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Hemorrhagic shock: an overview of animal models

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1. ABSTRACT

Extensive efforts have been made to try to elucidate the pathophysiological mechanisms and the immunologic alterations associated with severe hemorrhage. A broad variety of experimental conditions have been established that enable investigators to study the effects of hypovolemic shock and to assess the potential benefits of a wide spectrum of treatment options. However, translating these experimental findings into clinically applicable therapy has been challenging, suggesting the need for a better understanding of the animal models being used. As certain advantages and disadvantages are associated with the different models of hemorrhage (such as controlled and uncontrolled hemorrhagic shock and combined trauma with hemorrhagic shock models, for this review, we have selected representative studies that reflect the current status of experimental shock research that looks at acute blood loss, and that may serve as a guide when considering which model or models to apply

2. INTRODUCTION

Hemorrhagic shock accounts for majority of deaths in both combat injuries and civilian trauma. Data from Vietnam War shows that around 50% of deaths are caused by torso and peripheral exsanguinations(1). Also, trauma and bleeding are the reasons for most of the deaths in young people, even more than all other reasons together.

Most of what we know about hemorrhagic shock is from studies on animal models. For decades, considerable efforts have been made to develop experimental hemorrhagic shock model to investigate the pathophysiological mechanisms of shock and to evaluate the efficacy of different therapeutic options. However, transiting the experimental results to clinical application is challenging, and there is still a need for better understanding of the animal models being used.

In this chapter we have reviewed currently used hemorrhagic shock models of different animal species and

for various purposes. The advantages and disadvantages of these models have also been discussed.

3. MODELS OF HEMORRHAGIC SHOCK – CONTROLLED AND UNCONTROLLED

Basically, there are two types of experimental animal model of hemorrhagic shock: controlled hemorrhage and uncontrolled hemorrhage. Controlled models are either of fixed-pressure or of fixed-volume.

3.1. Fixed-pressure hemorrhagic shock model

Many investigators today use a modification of the fixed-pressure model of hemorrhagic shock described by Wiggers(2). In this model, anesthetized animals are bled to a predetermined mean arterial pressure and are maintained at that pressure, with periodic bleeding, for a specified period of time based on the animal species as well as on the degree or outcome of hypotensive shock. Mean arterial pressures varying from 70 to 35 mm Hg and durations as short as 30 min(3,4,5,6,7,8,9,10) and as long as 5 h have been studied. Fixed-pressure hemorrhage enables the investigator to regulate the intensity of hypotensive shock administered based on physiological and end-organ injury outcome, an important consideration in designing therapeutic interventions. This model has been used to study the effects of hypotensive shock on inflammatory responses, and on gut(11,12,13), liver(14,15), lung(16,17), adrenal(10), cardiovascular function alterations(18,19,20), immunological system changes(21,22) as well as the effects of various resuscitation strategies(23,24) on organ function and outcome .

Several studies have examined the physiological complications of severe blood loss. Also, the significant advantage of fixed-pressure hemorrhagic shock model is its excellent reproducibility and standardization. However, this model does not reveal the real life situation of uncontrolled hemorrhage in field settings. Moreover, fixed-pressure model eliminates the physiological self-compensation mechanisms that occur as the patient bleeds.

3.2. Fixed-volume hemorrhagic shock model

Besides fixed-pressure hemorrhagic shock model, fixed-volume hemorrhagic shock model is another commonly used model by investigators. In this model, a fixed blood volume, usually calculated by the percentage of body weight, and then translated to the percentage of total circulating blood volume, is drawn. After withdrawal of certain volume of blood, the blood pressure is not maintained during the shock period. Although fixed-volume bleeding can be performed without catheterization (for example, orbital bleed or cardiac stick), the animal typically is anesthetized and catheterized for blood withdrawal, physiological monitoring, and resuscitation and administration of therapy. After hemorrhage, the animal is either monitored or resuscitated.

The shed volume varies from 20%(25,26), 33%(27), 35%(28), 40%(29,30), 50%(31), 55%(32,33,34), to 60%(35) of total circulating blood volume, or 30ml/kg(36), 45ml/kg(37) of body weight.

This model is usually used to investigate organ damages such as gut(38), cardiovascular function alterations(26,33), subsequent central nervous system and spinal injuries(39), immunological changes(32) and fluid resuscitation(26,28,30,32,33,35,40).

An advantage to this model is the ability to elucidate an animal's hemodynamic response specific to a fixed volume of blood loss. However, conversion from volume-to-body weight to volume-to-total circulating blood volume differs from species to species and even differs from individual to individual within same species. The reproducibility and standardization of this model, thus are not as reliable as fixed-pressure model.

Both fixed-pressure and fixed-volume hemorrhagic shock model provide investigators with standardized and easy-to-handle models and allow the studies of shock mechanisms and therapeutic strategies under controlled condition. Shock severity and duration can be controlled to satisfy the purpose of the research.

3.3. Uncontrolled hemorrhagic shock model

Although fixed-volume and fixed-pressure hemorrhagic shock models offer a controlled manipulation of blood loss, these models do not truly resemble the uncontrolled hemorrhage situation observed in trauma patients. Of primary interest have been the timing, volume, and nature of resuscitation fluid given to hemorrhaging trauma patients. Fluid resuscitation has been studied in different animals by a number of investigators. Uncontrolled hemorrhagic shock model allows free bleeding from either organ transaction or aorta laceration. The commonly used uncontrolled hemorrhagic shock models include: liver injury in pigs(41,42,43,44) and rats(45), 75% tail amputation in rats(46,47,48), infrarenal aorta(49,50,51), abdominal aorta(52), or aorta(53,54) laceration in pigs, common iliac artery tear in pigs(55,56) and dogs(57), and massive splenic injury in rats(58,59). In some animal models, a combination of fixed-volume blood withdrawal and uncontrolled hemorrhage is generated(46,60,61).

Uncontrolled hemorrhagic shock model is widely used to evaluate different fluid resuscitation strategies. Takasu *et al* concluded that therapeutic mild hypothermia prolongs animal survivability in a lethal uncontrolled hemorrhagic shock model in rats(62). In the rat infrarenal aorta puncture model, Burris *et al*(63) found that attempts to restore normal MABP (100 mmHg) lead to increased blood loss and mortality. Moderate improvement in MABP (80 mmHg) achieve better survivability and lower bleeding. They concluded that controlled fluid use should be considered when surgical care is not readily available.

Stern *et al*(64) evaluated the effects of comparable and clinically relevant resuscitation regimens of 7.5% sodium chloride/6% dextran 70 (HSD) and 0.9% sodium chloride (NS) in a near-fatal uncontrolled hemorrhage model. The results showed that resuscitation with HSD or NS, administered in volumes that provided equivalent sodium loads at similar rates, had similar effects

Table 1. Animals utilized for studying hemorrhagic shock

	A. Small Animals: Mouse	B. Small Animals: Rats	C. Large Animals (non-primates): Sheep, Dogs, Pigs, Rabbits	D. Primates
Advantages	-Minimal genetic variability (inbreds, knock-outs and transgenics) -Numerous reagents for mice available -Use minimal amounts of precious reagents -Low cost -Rapid reproduction	-Less genetic variability (inbreds) -Minimal physiological measurements -Large (relative to mouse) sample volume -Ease of instrumentation -Better reagents availability -Rapid reproduction	-Can obtain most clinical/physiological measurements -Large sample volume (blood & tissue) -Ease of instrumentation	-Often human reagents can be applied in this model -Can obtain most clinical/physiological measurements -Most genetically similar to humans
Disadvantages	-Physiological measurements difficult -Small sample size -Genetically different from human	-No knockouts or transgenics(increasingly being available) -Fewer reagents than for mice -Genetically different from humans	-Reagents not readily available for many cell/mol./immune assays in these models -Individual variability (not inbred) -Material costs- moderate to high -More numerous differences genetically than humans	-Individual variability (not inbred) -Costly to conduct experiments -Restricted availability and usage
Shock Models Applied	-Fixed volume/fixed pressure/uncontrolled	-Fixed volume/fixed pressure/uncontrolled	-Fixed volume/fixed pressure/uncontrolled	-Fixed volume/fixed pressure

Table 2. Advantages and disadvantages of hemorrhagic shock animal models.

Shock Model	Generation of shock	Advantage	Disadvantage
Fixed-Pressure Model	Blood is drawn until MABP decreases to a certain level. The blood pressure is then maintained, with further withdrawals, for a pre-determined period.	High reproducibility and standardization.	Does not reflect real clinic situation. Self-compensation mechanisms are not allowed.
Fixed-Volume Model	A fixed blood volume is drawn. The blood pressure is not maintained during the shock period.	High reproducibility and standardization. Self-compensation mechanisms are allowed.	Does not reflect real clinic situation.
Uncontrolled Hemorrhage Model	Bleeding is allowed freely from either organ transaction or aorta laceration.	Self-compensation mechanisms are allowed. It reflects real clinic situation.	Low reproducibility and standardization.

on mortality, hemodynamic parameters, and hemorrhage from the injury site. Bruttig *et al*52 hypothesized that a slow rate of infusion after delayed resuscitation, reflecting the clinical environment, might improve survival in the presence of uncontrolled hemorrhage. They investigated resuscitation strategy with 30 min-delay and slow infusion of 4 mL/kg hypertonic saline/Dextran solution (over 12 min) Their results showed that slow infusion of hypertonic saline/Dextran solution significantly improved animal survivability, reduced blood loss, and increased cardiac output and blood pressure.The disadvantage of this model is also obvious, that is low reproducibility and standardization.The advantages and disadvantages of each animal model utilized (Table 1) and type of hemorrhagic shock model (Table 2) respectively are summarized below.

4. CONSCIOUS ANIMAL HEMORRHAGIC SHOCK MODEL

Both controlled and uncontrolled hemorrhagic shock models usually operate under general anesthesia, which is either injectable or gaseous inhalation. However, it has been reported that anesthesia may affect the animal's cardiovascular and immunological functions(65,66,67).

Pagel *et al* demonstrated the cardiac depressant effects of various inhalational anesthetic agents(68,69). In hemorrhaged animals, anesthetic agents cause changes in basic physiologic control mechanisms, subsequently, resulting in alterations in blood flow, oxygen delivery, tissue oxygenation and even survivability(70,71,72,73,74). Therefore, the hemorrhagic shock model without anesthesia is worthy of consideration, for it most closely mimics the clinical scenario.

In a model of delayed hemorrhagic shock in conscious rats, Shirhan et al(75) found that selective inducible nitric oxide synthase inhibitors significantly reduced brain infarct volume and improved neurological performance and animal survival rate. Wettstein et al(76) resuscitated hemorrhaged conscious rats with shed blood, hydroxyethyl starch and modified human hemoglobin. They found that modified human hemoglobin greatly improved microvascular blood flow and oxygen transport. In conscious sheep hemorrhagic shock model Landau et al reported that combination of military antishock trousers and hypertonic saline increased MABP and improved cardiac output and tissue perfusion.

5. COMBINED HEMORRHAGIC SHOCK WITH MULTIPLE INJURIES

In real scenario, hemorrhagic shock usually combines with traumatic injuries. The release of cytokines and other mediators from injured tissue contributes

significantly to organ function disorders associated with shock. Various combined trauma and hemorrhagic shock models have been developed by different investigators.

5.1. Combined soft tissue injury and hemorrhagic shock

Rupani *et al*(77) investigated the effects of combined laparotomy and hemorrhagic shock on the morphological and functional changes in intestine of rats. They found that soft tissue injury and hemorrhagic shock leads to changes in the intestinal mucus layer as well as increased villous injury, apoptosis and gut permeability. Additionally, increased gut permeability was associated with loss of the intestinal mucus layer suggesting that T/HS-induced injury to the mucus layer may contribute to the loss of gut barrier function.

The premature, mature and aged mice, both male and female, were challenged with trauma and hemorrhagic shock. Sex- and age-specific effects in bone marrow differentiation and immune responses occur after trauma-hemorrhage, which are likely to contribute to the sex- and age-related differences in the systemic immune responses under such conditions.

Szalay *et al*(78) hypothesized that the induction of heat shock proteins (HSPs) contributes to the salutary effects of estradiol on cardiac and hepatic functions after trauma-hemorrhage. In rat laparotomy and hemorrhagic shock model, 17 beta-estradiol increased heart/liver HSPs expression, ameliorated the impairment of heart/liver functions and significantly prevented the increase in plasma levels of ALT, TNF-alpha and IL-6. The ability of estradiol to induce HSPs expression in the heart and the liver suggests that HSPs, in part, mediate the salutary effects of 17beta-estradiol on organ functions.

5.2. Combined traumatic brain injury (TBI) and hemorrhagic shock

Atan *et al*(79) investigated the effects of nitric oxide synthase (iNOS) inhibitors in the rat model of combined traumatic brain injury and hemorrhagic shock. Aminoguanidine (AG), a selective iNOS inhibitor, showed a significant increase in mean survival time and cerebral tissue perfusion and decreased the number of apoptotic neurons. The authors asserted that treatment with AG, which causes the inhibition of iNOS, might contribute to improved physiological parameters and neuronal cell survival following TBI and hemorrhagic shock.

Sanui *et al*(80) resuscitated TBI and hemorrhagic shocked pigs with crystalloid solution and arginine vasopressin. The results showed that early supplemental arginine vasopressin rapidly corrected cerebral perfusion pressure, improved cerebrovascular compliance and prevented circulatory collapse during fluid resuscitation after traumatic brain injury.

Gibson *et al*(81) evaluated different resuscitation regiments (saline, shed blood, and blood substitute) for combined TBI and hemorrhagic shock in pigs. They reported that resuscitation with shed blood effectively increased arterial O2 saturation (SaO2), mixed venous O2 saturation (SvO2), cerebral perfusion pressure (CPP) and cerebral venous O_2 saturation ($ScvO_2$), decreased intracranial pressure (ICP) and improved animal survival rate. Thus, whole blood was found to be more effective than saline for resuscitation of TBI/hemorrhagic shock, whereas blood substitutes were less effective than saline resuscitation.

5.3. Combined sepsis and hemorrhagic shock (two-hit model)

In laparotomy-hemorrhagic shock-sepsis (induced by cecal ligation and puncture) rats, Suzuki *et al*(82) found that androstenediol markedly decreased plasma IL-6 and TNF-alpha levels, prevented the increased production of IL-6 and TNF-alpha by Kupffer cells and alveolar macrophages and attenuated the decrease in IL-6 and TNF-alpha production by splenic macrophages. The depressed IL-2 and IFN-gamma production by splenocytes was attenuated by the administration of androstenediol. Furthermore, survival rate was improved by androstenediol treatment.

Schulman *et al*(83) investigated immune response and lung injury caused by hemorrhagic shock and sepsis. Hemorrhagic shock blunted serum TNF-alpha expression to lipopolysaccharide (LPS), but primed for increased bronchoalveolar lavage TNF-alpha. Elevated serum TNF-alpha corresponded with greater bronchoalveolar lavage neutrophil infiltration.

Coimbra *et al*(84) hypothesized that improvements in cellular immune function after hypertonic saline (HTS) resuscitation alter the outcome of sepsis after hemorrhage. Their results suggest that HTS resuscitation leads to increased survival after hemorrhage and CLP. Marked improvements were observed in lung and liver injury compared with isotonic resuscitation. The better containment of the infection observed with HTS resuscitation corresponds to a marked decreased in bacteremia. HTS resuscitation stands as an alternative resuscitation regimen with immunomodulatory potential.

6. CONCLUSION

There are wide variety of hemorrhagic shock models (controlled/uncontrolled and combined hemorrhagic shock with poly trauma) which can provide investigators with more options to investigate the pathophysiological mechanisms and therapeutic strategies. However, there must be a desire to establish a balance between clinical relevance and the need to maximize experimental standardization and reproducibility. Therefore, it is necessary for every

investigator to choose carefully which model to use to address a particular question. This chapter may serve as an initial guide in selecting a model or models of hemorrhage. In addition, we also hope to encourage the development of new models of hemorrhagic shock to better elucidate pathophysiological mechanisms and immunological alterations that shock produces, and to relieve the human, medical and economic burden of traumatic injury.

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