Impact of Hemorrhage on Trauma Outcome: An Overview of Epidemiology, Clinical Presentations, and Therapeutic Considerations

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The world-wide impact of traumatic injury and associated hemorrhage on human health and well-being cannot be overstated. Twelve percent of the global disease burden is the result of violence or accidental injury. Hemorrhage is responsible for 30 to 40% of trauma mortality, and of these deaths, 33 to 56% occur during the prehospital period. Among those who reach care, early mortality is caused by continued hemorrhage, coagulopathy, and incomplete resuscitation. The techniques of early care, including blood transfusion, may underlie late mortality and long-term morbidity. While the volume of blood lost cannot be measured, physiologic and chemical measures and the number of units of blood given are readily recorded and analyzed. Improvements in early hemorrhage control and resuscitation and the prevention and aggressive treatment of coagulopathy appear to have the greatest potential to improve outcomes in severely injured trauma patients.

Key Words: **Trauma, Hemorrhage, Epidemiology, Shock, Mortality, Multiple organ failure, Coagulopathy.**

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Trauma accounts for a significant proportion of annual mortality world-wide. The World Health Organization (WHO) estimates that in the year 2000, 5 million people died of injuries, accounting for 9% of global annual mortality. That same year, 12% of the global burden of disease resulted from injury. Over 90% of the world's trauma mortality occurs in low- and middle-income nations, with those in Eastern Europe having the highest rates. Almost 50% of those who die are between 15 and 44 years of age, with males accounting for twice as many deaths as females; death due to traumatic injury is, therefore, the leading cause of life years lost.[1] Violence—self-inflicted, interpersonal, and war-related—accounts for half of trauma mortality, with 1.6 million deaths in the year 2000. Road traffic accounts for the next largest proportion, roughly 1.2 million deaths, per year, 2.1% of overall mortality. An additional 20 to 50 million people are injured annually in road traffic incidents.[2,3]

Though most of the world's trauma mortality occurs in developing countries, trauma is a significant cause of morbidity and mortality in industrialized nations as well. In the United States in 2003, over 29 million people, more than 10% of the population, suffered nonfatal injuries. Injury was the third leading cause of death overall and the leading cause of death among those aged 1 to 44 years. In the U.S., nearly 30% of years of potential life lost before age 65 results from traumatic injury, the largest contribution of any cause of death and nearly twice that of the next leading cause, cancer.[4]

The direct economic burden of trauma care is also considerable. The youth of the affected population and the potential chronicity of disease and complications contribute greatly to the resulting social and economic burdens. A number of studies have documented the lasting impact of trauma-related morbidity and its effect on quality-of-life,[5–7] and the WHO estimates that nations can spend up to 2% of their gross domestic product caring for patients injured as the result of road traffic incidents alone.[1] The Centers for Disease Control and Prevention estimate that in the U.S. $117 billion was spent on medical care for injuries in the year 2000, representing approximately 10% of national health care spending.[8] The economic burden of trauma is also felt indirectly as lost work hours and productivity among injured patients and their caregivers. A regional study of trauma patient recovery conducted 18 months following hospital discharge revealed a 16% decrease in a standard measurement of functional well-being among trauma patients with a mean Injury Severity Score (ISS) of 13.[5] In a recent 24 month follow-up study of German multi-system trauma victims with mean ISS of 23 conducted by one of the authors (RL), the return-to-work rate was only 50%. A similar study in Spain revealed a return-to-work rate of 58% at two years.[7]

The Epidemiology of Hemorrhage in Trauma

Independent of the mechanism of injury, hemorrhagic shock consistently represents the second-leading cause of early deaths among the injured, with only central nervous

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Table 1 Studies of Trauma Mortality

Authors	Period	Location	Setting	Mechanism		Cause of Death		Comment
				% Blunt	% Pen	% Hem	% CNS	
Baker, et al[10]	1977	San Francisco	Regional	54	31	31	50	
Acosta, et al[9]	1985–95	San Diego	Center	40	60	28	43	
Shackford, et al[14]	1986–87	San Diego	Regional	71	29	31	40	
Sauaia, et al[13]	1992	Denver	Regional	49	48	39	42	6% combined Hem/CNS
Stewart, et al[15]	1995–01	San Antonio	Center	71	21	21	51	16% combined Hem/CNS
Mean				57	38	30	45	

Observational studies performed over the past 3 decades have identified the central roles of hemorrhage and head injury in producing mortality from trauma. All trauma deaths occurring in these regions or centers were included. Regional studies include prehospital and in-hospital deaths. Not included are other causes of death such as sepsis and organ failure.

Pen indicates penetrating; Hem, hemorrhage; CNS, Central Nervous System.

system (CNS) injury consistently more lethal (Table 1).[9–15] Severe CNS injury is devastating and has a high rate of prehospital mortality; and there are few interventions offering hope for survival and functional recovery.[16] In contrast, hemorrhage and hemorrhagic shock, which account for 30 to 40% of trauma deaths, are more amenable to interventions to reduce mortality and morbidity. Furthermore, about 25% of CNS injuries are complicated by shock.[15,17] Among those with multiple injuries, brain injury remains the primary cause of death, but hypotension increases mortality in this group two- to three-fold.[17,18] The significant contribution of hemorrhagic shock to brain injury mortality further illustrates the role of hemorrhage control in reducing traumatic mortality.

Early Mortality

The majority of trauma deaths occur in the first few hours following injury, often before the injured patient reaches a hospital (Fig. 1).[9,13,15] Hemorrhage contributes to death during the prehospital period in 33 to 56% of cases, and exsanguination is the most common cause of death among those found dead upon the arrival of emergency medical services (EMS) personnel.[13] Hemorrhage accounts for the largest proportion of mortality occurring within the first hour of trauma center care, over 80% of operating room deaths after major trauma, and almost 50% of deaths in the first 24 hours of trauma care.[9,12,13] After the first hours of trauma center care, CNS injury replaces hemorrhage as the leading cause of trauma mortality. Very few hemorrhagic deaths occur after the first day.[9,13]

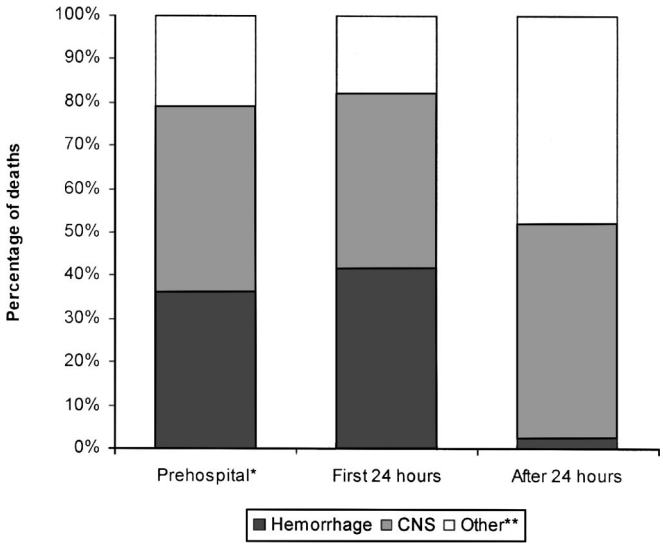

Fig. 1. *Timing and mechanism of traumatic death.*

Data adapted from Acosta et al.[9] and Sauaia et al.[13] Nearly all deaths due to hemorrhage occur within the first 24 hours of injury. The rate of death from CNS injury remains relatively constant over time. After the first 24 hours, critical care complications such as organ failure and sepsis replace hemorrhage as a major cause of trauma death.

** Prehospital data from Sauaia et al.[13] only.*

*** Other causes of death include combined hemorrhage/CNS, multiple organ failure, sepsis, and pulmonary embolism.*

CNS, central nervous system.

Late Mortality and Morbidity

Early hypotension as a marker for late mortality

The presence of hemorrhagic shock is a predictor of poor outcome in the trauma patient, and the volume of hemorrhage is tied to outcome. As the amount of blood loss increases, so do resuscitation requirements and physiologic derangements including hypotension and acidosis. The volume of blood lost has proven impossible to reconstruct, but blood pressure and the number of blood units replaced are readily measured. Hypotension noted in the field or upon initial hospital evaluation is associated not only with late mortality but also specifically with the development of eventual complications including multiple organ failure (MOF) and infections such as pneumonia and sepsis.[19,20] The presence of early hemorrhagic shock as defined by a systolic blood pressure less than or equal to 90 mm Hg in the pre-hospital setting or emergency department is associated with high rates of organ failure (24%) and infection (39%).[20]

Acidosis/Base Deficit

Early acidosis, measured as base deficit in the first hour of admission, is associated with significant hemorrhage, injury severity and hypotension.[21] Early and overall red blood cell transfusion requirements increase with increasing base deficit from a mean of 2.6 units (1.4 in the first 24 hours) in patients with mild base deficits (−3 to −5) to 9.7 units (8.3 in the first 24 hours) in patients with severe base deficits (≤−10). Base deficit also predicts the development of coagulopathy, organ failure, and mortality. Patients with mild base deficits have survival rates near those of patients without acidosis (89% versus 94%), while those with severe acidosis have a nearly 50% mortality rate.[21]

Multi-organ Failure

Not surprisingly, trauma patients die more often of the immediately uncontrollable consequences of their injuries than of late sequelae.[9,10,13,15] Delayed death is also most often due to complications developing during care rather than directly to the injuries themselves.[9,10,13] Multiple organ failure, the synchronous derangement of more than one critical organ system, is the leading cause of morbidity and mortality in the trauma intensive care unit (ICU).[22] The incidence of MOF following injury occurs in a bimodal pattern, with an initial peak within the first three days of hospitalization, and a second between 5 and 7 days.[23,24] The combined impact of this delayed mortality is 7 to 9%. The mortality rate for patients who develop organ failure is directly related to the number of involved organ systems and can exceed 50% overall, reaching over 80% fatality with four involved systems.[23,25]

Despite differences among sources in the definition of failure for individual organ systems, the incidence of MOF following major trauma does appear to have decreased over the past 15 years (Fig. 2).[26] In the early 1990's, among trauma patients with injury severity scores (ISS) 19–25, mortality was reported at 13 to 15%, while by the latter part of the decade, mortality had decreased to 5%.[23–25] A recently published, prospective, 12-year single-center study of MOF in trauma patients with a mean ISS of 29 reported nearly half the incidence of MOF in 2003 than in 1992 despite increasing injury severity over the same period.[26] Despite the apparently decreasing incidence of MOF, however, the proportion of trauma patients with MOF listed as the cause of death remained essentially unchanged; 7% in the early 1990's and 9% later in the decade.[13,15] Similarly, throughout the follow-up period, essentially half of all trauma patients diagnosed with MOF died.[23,25]

Sepsis

Contaminated and devitalized tissue leading to post-injury derangement of immune function puts trauma patients at high risk for sepsis. The inflammatory modulation and resulting derangement of immunity induced by hemorrhagic shock is similar to that seen in sepsis and MOF and is likely mediated through the activity of similar cytokines and pathways.[27] The statistical association of massive transfusion for hemorrhagic shock with the development of MOF and with overall mortality may also be a reflection of immuno-modulation but this link has not yet been fully elucidated.[23,25,28,29]

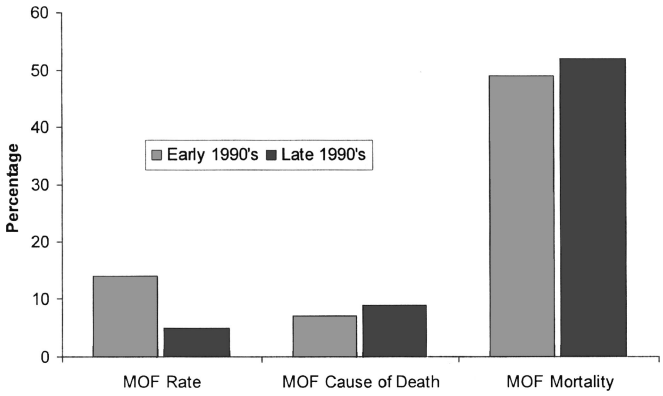

Fig. 2. *Multiple organ failure in trauma patients through the 1990s. Data adapted from Sauaia et al. 1994,[23] Sauaia et al. 1995,[13] Moore et al.,[22] Stewart et al.,[15] and Durham et al.[21] While the rate of MOF has decreased in trauma patients, reflective of improvements in critical care, the proportion with it as a cause of death has not decreased over time. The mortality of MOF remains stable as well. Ciesla et al.[20] have recently published their experience with MOF from 1992 through 2003 and reported that these trends continue.*

MOF, multiple organ failure.

Clinical Presentations in Trauma Hemorrhage

Causes of injury

Patients who present with penetrating wounds to the thorax and abdomen are at risk for severe injuries to major vessels, and therefore for massive hemorrhage, and are most likely to die during the acute phase of care.[9,13] For these patients, rapid identification and control of hemorrhage is paramount, and they often require immediate surgery, especially if they are in shock.[19] The difference in severity of hemorrhage from vascular injuries caused by blunt and penetrating mechanisms is unclear. Major hemorrhage from penetrating injuries is frequently not difficult to localize; however the diagnosis of the source of even severe bleeding in blunt trauma can be more challenging. In the patient with blunt trauma, the localization of hemorrhage frequently requires specialized diagnostic procedures such as computed tomography, ultrasound, and angiography to optimally control bleeding.

Causes of Shock

Hypovolemia from hemorrhage is the most common cause of shock in the trauma patient but not the only possible cause. High spinal cord injuries can cause hypotension, so-called neurogenic shock. Myocardial contusion, as well as intrinsic dysfunctional states such as myocardial infarction or heart failure, can cause cardiogenic shock. In addition, cardiovascular physi-

ology and the response to injury can be affected by exogenous influences, most commonly beta and calcium channel blockers and ethanol.

Causes of Bleeding

Direct injury

The term "surgical bleeding" is not well-defined and not particularly helpful. Traditionally, it was intended to describe vascular and tissue disruption amenable to surgical intervention, that is, direct operative visualization and suture repair. The advent of damage control surgery, interventional radiology with embolization, and novel topical hemostatic agents has blurred the utility of this definition. Regardless of precise definition, most of what has been called surgical bleeding in the past is severe and will be rapidly fatal if not controlled.

Coagulopathy

Overt coagulopathy affects at least 1 in 4 seriously injured trauma patients.[30] Etiologies include the direct effects of hemorrhage, hemodilution, hypothermia, and acidosis. The coagulopathy of trauma is directly proportional to injury severity, massive resuscitation and transfusion, and hemorrhagic shock.[30–33] The presence of an abnormal prothrombin time (PT) on admission is associated with a tripling of the mortality rate of injured patients, and this mortality tends to occur early.[30] Irreversible bleeding due to the coagulopathy of trauma causes the largest proportion of post-operative trauma fatalities and contributes substantially to the overall mortality of trauma.[30,32–38]

Coagulopathic comorbidities such as cirrhosis and hemophilia that predispose to bleeding diatheses may also be present in trauma patients. Much more commonly however, intentional or unintentional anti-coagulation due to exogenous agents, that is, pharmaceutical anti-coagulants like warfarin or anti-platelet agents like aspirin or ethanol,[39] may complicate the coagulation capability of the trauma patient. As examples, clopidogrel (Plavix®) inhibits platelet function and has been demonstrated to nearly double the red blood cell transfusion requirement in cardiac surgery while increasing the platelet requirement by a factor of almost eight.[40] Ibuprofen has been shown to increase operative blood loss by nearly 60% in hip arthroplasty.[41] Warfarin and aspirin can increase the mortality rate of traumatic brain injury four-to-five fold.[42,43]

Therapeutic Considerations: Preventing Complications and Improving Outcomes

Critically injured trauma patients are treated in three, often overlapping phases: the initial control and resuscitation phase, when initial hemorrhage control and lifesaving stabilization efforts occur; the interventional phase, when definitive control of bleeding is attained; and the critical care phase, when support and restoration of normal physiology are accomplished.

Initial Control and Resuscitative Phase

Early trauma care focuses on minimizing hemorrhage and resuscitating effectively. There is no debate about the importance of hemorrhage control as a first-line measure. The optimal development and deployment of novel hemostatic agents, dressings and tourniquets are subjects of active research.

Novel Agents for Early Hemostasis

The control of bleeding and limitation of blood loss is the only means of avoiding the problems associated with massive hemorrhage in trauma. Novel methods of early hemorrhage control are under investigation. Recombinant factor VIIa (NovoSeven®, Novo-Nordisk Pharmaceuticals, Inc.) has demonstrated promise in clinical series as an adjunct to traditional measures in controlling hemorrhage in acute, life-threatening traumatic coagulopathy.[44,45] Prospective trials investigating the utility of this powerful but expensive agent in traumatic hemorrhage are ongoing. Progress is also being made in the development and testing of novel dressings and dressing-adjuncts for use on externally compressible or visceral hemorrhage. The most promising of these in pre-clinical studies has been the fibrin dressing developed by the American Red Cross which has shown superior hemostatic effect in models of severe arterial (femoral and aortic) and hepatic hemorrhage.[46–49] The fibrin dressing is distinguished from other available agents such as poly-N-acetyl glucosamine (chitosan and rapid deployment hemostat) bandages and granular mineral zeolite (QuickClot) in that it contains purified human fibrinogen and thrombin and thus is inherently hemostatic while other products support hemostasis primarily through adherence to and dessication of the bleeding wound, not directly through thrombogenesis.[48,50–52]

Tourniquets

Though uncommon in civilian trauma, exsanguination from traumatic extremity amputation has historically been a common cause of potentially preventable deaths from combat injuries.[53] Tourniquet use in civilian situations is controversial and has been avoided in recent years due to what appears to be primarily a theoretical fear of limb damage or loss,[54] however, military medical doctrine has adopted a liberal policy on the prehospital use of field tourniquets to prevent excessive blood loss and mortality from extremity vascular wounds.[55,56]

Other New Agents and Techniques

Emerging areas of research in early hemostasis for trauma include intra-cavitary agents for non-compressible bleeding and transcutaneous high frequency ultrasound. Intra-cavitary hemostatic agents are foams that can be instilled into a closed abdominal or thoracic cavity and will expand to compress a bleeding vessel, limiting blood loss before definitive control.[57] Transcutaneous high frequency ultrasound claims to merge the utility of ultrasound for both

the localization and control of hemorrhage by using the same ultrasound probe for the low-frequency localization of internal bleeding followed by the targeted application of high frequency sound waves to the source for coagulation of the bleeding point.[58]

Resuscitation

In contrast to the obvious logic and relative uniformity of opinion on hemorrhage control, current opinion on resuscitation is not as clear. There is no argument that the hemodynamically unstable patient must be supported; however, the optimal degree and agents of that support remain unclear. In a patient whose bleeding has not been definitively controlled, resuscitation to physiologically normal blood pressure may lead to "popping the clot", that is, dislodgment of hemostatic thrombus, and further bleeding. Resuscitation to a physiologically adequate but subnormal blood pressure, so-called "hypotensive resuscitation", before definitive hemorrhage control can be attained, has been used to avoid some of the rebleeding that occurs with resuscitation to conventional degrees.[31,59–64] However, in head injury patients, the prevention of rebleeding may be outweighed by decreased cerebral perfusion: even transient hypotension in patients with combined hemorrhage and brain injury is associated with increased mortality.[17,18]

Blood Product Use in Resuscitation

Although powerfully intuitive and almost universally practiced, the use of blood products in resuscitation has not been examined by the kinds of controlled clinical trials demanded now for the introduction of new clinical care products and techniques. This is because blood transfusion and resuscitation were synonymous when the practice and the term first became generally accepted in trauma care during World War I.[65] However, the increasing number of studies questioning the long-term consequences of early massive transfusion for trauma[28,29] make the planning and implementation of trials to try to answer some of these questions both likely and important.

Operative Phase

Approximately 50% of patients in hemorrhagic shock are taken directly from the emergency department to the operating room.[19] Because anatomically defined, so-called "surgical" bleeding, tends to be severe and can only be controlled by specialized intervention, early identification of these injuries is essential. Prompt definitive control of this kind of hemorrhage, by surgical or angiographic embolization techniques, is unarguably essential to preserve life and minimize morbidity. However, in the trauma patient who is cold and hypovolemic and becoming acidotic and coagulopathic, a "damage control" approach is now widely advocated.[66] That is, life-threatening injuries, bleeding, and contamination are addressed emergently, and then the patient is taken to the ICU for warming and continued resuscitation with the goal of restoring normal hemostatic physiology before definitive surgery is attempted.

Critical Care Phase

The critical care phase begins after definitive hemorrhage control has been attained and involves completion of resuscitation, intensive monitoring, and optimization of the physiologic milieu for injury recovery. Correction of hypothermia, coagulopathy, and resuscitation to physiologic endpoints occur in this phase. As noted earlier, hemorrhage itself is not a large problem in this phase; however the degree to which massive hemorrhage and/or the blood products used to treat life-threatening hemorrhage set the stage for the principal causes of morbidity and late mortality, that is, sepsis and MOF, are of concern and remain to be adequately explored.

Unfortunately, iatrogenic injury is a well-described cause of late morbidity and mortality in trauma patients. Infections of central venous catheters are common, causing over 40% of episodes of bacteremia in patients with organ failure and much attention has been paid to preventing these infections.[23] Adult respiratory distress syndrome (ARDS) occurs in between 70 and 80% of patients with MOF.[24] Protective ventilatory strategies in patients with ARDS have improved outcomes.[67,68]

SUMMARY AND CONCLUSIONS

Injury is a world-wide problem with severe and far-ranging consequences. Much of the mortality and morbidity resulting from injury arises from hemorrhage, but many of the problems associated with severe traumatic hemorrhage are potentially solvable. Improving outcomes will require improved early hemorrhage control, resuscitation procedures, and more complete understanding of the patho-physiology of the coagulopathy of trauma, sepsis, and MOF. If the physiologic derangements of injury can be minimized with better hemorrhage control measures early in care, it seems likely that the rates of late complications and mortality will be decreased and outcomes improved.

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DISCUSSION

Dr. Jeff Johnson: The experienced trauma clinician understands that all bleeding stops. However, as Dr. Kauvar has pointed out, the demise of the patient too often precedes the cessation of bleeding. Through a series of well-thought-out experiments Carl Wiggers nicely described that the depth of shock and the duration of shock are the primary determinants of outcome. While we now have more elegant ways of describing the depth of shock and studying oxygen debt and oxygen delivery, we don't yet understand the best way to reverse shock.

I have three general questions. The first relates to the argument that limited resuscitation strategies should prevent or limit further hemorrhage. The human data for this are largely derived from a study of patients with penetrating torso injuries who are very close to definitive care of their injuries. Looking at blunt or mixed trauma populations, limited resuscitation, while apparently doing no harm, appears to be no better. In recent US military operations, with smaller units in more dispersed areas and using body armor, extremity injuries are what we're seeing. My question is: How are we going to assess the efficacy of limited resuscitation in this kind of setting? What kind of data are needed to see whether limited resuscitation is effective in an extremity injury, distant from definitive care? Further, does this concept apply to the patient with a successfully applied tourniquet or a successfully applied hemostatic bandage?

My second question relates to the "bloody vicious cycle". As the authors point out, coagulopathy, hypothermia and acidosis can doom either operative or non-operative management. My question relates to the timing of intervention. With the inherent delay in laboratory testing, are we identifying these patients quickly enough? What is the best way to predict the patient who will suffer that problem? If you had one test at the arrival of the patient to help predict that, what would it be?

Lastly, a question for the trauma surgeons in the group. Hemorrhage control is no longer just about stitches. It is a multi-disciplinary project. Should we as surgeons abdicate our role as those who are the champions of hemostasis, or shall we make sure that we are adequately trained in techniques of angio-embolization, hemorrhage control, transfusion medicine, and component therapy?

Dr. Angus Wells: I would like to make some comments about the epidemiology of trauma from a blood bank point of view. The international and national data that you used to illustrate the problem of trauma is very illuminating. We've collected population-based data on blood use in the north of England for some years now. The area has a population of about 2.9 million and we've consistently found that trauma needs 6% of our blood supply, less than the estimates for America. Yet within that, half is for fractured neck or femurs, that is, frail elderly patients who have perhaps been topped up before surgery. Hospital episode statistics for the National Health Service in England, show only 2.4% of admissions were for trauma. And within that group, only 0.28% were major or multiple trauma. Therefore I am suggesting that there is a very small group of heavily transfused trauma patients who don't use a huge amount of the blood supply but, as individuals, are a high-volume, high-risk group.

Dr. David Kauvar: Dr. Johnson asked about limited resuscitation. ISR researchers have been working on animal models of limited resuscitation or hypotensive resuscitation, and their shock models show that hypotensive resuscitation

prevents re-bleeding and limits further blood loss before definitive control can be attained. Human studies are limited. One problem in implementing hypotensive resuscitation strategies, whether in a study or if this becomes accepted practice, is coordination, because you have to start in the initial, or control, phase. Do you have anything to add, Dr. Wade?

Dr. Charlie Wade: Well, the question basically is how low for how long? This is the axiom that Drs. Sondeen, Dubick and Holcomb of our group here at ISR have come up with. We're still trying to understand those parameters. We have an idea, as mentioned, that the penetrating trauma patient is probably the place to apply this strategy. But then how long can you sustain that patient in the hypotensive state? In the animal models, it looks on the order of about four hours at 80 mm Hg systolic arterial pressure. This still has to be addressed in the clinical setting.

Dr. Rick Dutton: When we did a hypotension trial in Maryland, we used definitive control of hemorrhage as an end point. It's usually easy to tell clinically when a person has stopped bleeding. Extremity injuries have usually stopped bleeding by the time they arrive at the trauma center because hemostatic mechanisms are very effective in controlling the bleeding. It isn't until we start working on the patient that we make them re-bleed, whether through fluid resuscitation or surgery. I think that is going to be a very important point, in defining how we approach this and define future studies.

Dr. Harvey Klein: Can you define what you mean by limited resuscitation? Are we talking just about hypotensive resuscitation, no matter what you use, or are there other aspects to that? Are you using blood pressure as your measurement?

Dr. Dutton: When all you have is a hammer, everything looks like a nail. We use blood pressure because that's what we have. But obviously there's a huge difference whether you're resuscitating with water or with blood products. And there's a huge difference whether you're vasoconstricted or vasodilated. So anesthetic state is important as well.

Dr. Fred Moore: I moved from Denver General, which was a knife and gun club, to Memorial Hermann Hospital in Houston, which is basically a blunt trauma hospital. And my second round of education as a trauma surgeon began, because a blunt trauma patient is very complex. And probably the biggest problem is assessing the severity of shock when the patient arrives. It's hugely variable, and it's not that easy. If we just had something we could slap on somebody, and say, this patient is really in shock, so we can't be wasting time. Or, this patient isn't in very bad shock, so we can let their blood pressure sit at 80 while we call in the OR team, that would be real nice. But we don't have that right now.

Dr. John Holcomb: I think we've identified several issues here so far. One is that only a small proportion of trauma patients receive blood. That small group of patients gets a large amount of blood, so that's our study target for just about anything that deals with shock and resuscitation.

Dr. Mauricio Lynn: To be a little bit controversial, why do we need to focus on doing pre-hospital clinical trials on hypotensive resuscitation if the time frame in major urban centers, which is most of our trauma patients, from injury to arrival at the trauma center, is extremely short?

Dr. Holcomb: I think we must do prehospital studies. As many hemorrhagic deaths occur prehospital as occur early in hospital care. Most of us in this room represent the in-the-hospital care group. But you have an equal number of patients who do poorly prehospital. It is less controlled and more difficult, but it's just as big a problem. And if you're going to apply your solution, whatever that is, your studies probably need to start prehospital.

Dr. Jeffrey Lawson: I want to debate one of the paper's theses, that stopping bleeding directly relates to changes in multi-system organ failure. I think that's implied data. Coagulation is an inflammatory pathway; it's a host-defense system set off by a number of different mechanisms. Overdriving coagulation is probably the same as overdriving inflammatory pathways. So one needs to be very careful, especially with the systemic biologics that are becoming available. Assuming that using potent, potentially inflammatory, molecules is also going to limit multi-system organ failure, when in fact it might drive systemic inflammation, is somewhat improbable, given what we already know.

Dr. Kauvar: It's overwhelmingly intuitive, though, that stopping the blood loss and decreasing the early physiologic derangement that occurs as a result of the blood loss will improve the outcome later on.

Dr. Lawson: My fear is that if we think of stopping bleeding as a uni-directional path that we will drive microvascular thrombosis systemically into inflammatory pathways.

Dr. Uri Martinowitz: The multicenter trauma trial, which was published in *J Trauma* found the opposite (Boffard KD et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59:8–18). Earlier control of hemorrhage showed a trend toward reducing ARDS and multi-system organ failure. We were very concerned that the complex formation between rFVIIa and tissue factor can increase inflammation, and apparently it is the opposite. And the same was in the brain: it decreases not only the hematoma but also edema.

I would like to make a comment. It's time to realize that there is no such thing as coaguloapathic versus surgical bleeding, unless you cut the vessel. But after half an hour this also becomes coagulopathy because these patients are also coagulopathic. Every trauma patient is coagulopathic; it's just our primitive tests that cannot measure most of the coagulopathy. We just miss 90% of the coagulopathies.

Dr. John Owings: I'm going to cautiously agree with Dr. Martinowitz. Coagulopathy means you have derangement of the coagulation cascade. We had the opportunity to study

about 200 trauma patients and do a battery of coagulation assays from the moment they hit the emergency department. They were all coagulopathic, that is, the patients that come in at least sick enough to activate a physiologic or a mechanistic criterion. And those are the ones you care about, the injured patients who, as a rule, all have up-regulation of their coagulation cascade. The question is whether they go off the end of that spectrum into the disorganized coagulopathy that gets called medical bleeding. It's all exactly the same thing and it comes from the same place.

Dr. Martinowitz: We have to be very careful in interpreting the tests. Like with TEG tests, you demonstrate the shortening of the clotting time and you interpret it as hypercoagulation. First, it is not necessarily hypercoagulation. And second, there are about 50 different changes in the coagulation system. So you cannot take one or two or three simple measurements and decide about the global response of the coagulation system. Now, every hypothermic patient is coagulopathic by definition. We usually underestimate the effect of hypothermia since we take the blood samples at the low temperature of the patient and the samples are warmed to 37°C. In addition we are measuring a test tube phenomenon. Nobody is checking what's actually happening in the body. Another example: acidosis. The acidotic patient is severely coagulopathic, there is 70% inhibition in thrombin generation at pH 7.2, but we don't measure it. Another example: hyperfibrinolysis. Do we measure fibrinolysis? So I think we should really start to think that every massively bleeding patient is coagulopathic. It's just a matter of timing. As Marcel Levi demonstrated, the patients are hypo-coagulopathic initially, and the next day they start to be more hypercoagulopathic.

Dr. Holcomb: I think many of you can now understand why it was so difficult to design some of the controlled studies that we've been working on for several years. The definitions are not consistent, the epidemiology is unclear, the intended study group is small, the tests are not very good and the variation is very broad.

I have a question for Dr. Moore, or anyone else in the group about improved hemostasis preventing multi-organ failure. That's been discussed extensively in a lot of small groups around the country. Do you believe that implied the link of the data?

Dr. Moore: It depends on how you're controlling it. I'm concerned that coagulopathy may just be a marker of adverse outcome. If you treat the coagulopathy with whatever hammer you have, you might hurt patients. A good example is blood transfusions. I was trained to transfuse liberally but the most recent data (some of which I generated) strongly suggests blood transfusions are harmful and may be a contributing factor in MOF pathogenesis.

Dr. Holcomb: Dr. Pruitt has made the point that all bleeding will stop within the first 12 to 24 hours, one way or the other. So our timeline to intervene is very short. And if we're not successful, our patients die.