Experimental Models of Hemorrhagic Shock: A Review

A. Fülöp  Z. Turóczi  D. Garbaisz  L. Harsányi  A. Szijártó
1st Department of Surgery, Semmelweis University, Budapest, Hungary

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Abstract
Massive blood loss leading to hypovolemic shock is still a life-threatening situation. Recently, a great number of investigations have been conducted in order to understand the pathophysiological and immunological changes taking place during shock and to develop treatment strategies. These preclinical trials are based on animal studies. Although a wide spectrum of species and experimental models are available to researchers, it is rather difficult to create an ideal animal model to study hemorrhagic shock. A major challenge for investigators is the generation of a system which is simple, easily reproducible and standardized, while being an accurate replica of the clinical situation. The goal of this review is to summarize the current experimental models of hemorrhagic shock, highlighting their advantages and disadvantages to help researchers find the most appropriate model for their own experiments on hypovolemic shock.

Introduction

Shock is a functional abnormality of the circulatory system. During this condition there is a permanent difference between the capacity of blood vessels and the intravascular volume, which leads to decreased tissue perfusion, cellular hypoxia and metabolic damage (anaerobic glycolysis and lactacidemia) caused by microcirculatory disorder.

Hemorrhagic shock is one of the most common types of shock. Hemorrhage is the leading cause of morbidity and mortality in surgery and trauma patients [1]. As a result of blood loss, the ventricular diastolic filling becomes insufficient and the heart is unable to provide optimal blood flow to cells and tissues. Initially, compensatory mechanisms (neurohumoral changes such as release of catecholamines, antidiuretic hormone and atrial natriuretic peptide...
resulting in arterial vasoconstriction and increased heart rate) are able to maintain blood pressure and redistribute cardiac output in favor of vital organs such as the brain and heart [2, 3]. However, the compensatory mechanisms are limited, and without early and effective therapy, severe cellular hypoxia and organ damage may occur, which may lead to death [4].

In recent decades, serious efforts were made to understand hypovolemic shock. A great number of preclinical trials were conducted to study pathophysiological and immunological changes during shock and to find sufficient treatment strategies. These preclinical trials are based on animal studies.

The goal of this review is to summarize the current experimental models of hemorrhagic shock, highlighting their advantages and disadvantages to help researchers find the most appropriate model for their own experiments.

Animal Models

Most of our knowledge about the pathophysiology of hemorrhagic shock comes from examination of different species. As Swanson et al. [5] wrote, ‘the biomedical models are determined as surrogates for a human biologic system, that researchers use to understand physiological and pathological function of the human body and to provide a basis therapeutic intervention in diseases’.

An ideal animal model is easy to perform and suitable for drawing meaningful conclusions. A good model is a simplified, miniature counterpart of the mimicked system, which creates conditions essential for investigation. While important information can be obtained from studying model organisms, one should be extremely careful when drawing generalizations about various organizations. The different genetic background of different species can result in distinct systemic responses to the same insult. Therefore, it is by no means certain that the results can be applied to human cases.

Various types of species are used as models for the study of hemorrhagic shock. When selecting the appropriate species, several factors should be considered, for instance availability, costs (food and housing requirements), ethical issues (government laws and restrictions) and similarities to human anatomy and physiology.

Using hemorrhagic shock models for studies has two basic aims: (1) to investigate the underlying pathophysiological and pathological changes of disease and (2) to test potential preclinical approaches of therapies. Small animals are primarily used to examine the pathogenetic mechanisms of hemorrhage, while large animals are more suitable for preclinical evaluation of treatment strategies [6].

Small Animal Models

Mice are commonly used to study hemorrhagic shock. The important advantages of these animals are their cheapness, easy accessibility, short breeding time and life span, as well as the easy possibility to perform genetic modifications (knock-outs and transgenic animals). Their main disadvantages are small size and low total blood volume, which significantly complicate surgical and sampling procedures [7].

Rats are popular experimental animals as well. Because of their larger size, surgical maneuvers are technically easier to perform and more sophisticated shock models can be designed as compared to mice. Moreover, Hauser [8] reported that in rats, certain immune responses to hemorrhage may be parallel to those in humans.

However, both mice and rats are genetically distant from humans, and their cardiovascular responses to blood loss may differ as well; thus, studies carried out on small animals often require further investigations in larger animals before clinical testing.
Large Animal Models

Dog preparations are among the oldest and best studied models in hemorrhagic shock research. Their larger size makes them ideal for investigations in the field of trauma and surgery (surgical maneuvers and sampling procedures are simpler); therefore, a number of relevant methods for creating hypovolemic shock have been described. Unfortunately, cardiovascular shock responses in dogs may not parallel those of humans. Dog spleen – as a blood reservoir – contracts during hemorrhage and increases circulating blood volume, left ventricular preload, cardiac output and hematocrit [9]. For this reason many researchers perform splenectomy before induction of hemorrhagic shock to avoid the variable degrees of autotransfusion [10, 11].

Pigs have also long been used in the study of hemorrhagic shock owing to their similarities to humans with regard to blood clotting mechanisms and cardiovascular and hemodynamic responses to hemorrhagic shock [12].

However, the use of pig, dog and other large animal (e.g. sheep) models has some practical disadvantages. Animal handling is financially demanding, there are very few immunologic markers available to follow the progress of the posttraumatic immune responses [13] and ethical issues are involved as well. Furthermore, these animals are also genetically distant from humans.

Primate Models

Genetically, primates are the closest animals to humans [14]. They possess similar physiologic responses to stress and hypovolemic shock, and their drug metabolism is highly homogeneous to that of humans [15, 16]. Despite these advantages, experiments with primates are almost unaffordable for most laboratories; moreover, the use of these animals raises a number of ethical problems as well. For this reason, they are used relatively rarely.

Types of Models

In the case of hemorrhagic shock, the major challenge in setting up an adequate model is to mimic accurately the clinical situation, while maximizing reproducibility and standardization.

There are 3 basic models generally used in the study of hemorrhagic shock: (1) fixed-volume hemorrhage; (2) fixed-pressure hemorrhage, and (3) uncontrolled hemorrhage.

Fixed-Volume Hemorrhage

In these animal models, a predetermined percentage of the total calculated blood volume is removed over a time period set by the observer. Another strictly defined interval is then allowed for natural compensation. Finally, the animals are returned to their cage or are resuscitated usually with collected blood or lactated Ringer’s solution [17].

The primary advantage of such models is that the physiological hemodynamic responses and the other natural compensatory mechanisms can be investigated following a specific volume of acute blood loss. On the other hand, the degree of hypotension is not properly defined; thereby, its effect cannot be adequately assessed and it is difficult to maximize experimental standardization and reproducibility. Moreover, in rats, the blood volume/body weight ratio decreases linearly with animal weight between 100 and 400 g (larger animals have more fat and therefore relatively less blood), significantly affecting the results. It is therefore imperative to control weight during the trial [18].

Nevertheless, this method is widely used by researchers to study shock-induced physiological and pathophysiological changes (carbohydrate metabolism, blood glucose and liver glycogen levels, anaerobic glycolysis and lactacidemia), histopathological abnormalities and...
the efficacy of different therapeutic interventions (table 1). According to Advanced Trauma Life Support, if the bleeding rate exceeds 40% of circulating blood volume (class IV), the mortality rate is more than 30% in the clinical scenario [19]. Most investigators attempt to recreate this level of shock [12, 20–49] (table 2).

**Fixed-Pressure Hemorrhage**

Penfield [50] was the first to create the basics of the fixed-pressure system. In his experiment, the animals were bled until the arterial pressure reached a predetermined level, which was then maintained as best as possible by repeated hemorrhage or by fluid infusion if necessary. Later, Wiggers [51] created the classic model of fixed-pressure hemorrhage. In this experiment, animals were catheterized under anesthesia, enabling control of the volume of

<table>
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<td>Hemodynamic variables (see above)</td>
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<td>Cytokine levels and other markers of systemic inflammatory response</td>
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<td>Amount of blood loss/evidence of rebleeding</td>
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<td>Amount of fluid/blood required for resuscitation</td>
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<td>Coagulation function/hemostatic potential</td>
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<td>Hemodynamic variables (see above)</td>
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<td>Cytokine levels and other markers of systemic inflammatory response</td>
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blood removed and of the desired intensity of hypotensive shock. Catheters also provided access to resuscitation and drug delivery.

The primary advantage of this model is that the degree and duration of hypotension are accurately controllable by means of monitoring the blood pressure. Therefore, regarding experimental standardizations and reproducibility, the constant-pressure approaches are more reliable compared to fixed-volume models. Thus, this method can be used as a pathogenesis model to evaluate physiological changes and organ/tissue injuries at specific central pressures after hemorrhagic shock (table 1). However, isobaric models do not adequately reflect the clinical situation. The animals are under general anesthesia, and heparin is often used to suppress thrombosis and to protect the blood flow through the catheter; however, these drugs affect the results significantly (see below) [52].

Modifications of the Wiggers hemorrhagic shock preparation are widely used to this day, although there is no agreement on the blood pressure level and shock length required to set up a reliable hemorrhagic shock model. The mean arterial pressure varies between 20 and 55 mm Hg depending on the examiner and the species. This hypotensive shock state is maintained for 15 min, or in some studies for more than 3 h [53–76] (table 3).

### Uncontrolled Hemorrhage

The fixed-volume and fixed-pressure models detailed above are easily reproducible and the individual test results are closely comparable. In an uncontrolled hemorrhage model, which is induced by a standardized vascular trauma (crush/laceration of liver and spleen, artery injury, amputation of appendage), the aforementioned experimental control cannot be achieved precisely; nonetheless, this model is clinically the most relevant. Considering that only the normal hemostatic mechanisms of animals can influence the progression of hemorrhage, these models seem to be the best way to preclinically test the various therapies.

According to earlier researches – performed in the 1950s and 1960s and based mostly on controlled (closed-vessel) hemorrhagic shock models – rapid fluid administration was the approved therapy for hypotension due to blood loss. In the 1990s, the use of uncontrolled (open artery) hemorrhage models led to a paradigm shift. These studies showed that aggressive fluid resuscitation before surgical control of hemorrhage increases bleeding and decreases survival due to inhibition of the formation of thrombus [17]. It should be mentioned that Cannon et al. [77] had already suggested this possibility in the early 1900s: ‘Injection of a fluid that will increase blood pressure has dangers in itself. Hemorrhage in case of shock may not have occurred to a marked degree, because blood pressure has been too low and the flow too scant to overcome the obstacle offered by the clot. If the pressure raised before the surgeon is ready to check the bleeding that may take place, blood that is sorely needed may be lost.’

### Table 2. Fixed-volume hemorrhage

<table>
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<tr>
<th>Species</th>
<th>Estimated blood volume ml/kg</th>
<th>Shed blood volume % of EBV</th>
<th>Ref. No.</th>
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</table>

EBV = Estimated blood volume.
In the last decade, more sophisticated uncontrolled hemorrhagic shock models evolved, especially with regard to studies on the efficiency of different fluid resuscitation strategies and other interventions such as hypothermia and hemostatic products [78–93] (tables 1, 4).

Recently, some authors have reported initial differences in the hemodynamic responses between controlled and uncontrolled hemorrhage. In cases of fixed-pressure and fixed-volume hemorrhage, there is a predictable relationship between blood volume and blood pressure; in the event of uncontrolled hemorrhage there is inequality in the extent of hypotension and the magnitude of blood loss. Based on this observation, certain other factors are suggested to influence blood pressure regulation in uncontrolled hemorrhagic shock. Sondeen et al. [94] hypothesized that the rate of blood loss may attenuate the baroreflex response in uncontrolled hemorrhage, perhaps by the Bezold-Jarisch reflex (depressor reflex), leading to a vagal nerve-mediated withdrawal of venous sympathetic tone and consequential reduction of cardiac output and mean arterial pressure. Other studies showed that the nociceptive stimulation of somatic afferent nerves or tissue injury (caused by induction of uncontrolled hemorrhage) can also modify the hemodynamic response to hemorrhage [95]. Nevertheless, further investigations are needed to understand this hemodynamic difference between controlled and uncontrolled hemorrhage.
Hemorrhagic Shock Models Based on Oxygen Debt

The last century brought significant developments regarding the definition of shock. In 1941, Blalock [96] characterized shock as ‘a peripheral circulatory failure, resulting from a discrepancy in the size of the vascular bed and the volume of the intravascular fluid’. Nowadays, the attention of researchers is focused on inadequate tissue perfusion and oxygenation. This is reflected in the present definition of shock by the American College of Surgeons [97]: ‘Shock is an abnormality of the circulatory system that results in inadequate organ perfusion and tissue oxygenation.’ Due to the critical decrease of tissue perfusion, disparity occurs between the oxygen consumption and oxygen delivery of cells, and oxygen debt develops [98]. Crowell and Smith [99] were the first to describe the relationship between oxygen debt and shock severity. This study led to the development of the fourth general category of hemorrhagic shock models, based on shock-induced oxygen debt [100]. Dunham et al. [101] were the first to create a dog model in which the primary endpoint was oxygen debt independent of blood pressure or hemorrhage volume. This and subsequent studies highlighted that oxygen debt and the metabolic consequences (lactic acidemia and base deficit) reflect the extent of tissue and organ damage better than the traditional variables such as bleeding volume and blood pressure.

Confounding Variables

Despite careful planning of experiments, complications may be caused by several variables; the most important ones are detailed below.

Gender is a determining factor in these experiments. Several clinical and experimental studies show some differences between males and females in terms of susceptibility to shock, trauma and sepsis. Diodato et al. [102] showed that females have a survival advantage over males in a ‘two-hit’ model of hemorrhagic shock (first hit) and subsequent sepsis (second hit). It was previously demonstrated that the cell-mediated immune response is depressed in males, while it is maintained or increased in females after hemorrhage. It is assumed that female sex hormones are responsible for maintaining immune function following hemorrhage [103].

Age is also an important factor in clinical and experimental models of hemorrhagic shock. Nickel et al. [104] showed that in mice, the immune response decreases with age following the presence of a harmful agent. Later, Matsutani et al. [105] demonstrated that hepatic damage after shock in combined multiple traumas and hemorrhage is dependent on age in mice.

Hemorrhagic animal models, in particular when combined with other types of tissue trauma, require anesthetic and analgesic drugs to eliminate pain. However, anesthesia usually depresses respiration, reduces metabolic demand [106], influences the central nervous system [107] and moderates cardiovascular compensatory mechanisms [108]. Furthermore, certain anesthetics change the immune function (production of cytokines and activity of natural killer cells) [109] and may facilitate bacterial translocation [110].

As a result, the use of conscious models is essential in order to estimate the cardiovascular, neuroendocrine and immune responses to hemorrhage correctly. Accordingly, many researchers seek to minimize the length of anesthesia. Le Page [111] was the first to study fixed-volume hemorrhagic shock in the absence of anesthesia; rats were temporarily anesthetized with ether and restrained in the supine position, then after awakening bleeding was induced by cutting the tail until circulatory failure occurred. As an alternative to this, Collins and Stechenberg [112] used femoral arterial catheters to induce shock. Sayeed and Baue [113] transformed the latter procedure into a fixed-pressure model; rats were anesthetized with ether and restrained in a sling, and both femoral arteries were cannulated. One of the arteries was used to check blood pressure, the other for blood withdrawal until the mean arterial pressure decreased to 40 mm Hg. This pressure was then maintained as best as possible by means of repeated hemorrhage or saline in fusion when required [113].
An essential issue is the use of heparin, especially in the case of fixed-pressure models. In his experiment, Wiggers [51] already observed that blood clots increased after bleeding; he therefore used heparin to prevent catheter clotting. This approach differs significantly from the clinical situation. In addition, preheparinization significantly ameliorates the microvascular status. The underlying mechanism is still not fully understood. It is assumed that heparin influences the serum levels of catecholamines and cytokines, blood viscosity, endothelial cell interactions and the coagulation cascade [114].

Trauma and surgery patients usually suffer from other tissue or organ injuries besides hemorrhagic shock. It is known that tissue damage can alter hemodynamic and inflammatory responses to acute blood loss. Cytokines released from injured tissue significantly alter organ dysfunction related to bleeding [115]. Thus, a clinically relevant model must take into account these conditions as well. In the following, hemorrhagic shock models combined with other injuries are detailed.

**Hemorrhagic Shock Combined with Traumatic Injury**

Trauma (caused by accidents, especially car crashes) is one of the leading causes of hypovolemic shock and death. Trauma patients suffer from soft tissue injuries and fractures as well as internal organ damage. Many models combined with hemorrhagic shock and other injuries were developed for the more accurate understanding of such life-threatening clinical conditions.

Mostly fixed-pressure hemorrhagic models are used to examine the aggravating effect of soft tissue injury on blood loss. In this instance, after the state of shock, tissue damage is usually caused by abdominal incision. Chaudry et al. [116] observed that mortality after laparotomy and hemorrhagic shock was significantly higher than after shock alone. The studies of Lu et al. [117] showed that ischemic damage of the small intestine was increased considerably after laparotomy.

Bone fractures, especially long bone fractures, may result in severe tissue injuries and significant blood loss. Most often, models combined with hemorrhagic shock and femur/tibia fracture are used for examination of this condition. Redl et al. [72] created hind limb fracture in a fixed-pressure hemorrhagic dog model. They were able to draw useful conclusions related to a trauma-induced increase in lung water content. Gill et al. [118] assessed systemic inflammation and subsequent organ damage caused by bilateral femur fracture connected to hypovolemic shock.

A number of models combined with internal organ injuries and hemorrhage were also developed. Significant abdominal bleeding and a subsequent state of shock are often caused by liver and spleen laceration. During such experiments, the rate of bleeding is not controlled, which complicates standardization of these operations. Krausz et al. [119] provoked circulatory failure by spleen injury in rats, while Brundage et al. [120] induced the same in pigs by grade V liver injury (parenchymal damage involving more than 75% of liver mass accompanied by juxtahepatic venous injuries) to examine the changes in serum cytokine levels after trauma.

The clinically most relevant experimental settings are the multiple trauma models combined with hemorrhagic shock. However, during these experiments the animals suffer from excessive stress, causing their death in an early phase of the studies. Moreover, because of the complexity of the operations, repetition of measurements is complicated. Howes et al. [121] investigated the effect of recombinant factor VIIa in a polytraumatic (femur fracture, liver laceration and soft tissue crush injury) pig model. Alam et al. [122] examined the efficacy of treatment with valproic acid in pigs using a highly lethal polytrauma and hemorrhagic shock model (femur fracture, 60% hemorrhage (mean arterial pressure 25–30 mm Hg) and grade V liver injury).
Lower Limb Ischemia-Reperfusion Injury and Hemorrhagic Shock

An extremity wound with macrovascular injury and bleeding quickly leads to a state of shock and, without intervention, to death. Recently, tourniquets have been used for hemorrhage control, especially in military trauma care. After an extended period of time, the use of a tourniquet can result in ischemia-reperfusion injury of the skeletal muscle once the tourniquet is released. Kauvar et al. [123] compared the effect of Ringer’s lactate solution and Hextend in these conditions in rats. They used carotid arterial catheters to remove 67% of the total blood volume and to induce shock. At the time of development of shock, they placed a pneumatic digital tourniquet around a randomly selected hind limb on which they induced a 3-hour-long limb ischemia [123]. In a very similar model, Labruto et al. [124] examined the effect of lazaroid against ischemia-reperfusion injury. After the lazaroid pretreatment, they produced a 2-hour-long shock state, then performed fluid resuscitation with blood and Ringer’s lactate solution. From the beginning of shock to the end of resuscitation, they used a tourniquet around one of the lower limbs. After removal of the tourniquet, the animals were observed for a further 3.5 h [124].

Ruptured Abdominal Aortic Aneurysm and Hemorrhagic Shock

Critical levels of blood loss may develop during the most serious complication of abdominal aortic aneurysm, the rupture of the aneurysm sac. Prehospital survival is only possible if the bleeding does not break into the peritoneum and is tamponed by the surrounding tissues. The principal therapy of the disease is surgical, but appropriate pre- and intraoperative fluid administration is just as crucial. The mortality rate of the disease is still around 40–50%, so a great number of preclinical studies have been and are still currently being conducted [125].

The simulation of the clinical setting is usually achieved by abdominal aortic tear or aortotomy. Owens et al. [126] compared standard (to 100% of baseline) and limited (to 60% of baseline) prehospital resuscitation after abdominal aortic tear in pigs while examining the volume of intraperitoneal bleeding and hemoglobin loss. Later, numerous similar studies were conducted with a very low mortality rate in untreated control groups. Apparently, the resulting damage is incapable of causing life-threatening blood loss. Therefore, Kowalenko et al. [127] modified the procedure as follows: prior to creating an aortotomy, animals were exsanguinated from a femoral artery catheter to achieve a mean arterial pressure of 30 mm Hg. Animals were then bled with aortic tear until reaching an arterial pressure of 5 mm Hg [127].

Harkin et al. [128] set up a rat model to examine ruptured abdominal aortic aneurysm, including the vascular occlusion used during the surgical procedure. In this event, a ‘two-hit’ lower limb ischemia-reperfusion injury and a subsequent systemic inflammatory response syndrome are assumed, caused by hemorrhagic shock and aortic clamping. Anesthetized rats underwent 1 h of hemorrhagic shock (mean arterial blood pressure <50 mm Hg), followed by 45 min of supramesenteric aortic clamping, then 2 h of resuscitated (with shed blood and Ringer’s lactate solution) reperfusion [128].

Conclusions

Animal experiments still have an essential role in the field of medical research. A major challenge for investigators is to generate a system which is simple, easily reproducible and standardized, at the same time being an accurate replica of the clinical circumstances of patients with life-threatening hemorrhage.

Due to their unique characteristics, it is difficult to decide which of the hemorrhagic shock models is the most suitable. Considering controllability and reproducibility, the pressure- and volume-controlled models are preferred to uncontrolled hemorrhage models, since they
are more appropriate for studies on the pathophysiology of shock and exploratory assessment of therapies. On the other hand, uncontrolled hemorrhage models, especially combined with other traumas, are more clinically relevant and more suitable for preclinical testing of various treatment strategies.

However, it is important to recognize the conflict between the aims of researchers and the clinical reality. In order to reduce confounding variables, research scientists usually use healthy animals of the same sex and age and reduce the reality to a specific part of the whole complex clinical situation (bleeding, hypothermia, hypotension, hypoxia, acidosis, coagulopathy and commonly accompanying tissue or organ injury). Furthermore, the fact that differences exist between human and animal physiology makes it significantly difficult to draw conclusions regarding clinical reality. Despite these considerations, carefully planned, complex preclinical trials are necessary for more accurate analysis of the conditions of hemorrhagic shock.

**Disclosure Statement**

The authors report no conflicts of interest.

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