

A Brief Review of Traumatic Shock Leading to a New Theory and a New Treatment

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ABSTRACT

Shock was called wound shock until World War II and has always been associated with war wounds. The relationship between shock and hemorrhage has long been debated. A review of the literature supports the view that hemorrhage and trauma are both causes of shock, yet separate in etiology.

INTRODUCTION

The association of shock with trauma has been recognized since the 18th century. In 1731, Le Dran described a case of injury by a missile, which led to a collapse of vital function ending in death.¹ He called it *secousse* (jar). In fact, shock was called wound shock until World War II. It has since been subdivided into hemorrhagic (hypovolemic), traumatic and septic shock, all associated with war wounds. Shock can be defined as inadequate capillary perfusion, which would also encompass neurogenic, cardiogenic and anaphylactic shock as well as other types.² During the American Civil War, shock and hemorrhage were considered to be separate conditions. In the Army Surgeon General's report written in 1876,³ it was stated, "the collapse of bleeding resembles syncope as distinguished from shock. Rest in bed, opium and warm fomentation constitute the treatment."

In World War I, in 1918, traumatic shock was attributed to a toxin originating in dead or dying tissue.⁴ In the 1920's, Blalock⁵ proved that shock after trauma was due to blood loss into the tissues. He bluntly traumatized dogs' legs and measured the increase in volume of the legs. He estimated that the increase in weight of the legs, (which consisted of extravasated blood in the tissues), showed enough blood volume loss to account for the shock produced. However, if this is true, why is the mortality of severely traumatized patients high even if adequate blood volume has been achieved with IV fluids? According to the accepted classification scheme of Trunkey⁶ traumatic shock is considered a subset of hypovolemic shock but with features that make it more difficult to treat. It now seems likely that both a toxin and hypovolemia play a part in the development of traumatic shock.

Many trauma patients die with a normal blood volume. In Viet Nam, 153,303 American wounded were admitted to military hospitals.⁷ About 3000 died of shock despite being adequately treated with IV fluids and appropriate surgical procedures.⁸ Something else must be involved besides blood volume loss. Death after trauma is often due to multiple organ failure (MOF), especially acute respiratory distress syndrome (ARDS). What is the etiology of MOF? Many metabolic changes occur after massive injury, the most important of which have been grouped together as the

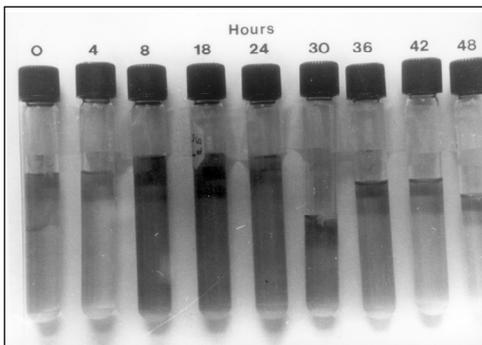


Figure 1. Spun down pig blood samples after trauma to both thighs. Hemolysis appears at about 8 hours, increases for a time and is gone by 48 hours.

systemic inflammatory response syndrome (SIRS), usually followed by a compensatory anti-inflammatory response syndrome (CARS).⁹ The inflammatory cytokines of SIRS can lead to cellular death and MOF if not adequately balanced by mediators of CARS. However, a number of anti-inflammatory drugs have failed to alter the mortality rate in clinical trials, despite successes in the laboratory and in animal studies.¹⁰ Perhaps a more important change is the frequent appearance of disseminated intravascular coagulation (DIC). It is rarely diagnosed in its early stages, because it is widely believed that bleeding and prolongation of prothrombin time and a fall in fibrinogen and platelets are signs of developing DIC. This is not true. Rather these are late developments in DIC and appear only late in the disease. The only accurate tests for the presence of early DIC are elevation of D dimer and fibrin split products.

What Initiates DIC?

It is widely accepted that endotoxin from the cell walls of gram-negative bacteria will induce thrombosis. This is undoubtedly true. However, there is a much more common factor which promotes clotting. It is present in all cell walls, animal as well as bacterial. Cell walls are made up of a bilayer of phospholipids, the inner layer differing from the outer in one important aspect. The external layer consists largely of

choline-containing phospholipids, which are not thrombogenic. The internal layer, however, is composed of aminophospholipids, which are strongly thrombogenic.¹¹ It has been shown that when the cell wall is inverted or broken, as during sickling in sickle cell disease or in paroxysmal nocturnal hemoglobinuria or malaria, the inner layer is exposed to the systemic circulation and promotes coagulation.¹² Cells, including red blood cells, may be broken due to trauma (Figure 1), heat or cold, and the resulting exposure of their internal membranes can promote coagulation, including DIC. These clots occlude the microcirculation of any and all organs and may in turn lead to MOF and ARDS.

Treatment

Many patients in shock due to trauma die of MOF or ARDS. The treatment of ARDS has been unsatisfactory. Actually, the most common cause of ARDS is septic shock. Treatment of ARDS in sepsis consists almost solely of respiratory support. If the ARDS does not respond to respiratory support, mortality approaches 100%. Many treatments have been tried, including external oxygenation using extracorporeal membrane oxygenation, intra-aortic oxygenation, vasoactive drugs, endogenous opiates, monoclonal antibodies, interleukin-1 receptor antagonist, nitric oxide antioxidants, ketoconazole, ibuprofen, indomethacin, sodium nitroprusside, pentoxifylline, antiendotoxin, anticytokines and aerosolized surfactant. A recent partial success is the use of activated protein C.¹³ This reduced the mortality of septic shock from 30% to 27%, but there were several cases of bleeding. The activated protein C was given to reduce the inflammatory response, but it has an additional beneficial effect in that it is also a thrombin inhibitor (hence the bleeding). The thrombin inhibitor effect may be helpful in preventing the onset of DIC.

A study using dogs¹⁴ showed that trauma alone to one thigh produced no mortality. Pure hemorrhagic shock (40 mm Hg for

Table 2. Trauma Patients with ARDS Unresponsive to Respiratory Treatment.

Case	Age	Gender	Diagnosis	PAO ₂ before PA therapy	PAO ₂ after PA therapy	Survival
1	47	F	Trauma with hemorrhage	33 mm Hg	256 mm Hg	no
2	50	F	Trauma	46 mm Hg	376 mm Hg	yes
3	31	M	Trauma with hemorrhage	39 mm Hg	52 mm Hg	no
4	11	F	Multiple trauma	35 mm Hg	206 mm Hg	no
5	25	M	Multiple trauma	65 mm Hg	318 mm Hg	no
6	27	M	Multiple trauma	43 mm Hg	54 mm Hg	no
7	10	M	Multiple trauma and sepsis	44 mm Hg	318 mm Hg	no
8	39	F	Multiple trauma	44 mm Hg	380 mm Hg	no
9	3	F	Multiple trauma with hemorrhage	61 mm Hg	360 mm Hg	yes
10	21	M	Multiple trauma	63 mm Hg	238 mm Hg	yes
11	80	F	Multiple trauma ruptured liver	40 mm Hg	110 mm Hg	no
12	58	M	Trauma	60mm Hg ruptured spleen	110mm Hg	yes
Average				47.7 mm Hg	231.5 mm Hg	66%Mortality

4 hours) produced near zero mortality (Table 1). Combined trauma and hemorrhagic shock produced 91% mortality. Trauma had damaged muscle cells as well as red cells, thus exposing the inner thrombogenic layer of the cell walls. The degree of tissue damage resulting from trauma to only one leg was not sufficient to cause death by itself, but if combined with hemorrhagic shock, the result was fatal. Thus, administering a small amount of hemolyzed (frozen and thawed) autogenous blood alone caused zero mortality, while administering a small amount of hemolyzed autogenous blood plus hemorrhagic shock produced 100% mortality. However, when

treated with fibrinolysin, this high mortality was significantly reduced by the lysis of the microclots of DIC. Fibrinolysin is an activated plasmin, which is no longer produced.

It is easy to produce ARDS in pigs by trauma alone as was shown by a study of trauma and ARDS published in 1990.¹⁵ In this study, the degree of tissue damage was increased over that in the study cited above, by the administration of 60 blows to each thigh (under anesthesia). This produced 100% mortality in ten pigs within 48 hours, even though normal blood volume was maintained with IV fluids. Administration of urokinase, a plasminogen activator, to

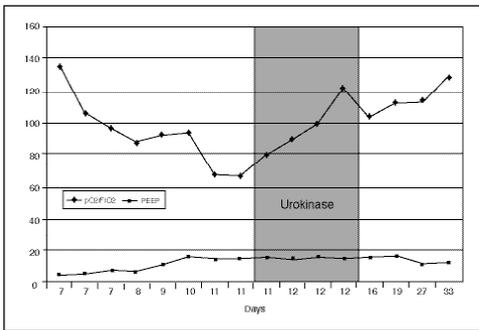


Figure 2. Traumatic shock in a 58-year old man with a ruptured spleen. PO₂/Fio₂ ratio was falling and the patient was comatose. After IV infusion of the urokinase, the PO₂/Fio₂ ratio rose and the patient recovered.

ten similarly traumatized pigs produced a zero mortality, indicating that microclots were the main culprit in the cause of death. Death of the control pigs was due to ARDS. The trauma produced hemolysis in all pigs (Figure 1), which would have produced DIC as described above.

In a clinical study, 12 trauma patients (among 20 ARDS patients)¹⁶ were enrolled after all developed ARDS unresponsive to respiratory support (with 100% O₂, respirator and PEEP) and had arterial PO₂ averaging 47.7 mm Hg. As all these patients were dying, with mortality likely to be 100% after failing ARDS treatment, the end point of this study was a significant rise in PO₂ rather than survival. All were given a 24-hour IV drip of urokinase, a plasminogen activator (PA). The protocol excluded any patients with bleeding, abnormal clotting parameters or head injury. At the end of the treatment, the average PO₂ was 231 mm Hg as compared with the original average of 47 mm Hg. All showed a highly significant rise in PO₂, with P=0.0001 (Table 2). The mortality was 66%, but none died of ARDS; rather they died of renal and liver failure. This is probably because, if the lungs are deprived of circulation for 24 hours and circulation subsequently restored, they will resume function, having been protected by their continued direct exposure to inspired oxygen and their low metabolic activity. On the other hand, if the liver and

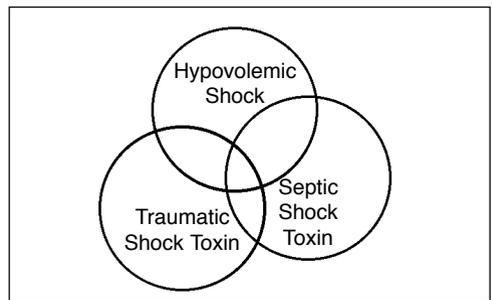


Figure 3. Relationship of the 3 types of shock. Hypovolemic (hemorrhagic) shock, traumatic shock, and septic shock are separate and distinct types of shock, but frequently overlap. Traumatic and septic shock are characterized by DIC produced by massive destruction of tissue or bacterial cells, exposing a thrombogenic toxin present in their inner cells.

kidneys are cut off from circulation for 24 hours, widespread cellular necrosis occurs, and the organs cannot function adequately.

One case is reported in detail (Figure 2).¹⁶ A 58-year-old man fell off a roof and suffered a broken ninth and tenth left rib, a bruised lung, and a ruptured spleen. The patient was closely watched to see if bleeding from the spleen progressed. It did, and a splenectomy was done the second day after injury. The patient developed severe ARDS, which was unresponsive to 100% O₂ and PEEP of 15 mm H₂O. The patient was comatose, and death seemed imminent. Oxygenation continued to decline, and the patient was entered in the protocol on the eleventh day after injury. (The FDA required a waiting period of 5 days after trauma or surgery.). The patient was given 1000 units of urokinase per pound of body weight per hour for 24 hours. PAO₂ rose to 110 mm Hg, but the patient was still comatose. The next day, PO₂ started to fall, and the patient was given a second treatment with urokinase the following day. The PO₂ again rose, but the patient was still comatose. Once again the PAO₂ started to fall 3 days after the second treatment. A third dose of plasminogen activator was given. PO₂ improved, and the patient woke up. He continued to improve and made a complete recovery. After a year, he was well and had

Table 1. Hemorrhagic Shock in Dogs*

Procedure	Dogs	No. of Deaths	Mortality Rate
Trauma alone (one leg)	19	0	0%
Hemorrhagic shock [†] alone (blood exposed only to plastic and treated carefully)	23	2	9%
Hemorrhagic shock [†] plus trauma	34	31	91%
Hemolyzed blood alone	13	0	0%
Hemolyzed blood plus hemorrhagic shock [†]	7	7	100%
Hemolyzed blood plus hemorrhagic shock [†] treated with fibrinolysin	13	5	38%

*Hardaway RM, BurnsVW. Mechanism of action of fibrinolysin in the prevention of "irreversible" hemorrhagic shock. *Ann Surg.* 1963;157:305-309.
[†]Blood pressure of 40 mm Hg for 4 hours

gone back to work.

None of the 12 patients had any bleeding before or after treatments.¹⁶ In fact, all clotting parameters were normal both before and after treatment. Fibrinogen was high in all cases both before and after treatment, as normally occurs following stress, although it fell somewhat during the treatment. Platelet counts consistently rose during treatments, probably due to the break up of platelet thrombi. Although urokinase has caused some bleeding when used to lyse large vessel thrombi (as in heart attack, stroke and pulmonary embolism), it has always been given as a large dose bolus. When given to treat DIC, it was given as a low dose continuous 24-hour IV infusion and never caused bleeding. In fact, it prevents the bleeding of severe DIC.¹⁷

Based on the above data, a theory of traumatic shock is postulated (Figure 3). Three types of shock are 1) hypovolemic or hemorrhagic shock, 2) traumatic shock, and 3) septic shock. They are separate and distinct, each with a different etiology and

treatment. Hypovolemic (hemorrhagic) shock is characterized by an inadequate blood volume due to hemorrhage, dehydration, or loss of plasma due to burns or third spacing. "Pure" hemorrhagic shock has little or no tissue damage. Its treatment is IV fluids in appropriate volume and kind and is very effective, provided hemorrhage can be controlled. Traumatic shock is characterized by severe tissue damage such as multiple fractures, severe contusions or burns. Its treatment is unsatisfactory, and mortality is high even if blood volume has been brought to normal and the injury repaired. DIC is usually present. Treatment may be the administration of plasminogen activator. Septic shock is due to infection by bacteria or viruses. Treatment is unsatisfactory in severe septic shock. Again, DIC is usually present. Many treatments by anti-endotoxin agents or drugs against cytokines and systemic inflammation have not been effective in saving any lives in either traumatic or septic shock. The exception is activated protein C, which has activity against both

inflammation and coagulation, although it did cause some bleeding tendency.¹³

Plasminogen activators have shown promise in treatment of traumatic and septic shock without causing bleeding when given in a low dose continuous infusion.¹⁵

Although these three types of shock are separate and distinct, they often overlap. There is usually some hypovolemia in both traumatic and septic shock, which must be corrected. Infection and sepsis often accompanies severe injury and elicits a marked inflammatory response. Pure hemorrhagic shock, uncomplicated by a traumatic or septic component, is easily treatable with IV fluids if hemorrhage can be controlled. If trauma is severe, treatment with IV fluids may not be sufficient. In this case the DIC may be lysed with a plasminogen activator. Traumatic and septic shock both frequently lead to DIC and ultimately MOF and death despite current treatment regimes. If the DIC can be diagnosed early by evaluation of D-dimer and fibrin split products, and a plasminogen activator given before tissue necrosis occurs, mortality could be significantly reduced.

CONCLUSION

Traumatic shock is an entity separate from hemorrhagic shock with a different etiology and treatment. If it fails to respond to volume therapy, it may be effectively and safely treated with a plasminogen activator. This treatment must be started at the first signs of DIC, but before clinical evidence of bleeding is noted and before prothrombin time is prolonged or fibrinogen levels fall, at which point plasminogen activator is contraindicated. DIC can be diagnosed only by elevation of fibrin split products or D dimer. Administration of plasminogen activator at this stage will actually prevent any clotting defect with might by caused by DIC.¹⁵

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