dilutional effects of crystalloid administration, and supports oxygen delivery to ischemic tissues. Unstable patients who have active ongoing hemorrhage are resuscitated with a "whole blood" solution: equal parts of RBCs, plasma, and platelets. Even with this mixture, it is difficult to restore normal blood composition because of anticoagulant dilution and losses during storage (Table 3). Many trauma centers maintain a supply of "universal donor" type-O

Table 3
Donated versus delivered composition of blood products

Component	When donated	After fractionation	When administered to a patient in a 1:1:1 ratio
Total volume	500 mL	700 mL	700 mL
Red blood cells	Hematocrit = 45%	450 mL Hematocrit = 55%	Hematocrit = 28%
Plasma	Clotting factor activity = 100%	200 mL Activity = 90%	Activity = 65%
Platelets	Approx. 300,000/hpf	50 mL	Approximately 65,000/hpf

Donated whole blood is diluted with an anticoagulant solution and then centrifuged and fractionated, resulting in the loss of potency when that unit is "reconstituted."

blood on hand for immediate transfusion. The use of uncrossmatched type-O RBCs in this setting is highly efficacious [26].

Clotting function is critical in the patient who has ongoing hemorrhagic shock. Plasma administration to support normal prothrombin time (PT) becomes necessary with acute blood loss of 30% to 40% of the normal blood volume (1500–2000 mL), whereas platelets are needed shortly thereafter. Patients requiring more than 10 units of RBC transfusion are likely to receive comparable amounts of plasma and platelets [27]. Because of the logistic barriers involved in administering blood products, it is advisable to order plasma and platelets early in resuscitation.

Patients who have severe shock, and those bleeding very rapidly, may be coagulopathic when first encountered. It is seldom possible to reverse coagulopathy once it has started. Interest is developing in a “jump-start” approach to achieve hemostasis in acutely coagulopathic patients. This approach consists of the rapid administration of concentrated fibrinogen (in the form of 8–10 units of cryoprecipitate), platelets (1–2 pheresis units), and recombinant clotting factor VIIa (FVIIa; 90 mcg/kg). Therapy with FVIIa in nonhemophiliacs is not approved by the Food and Drug Administration, and carries an unknown risk of provoking a thromboembolic complication [28], but has been reported to be a successful adjunctive therapy [29].

Rapid transfusion may lead to the development of hypocalcemia, caused by the binding of calcium by the anticoagulant in stored blood components. This “citrate intoxication” is diagnosed by decreased ionized calcium, and is treated by calcium administration to preserve cardiac contractile function [30]. Empiric calcium therapy should be considered in the hypotensive patient who is receiving blood quickly. Abnormalities in other electrolytes are less likely during massive resuscitation, although hyperkalemia can result from ongoing acidosis, wash-out of ischemic vascular beds, and lysis of transfused RBCs.

Hypothermia improves outcomes in carefully controlled animal models of shock, but is not recommended for humans [31]. Coagulation is affected strongly by temperature, and hypothermia may lead to increased hemorrhage. The use of fluid warming systems, warmed operating rooms, and forced hot air blankets is recommended strongly.

Controversies

Older patients have decreased physiologic reserve, compared with younger patients. Blood loss will produce hypotension earlier, and a smaller dose of shock will lead to organ system dysfunction. Diagnostic and therapeutic precision is important in this population, as is a high index of suspicion for medical conditions that predate the trauma. One of these is the routine use of anticoagulant medications such as aspirin, clopidogrel, or coumadin. Providers must seek medical history from the patient’s family, and act quickly to reverse acquired coagulopathies with plasma, platelets, or factor

VIIa [32]. A higher blood pressure target is appropriate in patients who have hypertension at baseline.

Traumatic brain injury per se does not contribute to shock, but it does have a profound effect on outcome [33]. Deliberate hypotension in hemorrhaging patients who have traumatic brain injury is controversial, because of the known association between hypotensive episodes and worsened outcomes from traumatic brain injury. Limited laboratory data indicate that control of hemorrhage is still the most critical variable, and that a lower than normal blood pressure target is appropriate if death from hemorrhage is the greater risk [34].

Summary

Hemorrhagic shock is triggered by hypoperfusion caused by blood loss, but perpetuated by ongoing systemic responses. Current treatment concepts focus on diagnosis by evidence of tissue ischemia (rather than abnormal vital signs), rapid anatomic control of hemorrhage, facilitation of hemostasis, and maintenance of blood composition. Future advances will be driven by the ability to manipulate clotting directly, by improved monitoring of tissue perfusion, and by an understanding of the inflammatory consequences of shock and how best to manage them.

References

- [1] Runciman WB, Sjowronski GA. Pathophysiology of haemorrhagic shock. *Anaesth Intensive Care* 1984;12:193–205.
- [2] Peitzman AB. Hypovolemic shock. In: Pinsky MR, Dhainaut JFA, editors. *Pathophysiologic foundations of critical care*. Baltimore (MD): Williams & Wilkins; 1993. p. 161–9.
- [3] Chun K, Zhang J, Biewer J, et al. Microcirculatory failure determines lethal hepatocyte injury in ischemic-reperfused rat livers. *Shock* 1994;1:3–9.
- [4] Peitzman AB, Corbett WA, Shires GT III, et al. Cellular function in liver and muscle during hemorrhagic shock in primates. *Surg Gynecol Obstet* 1985;161:419–24.
- [5] Eiseman B. Pulmonary effects of nonthoracic trauma. *J Trauma* 1968;8:649–50.
- [6] Committee on Trauma, American College of Surgeons. *Advanced trauma life support program for doctors*. Chicago: American College of Surgeons; 1997.
- [7] Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. *J Trauma* 1993;35:584–8.
- [8] Moore EE. Staged laparotomy for the hypothermia, acidosis, coagulopathy syndrome. *Am J Surg* 1996;72:405–10.
- [9] Scalea TM, Henry SM. Assessment and initial management in the trauma patient. *Problems in Anesthesia* 2001;13:271–8.
- [10] Wall MJ, Storey JH, Mattox K. "Indications for thoracotomy." In: Mattox K, Feliciano DV, Moore EE, editors. *Trauma*, 4th edition. New York: McGraw-Hill; 2000. p. 475.
- [11] Cowley RA, Turney SZ, Hankins JR, et al. Rupture of thoracic aorta caused by blunt trauma. *J Thorac Cardiovasc Surg* 1990;100:652–61.
- [12] Rotondo MF, Schwab CW, McGonigal MD, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993;35:375–82.

- [13] Olson SA, Burgess A. Classification and initial management of patients with unstable pelvic ring injuries. *Instr Course Lect.* 2005;54:383–93.
- [14] Stern A, Dronen SC, Birrer P, et al. Effect of blood pressure on haemorrhagic volume in a near-fatal haemorrhage model incorporating a vascular injury. *Ann Emerg Med* 1993; 22:155–63.
- [15] Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. *Lancet.* 2004;363:1988–96.
- [16] Shaftan GW, Chiu C, Dennis C, et al. Fundamentals of physiologic control of arterial hemorrhage. *Surgery* 1965;58:851–6.
- [17] Capone A, Safar P, Stezoski SW, et al. Uncontrolled hemorrhagic shock outcome model in rats. *Resuscitation* 1995;29:143–52.
- [18] Shoemaker WC, Peitzman AB, Bellamy R, et al. Resuscitation from severe hemorrhage. *Crit Care Med* 1996;24:S12–23.
- [19] Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105–9.
- [20] Hambly PR, Dutton RP. Excess mortality associated with the use of a rapid infusion system at a level I trauma center. *Resuscitation* 1996;31:127–33.
- [21] Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma* 2002;52:1141–6.
- [22] Blow O, Magliore L, Claridge JA, et al. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma* 1999;47:964–9.
- [23] Abou-Khalil B, Scalea TM, Trooskin SZ, et al. Hemodynamic responses to shock in young trauma patients: need for invasive monitoring. *Crit Care Med* 1994;22:633–9.
- [24] Rhee P, Koustova E, Alam HB. Searching for the optimal resuscitation method: recommendations for the initial fluid resuscitation of combat casualties. *J Trauma* 2003;54(5 Suppl): S52–62.
- [25] McIlroy DR, Kharasch ED. Acute intravascular volume expansion with rapidly administered crystalloid or colloid in the setting of moderate hypovolemia. *Anesth Analg* 2003;96: 1572–7.
- [26] Dutton RP, Shih D, Edelman BB, et al. Safety of uncrossmatched type-O red cells for resuscitation from hemorrhagic shock. *J Trauma* 2005;59:1445–9.
- [27] Como JJ, Dutton RP, Scalea TM, et al. Blood transfusion use rates in the care of acute trauma. *Transfusion* 2004;44:809–13.
- [28] O’Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;295:293–8.
- [29] Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004;57:709–19.
- [30] Maitra SR, Geller ER, Pan W, et al. Altered cellular calcium regulation and hepatic glucose production during hemorrhagic shock. *Circ Shock* 1992;38:14–21.
- [31] Dutton RP. Hypothermia and hemorrhage. In: Spiess BD, Spence RK, Shander A, editors. *Perioperative transfusion medicine*. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 481–6.
- [32] Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant factor VII concentrate. *Ann Intern Med* 2002;137:884–8.
- [33] Chestnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993;34:216–22.
- [34] Novak L, Shackford SR, Bourguignon P, et al. Comparison of standard and alternative pre-hospital resuscitation in uncontrolled hemorrhagic shock and head injury. *J Trauma* 1999; 47:834–44.